Rh sensitization

CPSP
CANADIAN PAEDIATRIC SURVEILLANCE PROGRAM

PROTOCOLS

Principal investigator

Michael Sgro, MD, FRCPC; University of Toronto, Adjunct Scientist, Li Ka Shing Knowledge Institute, Department of Paediatrics, St. Michael's Hospital, Room 014, 15th floor, Cardinal Carter Wing, 30 Bond St, Toronto ON M5B 1W8; tel.: 416-864-6060, ext. 6560; fax: 416-864-6073; sgrom@smh.ca

Co-investigators

Vinod Bhutani, MD, Stanford University School of Medicine, Stanford
Jillian Baker, MD, St. Michael's Hospital, Toronto
Douglas Campbell, MD, St. Michael's Hospital, Toronto
Mary Lou Decou, MSc, Public Health Agency of Canada, Windsor
Kathleen Hollamby, St. Michael's Hospital, Toronto
Thivia Jegathesan, St. Michael's Hospital, Toronto
Katerina Pavenski, MD, St. Michael's Hospital, Toronto
Alvin Zipursky, MD, The Hospital for Sick Children, Toronto

Background

Rh disease or Rh hemolytic disease is the result of maternal-fetal Rh(D) antigen incompatibility and refers to the sequelae associated with maternal sensitization. Rh sensitization occurs when women whose red blood cells are Rh(D) antigen-negative develop anti-Rh(D) antibodies, either during a previous pregnancy in which the fetus is Rh(D)-positive, or by exposure to Rh antigens from blood products/transfusion. Progressive anemia and hydrops fetalis (heart failure), resulting in stillbirths or early neonatal deaths, are all consequences of severe hemolytic disease in utero. Neonates who are affected by this condition and survive may present with severe jaundice, anemia, and death from acute or chronic bilirubin encephalopathy, or brain damage resulting from severe neonatal hyperbilirubinemia. The majority of these complications can be treated with prenatal interventions, including the use of Rh immunoprophylaxis, surveillance for the fetal anemia, early signs of cardiac failure, and hydrops, and if needed the timely use of intrauterine transfusion to correct hemolytic anemia.

Severe neonatal hyperbilirubinemia, for which Rh sensitization is a major risk factor, though rare, can be associated with significant morbidity, including bilirubin encephalopathy and death. During the acute phase of bilirubin encephalopathy, severely jaundiced neonates are noted to be lethargic and hypotonic with a poor sucking reflex. If the hyperbilirubinemia is not treated, the neonate can become hypertonic and develop a fever and a high-pitched cry. The hypertonia is manifested by backward arching of the neck (retrocollis) and trunk (opisthotonus). This condition may lead to neonatal death. On postmortem examination, deposition of bilirubin is noted in the basal ganglia and various brainstem nuclei and is termed "kernicterus" (yellow staining of the brain). Furthermore, if neonates survive the acute phase, they are at risk of developing chronic encephalopathy that presents later in life with athetoid cerebral palsy, sensori-neural hearing loss, dental dysplasia, and paralysis of upward gaze. They less often will develop intellectual and other handicaps. Several recent studies have found severe hyperbilirubinemia to be associated with other

developmental delays, such as autism, speech delay, and global developmental delay, even without the concomitant chorioathetotic cerebral palsy.

Based on epidemiological studies, a number of risk factors have been found to be associated with severe hyperbilirubinemia in the newborn. These include jaundice presenting in the first 24 hours, jaundice visible before discharge from hospital, previous sibling with jaundice, Asian race, gestational age between 35–37 weeks, exclusive breastfeeding, male gender, and infant bruising/cephalohematoma. Additional risk factors identified by laboratory investigations include ABO incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and Rh sensitization.

