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Neonatal hyperbilirubinemia and the risk of febrile seizures and childhood epilepsy

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ABSTRACT

Purpose: The aim of the study was to estimate the association between newborn children treated with phototerapy for hyperbilirubinemia and the subsequent risk of febrile seizures or epilepsy in early childhood.
Methods: We conducted a follow-up study of singleton children (N = 70 230) born between February 1998 and May 2003 from the Danish National Birth Cohort (DNBC). Information on exposure to phototherapy for hyperbilirubinemia was obtained from a questionnaire in the DNBC. Information on epilepsy and febrile seizures were obtained from the Danish National Hospital Registry (DNHR). Cox proportional hazard regression model was used to calculate hazard ratios (HRs) with 95% confidence intervals (CI).
Results: Newborns treated with phototherapy for hyperbilirubinemia had a higher risk of developing epilepsy in early childhood (HR: 1.66, 95% CI: 1.23–2.24) but not febrile seizures (HR: 1.04, 95% CI: 0.86–1.27). The increases risk of epilepsy were only present for boys (HR: 1.98, 95% CI: 1.40–2.78) not for girls (HR: 1.14, 95% CI: 0.64–2.02)
Conclusion: Phototherapy for hyperbilirubinemia in newborns was associated with an increased risk of epilepsy for males in early childhood. No excess risk was seen with febrile seizures.

1. Introduction

Jaundice is a common and often a benign condition in the transition from intrauterine to extrauterine life affecting up to 85% of newborns. Normally, jaundice resolves on its own within 2 weeks but around 4–8% of the newborns develop hyperbilirubinemia (Shapiro, 2003). High level of bilirubin is neurotoxic and sometimes causes bilirubin encephalopathy since free albumin-unbounded bilirubin can freely enter brain tissue (Shapiro, 2003). Hyperbilirubinemia increases the risk of neonatal seizures and cerebral palsy and is further associated with auditory disorders, development delay, autism disorders, and attention deficit disorders (Jangaard et al., 2008; Maimburg et al., 2009; Maimburg et al., 2010; Buchmayer et al., 2009). Phototherapy can help convert bilirubin molecules to watersoluble untoxic isomers to prevent short and long term brain damage in newborns with hyperbilirubinemia (Maisel and McDonagh, 2008).

Epilepsy is one of the most common neurological disorders in childhood and the incidence of epilepsy is high in early childhood (Beilmann et al., 1999). Pre- and perinatal risk factors such as gestational age, maternal infections, instrument-assisted and caesarean deliveries are associated with an increase risk of epilepsy in childhood (Sun et al., 2008; Bhalla et al., 2011). Febrile seizures are a common condition in childhood with a not fully known aetiology (Pavlidou et al., 2013). However, newborns exposed to seizures in the neonatal period have an increased risk of epilepsy in later life (Ronen et al., 2007).

Two studies have reported on a positive association between hyperbilirubinemia and the risk of epilepsy (Cansu et al., 2007; Huseyinoglu et al., 2012). Only one study has examined the

Abbreviations: HR, hazard ratio; CI, confidence interval; ICD, 10 *International Classification of Diseases 10th revision*; DNBC, Danish National Birth Cohort; DNHR, Danish National Hospital Register; DMBR, Danish Medical Birth Register; CDR, cause of death register; BMI, body mass index; G6PD, glucose-6-phosphate dehydrogenase deficiency.

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association between hyperbilirubinemia and the risk of febrile seizure in childhood and found no association between hyperbilirubinemia and febrile seizures in newborns with a serum bilirubin level higher than 300 μmol/L (Forsgren et al., 1991). We therefore examined the association between newborns treated with phototherapy for hyperbilirubinemia and development of epilepsy and febrile seizures during childhood.

2. Materials and methods

2.1. Study population

This study is a follow-up study based on the Danish National Birth Cohort (DNBC) on all single born children between February 1998 and May 2003 (Olsen et al., 2001). The cohort includes data collected during pregnancy and shortly after birth through four telephone-assisted interviews. Two of the interviews were collected at 12 and 30 weeks of gestation, and two at 6 and 18 months post partum. Children from the DNBC can be linked with nation-wide Danish registers to obtain information on diagnoses of epilepsy, febrile seizure and other potential confounders. A unique identification number is assigned to all residents in Denmark allows for the accurate linkage of information between registries at the individual level.

2.2. Exposures to phototherapy for hyperbilirubinemia

Information on phototherapy for hyperbilirubinemia of newborns was collected from the 3rd telephone-assisted interview in the DNBC. In the interview the mother was asked *¨Have your child had phototherapy treatment for neonatal jaundice*?.Ċhildren were classified as being exposed if the mother answered ÿesŏ this question. The mother's report on phototherapy was validated in a random sample of 100 children who were born at Aarhus University Hospital in Skejby comparing the mother's self-reported answer in the DNBC with information from the child's medical record.

