APS European Society for Paediatric Research SPR Society for Pediatric Research

CORRESPONDENCE

Neonatal hyperbilirubinemia and bilirubin neurotoxicity: what can be learned from the database analysis?

Pediatric Research (2022) 92:1204; https://doi.org/10.1038/s41390-022-01973-5

Understanding the epidemiology of bilirubin neurotoxicity is important for improving care. We were excited to read the study by Qattea et al., "Neonatal hyperbilirubinemia and bilirubin neurotoxicity in hospitalized neonates: analysis of the US Database."[1]

This study evaluated bilirubin neurotoxicity based on International Classification of Diseases (ICD) codes for bilirubin neurotoxicity from the newborn period. One way to confirm the accuracy of an ICD diagnosis is to assess its association with other ICD codes that should accompany it. In the case of kernicterus, one would expect that if bilirubin levels are high enough to cause neurotoxicity, the infants would be treated with exchange transfusion. However, in this study, only 14% (205/1437) of infants with codes for bilirubin neurotoxicity received exchange transfusion (20% of the infants with neurotoxicity and isoimmunization and 13% of infants with neurotoxicity without isoimmunization). This indicates that the ICD codes may lack specificity as the vast majority of infants with "bilirubin neurotoxicity" did not get exchange transfusion.

Assuming that the codes were accurate for bilirubin neurotoxicity in newborns, this should not be conflated with kernicterus. Codes from the newborn period lack sensitivity because kernicterus is often not diagnosed until after 6 months of age.[2] Many infants with acute bilirubin encephalopathy who receive timely treatment do not go on to develop kernicterus.[3,4]

Another important consideration when analyzing findings from large administrative dataset is the population and denominator under study. In this paper, the analysis is not clear as to the population studied. If the study focused on birth hospitalizations, then the study would miss readmissions or hospital transfers, both of which are common for bilirubin neurotoxicity. If the study included all hospitalizations for infants of specific ages, then the analysis would have to be careful not to include multiple hospitalizations per subject and would also need the method to define an appropriate population-level denominator. Using a denominator based on discharges instead of the population would be difficult to interpret.

The authors found an increased risk of bilirubin encephalopathy in Black infants, which they attributed to the increased prevalence of hemoglobinopathies. It should be highlighted that the drivers of bilirubin encephalopathy in Black neonates are more complex, including multiple biologic factors like G6PD deficiency or symptomatic ABO hemolytic disease and important non-biologic factors such as social determinants of health and structural racism.[5] Disorders of globin synthesis are usually not clinically evident until after the first few months of life and are not a reported cause of kernicterus in Black or other neonates.

We hope that these comments are helpful for the authors of this study and for the many readers invested in improving long-term neurologic outcomes for patients with hyperbilirubinemia.

Marie-Coralie Cornet[1]✉, Alex R. Kemper[2], M. Jeffrey Maisels[3], Jon Watchko[4] and Thomas B. Newman[1,5]

[1]*Department of Pediatrics, University of California San Francisco, San Francisco, CA, USA.* [2]*Division of Primary Care Pediatrics, Nationwide Children's Hospital, Columbus, OH, USA.* [3]*Department of Pediatrics, Oakland University William Beaumont School of Medicine, Beaumont Children's Hospital, Royal Oak, MI, USA.* [4]*Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.* [5]*Department of Epidemiology & Biostatistics, University of California San Francisco, San Francisco, CA, USA.*
✉*email: marie-coralie.cornet@ucsf.edu*

REFERENCES

1. Qattea, I., Farghaly, M. A. A., Elgendy, M., Mohamed, M. A. & Aly, H. Neonatal hyperbilirubinemia and bilirubin neurotoxicity in hospitalized neonates: analysis of the US Database. *Pediatr. Res.* https://doi.org/10.1038/s41390-021-01692-3 (2021).
2. Brooks, J. C., Fisher-Owens, S. A., Wu, Y. W., Strauss, D. J. & Newman, T. B. Evidence suggests there was not a 'resurgence' of kernicterus in the 1990s. *Pediatrics* **127**, 672–679 (2011).
3. Hansen, T. W. R. et al. Reversibility of acute intermediate phase bilirubin encephalopathy. *Acta Paediatr.* **98**, 1689–1694 (2009).
4. Harris, M. C., Bernbaum, J. C., Polin, J. R., Zimmerman, R. & Polin, R. A. Developmental follow-up of breastfed term and near-term infants with marked hyperbilirubinemia. *Pediatrics* **107**, 1075–1080 (2001).
5. Okolie, F., South-Paul, J. E. & Watchko, J. F. Combating the hidden health disparity of kernicterus in Black infants: a review. *JAMA Pediatr.* **174**, 1199–1205 (2020).

AUTHOR CONTRIBUTIONS

M.-C.C. drafted the article; all authors designed the article, interpreted the data, revised it critically for important intellectual content, and approved the final version to be published.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

No patient consent was required for this work.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Marie-Coralie Cornet.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 3 September 2021 Revised: 30 November 2021 Accepted: 23 January 2022
Published online: 8 February 2022