Rh disease was once the most common and most severe cause of fetal and neonatal hemolysis in Europe and the United States until the implementation of postpartum Rh immunoglobulin prophylaxis. This has been a highly effective public health measure for the prevention of neonatal morbidities and mortality. Prenatal Rh screening is now a routine part of prenatal and obstetrical care in every developed country, as is prophylaxis with Rh immunoglobulin for Rh(D) antigen-negative mothers. As such, Rh disease is now rare in countries where Rh prophylaxis is used, and the blood type and Rh sensitization status of the mother is usually known at the time of a delivery. However, the continued increase in immigration from various countries into Canada could result in the potential influx of mothers who have not received adequate Rh prophylaxis. The current incidence of Rh sensitization and well-associated Rh disease-associated neonatal severe hyperbilirubinemia in Canada is unknown.

Methods

Through the CPSP, a survey will be sent to approximately 2,500 Canadian paediatricians and paediatric subspecialists each month asking them to report any new cases of Rh sensitization. The CPSP is an ideal venue because it reaches paediatricians in a wide variety of community and academic health centres. Paediatricians who identify cases will be sent a questionnaire in order to provide detailed clinical information on the cases.

Case definition

Report any infant 60 days of age or less with Rh(D) sensitization fulfilling ALL of the following criteria:

- Mother is Rh negative (D-negative).
- Mother has positive antibody screen due to anti-D. This must be a maternal allo-anti-D, not passive anti-D from Rh immunoglobulin (RhoGAM).
- Cord or infant blood group is Rh positive (D-positive).

Objectives

1) To estimate the incidence of maternal Rh sensitization.
2) To estimate the incidence of Rh disease-associated neonatal severe hyperbilirubinemia.
3) To identify the timing of presentation, etiology, and associated triggers or risk factors for Rh sensitization and Rh disease-associated neonatal severe hyperbilirubinemia.

Duration

June 2016 to May 2018

Expected number of cases

Using the estimated incidence of Rh sensitization in the United States (approximately 10 per 10,000 live births), the estimated number of cases is approximately 400 cases captured by the CPSP. Despite public health measures in place across Canada, the research team expects to find a significant number of cases of Rh sensitization due to a number of factors, including immigration patterns, Rh immunoglobulin (RhoGAM) refusal, and Rh sensitization prior to 28 weeks' gestation (Bhutani et al, 2013).

Ethical approval

St. Michael's Hospital and Public Health Agency Canada

Analysis and publication

Descriptive data will be collected prospectively and will be entered from the detailed collection sheet into a Microsoft Excel program. Data will be summarized using descriptive statistics. Continuous variables will be analyzed using the independent Student's t-test. Chi-square or Fisher's exact test will be used to test associations between categorical variables. Statistical analyses will be done using statistical package SAS 8.2 (SAS Institute Inc., Cary, NC).

Analysis will be completed six months after study completion. Interim data will be presented at paediatric meetings, particularly the CPS Annual Conference and the Pediatric Academic Societies (PAS) meeting. Peer-reviewed publication will be pursued.

Bibliography

American Academy of Pediatrics, Subcommittee on Hyperbilirubinemia. Clinical Practice Guideline: Managament of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114(1): 297–316.

Bhutani VK, Zipursky A, Blencowe H, Khanna R, Sgro M et al. Neonatal hyperbilirubinemia and Rhesus disease of the newborn: Incidence and impairment estimates for 2010 at regional and global levels. Pediatr Res 2013;74(Suppl 1):86–100.

Canadian Paediatric Society, Fetus and Newborn Committee. Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants (35 or more weeks' gestation) – Summary. Paediatr Child Health 2007;12(5):401–7.

Moise KJ Jr. Management of rhesus alloimmunization in pregnancy. Obstet Gynecol 2002;100(3):600–11.

Sgro M, Campbell D, Shah V. Incidence and causes of severe neonatal hyperbilirubinemia in Canada. CMAJ 2006;175(6):587–90.

Sgro M, Campbell DM, Shah V, Fallah S. Canadian Paediatric Society 86th Annual Conference Abstracts: The incidence of kernicterus in Canada 2007–2009. Paediatr Child Health 2009;14(Suppl A):36–7.

Trikalinos TA, Chung M, Lau J, Ip S. Systematic review of screening for bilirubin encephalopathy in neonates. Pediatrics 2009;124(4):1162–71.

Zipursky A. Rh hemolytic disease of the newborn – The disease eradicated by immunology. Clin Obstet Gynecol 1977;20(3):759–72.