The Danish guideline for phototherapy treatment in mildly ill newborns recommends treatment if TsB level in μmol/L corresponds to 10% of the birthweight with a maximum of 300 μmol/L. For severely ill newborns (including conditions as respiratory distress, asphyxia, infections, and isoimmune haemolytic disease) the TsB level is 50 μmol/L lower, and for otherwise healthy newborns the level is 50 μmol/L higher. Furthermore, phototherapy is recommended if TsB increases with more than 8 μmol/L per hour (Ebbsen et al., 2012).

2.3. Outcomes, epilepsy and febrile seizures

Diagnoses of epilepsy and febrile seizures were obtained from the Danish National Hospital Register (DNHR) (Andersen et al., 1999), which was established in 1938 and computerized in 1969. The register includes all admissions to Danish hospitals and from 1995 all outpatients were also included. Diseases are recorded according to the *International Classification of Diseases, 10th Revision* (ICD-10). We identified children with epilepsy if they were registered with ICD 10 code G40-G41. We identified children with febrile seizures if they were registered with ICD 10 code R56 between 3 months and 5 years of age and without a history of epilepsy which is the definition of febrile seizures. Information on the diagnoses of epilepsy and febrile seizures obtained from the DNHR has been compared with data from medical records (Christensen et al., 2007; Vestergaard et al., 2005).

2.4. Confounders

Information on children's vital status and possible time of death was obtained from the Cause of Death Register (CDR) and information on births was obtained from the Danish Medical Birth Register (DMBR) (Knudsen and Olsen, 1998), which includes information on more than 99% of all deliveries in Denmark. The data stored in the register have been validated and are considered reliable (Kristensen et al., 1996).

2.5. Statistical analyses

We estimated Hazard ratios (HRs) of epilepsy and febrile seizures for newborns treated with phototherapy for hyperbilirubinemia using Cox proportional regression model with right censoring. When estimating the risk of epilepsy, children were followed from day 29 after birth until the onset of epilepsy, death, or the end of the follow-up on August 10, 2010. In the analyses for the risk of febrile seizure, children were followed from day 90 after birth until the onset of febrile seizure, death, or the end of 5 years old, whichever came first. Both crude and adjusted HRs of epilepsy and febrile seizures were estimated.

We estimated the adjusted HRs by adjustment for gender, gestational age (<33, 33–34, 35–36, 37–38, 39–41, 42+ gestational weeks), social economic status (high, middle, low, missing), maternal age (<25, 25–29, 30–34, 35–39, 40+), parity (1,2+, missing), infertility treatment (yes,no), and maternal risk factors during pregnancy (yes,no). Children were exposed to maternel risk factors during pregnancy if the mother had preeclampsia, diabetes in pregnancy, haemorrhage in early pregnancy, antepartum haemorrhage, infection of genitourinary tract, premature rupture of membrane, intrapartum haemorrhage, infection of amniotic sac and membranes, placenta praevia, or abruption placentae.

We further estimated the associations between neonates who were treated with phototherapy for hyperbilirubinemia and the risk of epilepsy or febrile seizures for boys and girls, for children born in different gestational ages (preterm, term, and postterm), children born by primiparous and multiparous mothers, children exposed to maternal risk factors during pregnancy or not, and children with or without a risk scenario. A risk scenario was defined as children with and without Apgar score <7 at 5 min, congenital malformations in the first year of life, and cerebral palsy. We used Stata 12 (Stata Corp, College Station, TX) for data analysis. The study was approved by the Danish Data Protection Agency.

3. Results

3.1. Study population

In the DNBC, we identified 70,294 children, whose mothers have completed the third interview in the DNBC. Children with missing information on phototherapy status (n = 40), birth outcome (n = 9), and twins (n = 15) were excluded leaving 70,230 children in the study population. There were 3162 children (4.5%) treated with phototherapy as treatment for hyperbilirubinemia according to their mother's report. The validated sub-sample of 100 children treated with phototherapy for hyperbilirubinemia in Aarhus University Hospital in Skejby revealed that 96% of the children had phototherapy according to their medical record, 2% of children had serum bilirubin tested twice but did not receive treatment for hyperbilirubinemia, and further 2% of the children had no treatment or serum bilirubin tested according to the medical records.

A total of 789 (1.1%) children had a diagnosis of epilepsy (G 40–41), and 2734 (3.9%) had a diagnosis of febrile seizures. Among 789 children diagnosed with epilepsy, 165 (20.5%) children were