Association of Early Direct Bilirubin Levels and Biliary Atresia Among Neonates

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Introduction

Biliary atresia (BA) is a fibrosclerosing cholangiopathy resulting in obstruction of the biliary tree. Diagnosis and early performance of the Kasai hepatic portoenterostomy improves outcomes.\(^1\) Current guidelines recommend measurement of direct bilirubin (DB) or conjugated bilirubin levels in neonates who are still jaundiced at age 2 to 3 weeks.\(^2,3\) However, recent studies have documented the elevation of DB or conjugated bilirubin levels within the first days after birth in neonates with BA,\(^4,5\) suggesting that BA is a developmental cholangiopathy associated with a genetic, prenatal, or developmental event. To test this hypothesis, this case series evaluated DB levels in the first days after birth among neonates who were subsequently diagnosed with BA.

Methods

We performed a retrospective review of all patients diagnosed with BA from 2 hospitals in the Beaumont Health System in Royal Oak, Michigan, and Troy, Michigan, from January 1992 to July 2018. We included only patients whose DB levels were measured at a Beaumont facility within the first week of life, whose liver biopsy results were consistent with BA, and who underwent a Kasai hepatic portoenterostomy. This study was approved with a waiver of consent by the Beaumont Health System institutional review board because the research involved data that had been collected solely for nonresearch purposes. This study followed the reporting guideline for case series.

We used Excel 2011 spreadsheet software (Microsoft Corp) to organize our data and calculate percentiles. Data were analyzed from August to September 2018.

Results

The median (range) total serum bilirubin (TSB) level in the population was 11.9 (4.2-17.6) mg/dL (to convert to micromoles per liter, multiply by 17.104), and the median (range) DB level was 1.7 (0.8-4.9) mg/dL. From DB measurements in 10,652 neonates, we established 1.0, 1.1, and 1.3 mg/dL as our 95th, 97.5th, and 99th percentiles, respectively (data not shown). We identified 8 neonates with BA (6 female; 2 male; gestational age, 34-41 weeks), all of whom had a DB level higher than 1.3 mg/dL (i.e., 99th percentile) within the first week (Figure). In 1 neonate, the DB level was 0.8 mg/dL (85th percentile) at age 8 hours and 1.0 mg/dL at 30 hours. Repeated measurements of DB levels were taken 10 to 104 hours later in 7 neonates and 1 month later in 1 neonate. Levels increased in 7 of 8 neonates (86%). Only 2 of 8 neonates (25%) had an initial DB-to-TSB ratio greater than 0.2.

Discussion

Our study had limitations, including the retrospective design and a small sample size. We could also have missed some cases of BA and excluded others because there was no measurement of DB in the first week. Nevertheless, our findings confirmed published data documenting that neonates with BA manifest direct hyperbilirubinemia within the first week of life (and, in some cases, as early as the first day) and that DB levels increase over time. Harpavat et al\(^5\) found that all 35 patients with BA in
their study had an elevated conjugated bilirubin or DB level within 60 hours of birth. Although previously considered relevant, a DB-to-TSBratio of more than 20% is no longer recommended as a diagnostic test that suggests the presence of cholestatic jaundice. The North American and European Societies for Pediatric Gastroenterology Guideline recommended that “an elevated serum direct bilirubin level (direct bilirubin levels >1 mg/dL or 17 μmol per liter) warrants timely consideration for evaluation and referral to a pediatric gastroenterologist or hepatologist.” Most of our patients had initial DB-to-TSBratios less than 0.2, which questions the clinical relevance of a ratio of 0.2 or greater as a screening modality for neonatal cholestasis.

Conclusions

This study confirmed published data documenting that neonates with BA manifest cholestasis within the first week and as early as the first day of life, that the cholangiopathy in BA begins in utero or in the early perinatal period, and that DB levels in neonates with BA increase over time. As others have also noted, we found that in neonates with BA, DB levels are initially less than 20% of TSB and, if the DB level in a neonate is higher than 1.0 mg/dL, a DB-to-TSBratio less than 20% does not rule out the possibility of cholestasis. These neonates should undergo 1 or more additional tests of DB levels. If the DB level does not decrease below 1.0 mg/dL, the neonate should be evaluated for any of the possible causes of neonatal cholestasis, including BA. Large, prospective studies are required to confirm the clinical relevance and cost-effectiveness of DB screening in neonates.
REFERENCES

1. Wang KS; Section on Surgery, Committee on Fetus and Newborn; Childhood Liver Disease Research Network. Newborn screening for biliary atresia. Pediatr.ics. 2015;136(6):e1663-e1669. doi:10.1542/peds.2015-3570

2. Fawaz R, Baumann U, Ekong U, et al. Guideline for the evaluation of cholestatic jaundice in infants: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2017;64(1):154-168. doi:10.1097/MPG.0000000000001334

3. Maisels MJ, Baltz RD, Bhutani V, et al; American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114(1):297-316. doi:10.1542/peds.114.1.297

4. Harpavat S, Finegold MJ, Karpen SJ. Patients with biliary atresia have elevated direct/conjugated bilirubin levels shortly after birth. Pediatrics. 2011;128(6):e1428-e1433. doi:10.1542/peds.2011-1869

5. Harpavat S, Ramraj R, Finegold MJ, et al. Newborn direct or conjugated bilirubin measurements as potential screen for biliary atresia. J Pediatr Gastroenterol Nutr. 2016;62(6):799-803. doi:10.1097/MGP.0000000000001097