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Research Article

Cholestasis in neonates with fetal growth restriction

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Abstract

Background: Neonatal Cholestasis (NC) is a sign of hepatobiliary disorder due to various etiologies. In the neonatal intensive care unit (NICU) extensive evaluation is done to rule out treatable causes. Neonates with fetal growth retardation (FGR) have an increased incidence of cholestasis.

Aim: To determine the prevalence, management, additional healthcare cost, and outcome of cholestasis in neonates born with FGR.

Methods: Retrospective review of all neonates admitted to the NICU at Valley Children's Hospital, from January 1, 2021 to December 31, 2022 was done. Data of the infants with FGR was collected.

Results: Out of 2,850 infants admitted in the 2-year period, 42 had a birth weight of less than 10th percentile, of which 19 developed cholestasis (45%). 12 of the 19 infants were preterm infants and 7 were term infants. Average gestational age at birth was 31.6 and average direct bilirubin of 5.2 mg/dL. The average length of stay was 54 days. Of the 19 infants who developed NC, 8 were discharged on ursodiol and followed up in gastroenterology clinic. 17 showed resolution of NC within 6 months of discharge. Some infants underwent extensive work-up. Costs for the work-up added up to an average of $8,920.

Conclusion: Prognosis for NC in the FGR neonates appears to be good with resolution in our study population within the first year of life. Hence, it may be safe to monitor these neonates with outpatient followup with early limited evaluation until complete resolution of cholestasis.

Keywords: Neonatal cholestasis, Fetal growth retardation, Preterm infants, Term infants, Biliary atresia

Introduction

Neonatal cholestasis (NC) is usually a result of hepatobiliary dysfunction and can lead to extensive workup and prolonged stay in the NICU. NC is never physiological but rather a sign of hepatobiliary and/or metabolic disorders, some of which can become fatal if it is not identified and treated in time. Timely evaluation is essential for identifying those causes amenable to treatment and to offer accurate prognosis. The incidence of neonatal cholestasis has been reported to be 1 in 2,500 to 5,000 term infants [1,2].

NC can occur due to multiple causes. For example, among 82 infants retrospectively analyzed at a pediatric tertiary center in Germany some conditions identified included biliary atresia (35-41%), progressive familial intrahepatic cholestasis (PFIC) (10%), preterm birth (10%), metabolic and endocrinological disorders (9-17%), Alagille syndrome (AS) (2-6%), infectious diseases (1-9%), mitochondriopathy (2%), biliary sludge (2%), and, finally, idiopathic cases (13-30%) [3,4]. Hence a structured and broad-based diagnostic approach is required. The recommendations by the cholestasis committee in 2017 by Fawaz et al., provide an approach to diagnose infants with cholestasis. However it clearly states that these guidelines should be tailored to individual patients and may not be applicable as standards of care for all infants with NC [2].

Cholestasis is a well-known occurrence in neonates born with FGR, which is also known as intrauterine growth restriction (IUGR) or small for gestational age (SGA). FGR is defined as a

condition in which the fetus fails to attain the growth potential as determined by the genetic makeup and is born with birthweight lesser than 10th percentile for gestational age [5]. The etiology of increased occurrence of cholestasis in this population is not clear, though we can speculate that inutero insult likely plays a part.

Currently there are no published data on the duration or resolution of cholestasis in the neonates with FGR. This retrospective study is aimed to determine the prevalence, management, additional healthcare cost, and outcome of cholestasis in all neonates born with fetal growth restriction admitted to a teritiary neonatal intensive care unit over a 2-year period.

Subjects and Method

We performed a retrospective review of all neonates admitted to the NICU at Valley Children's Hospital in Madera from January 1, 2021 to December 31, 2022. We reviewed the data of the eligible infants and selected all the neonates with FGR. Fetal growth restriction was defined as a neonate with birth weight less than 10 percentile. Preterm infants are infants born at a gestational age of less than 37 weeks. Infants are diagnosed with cholestasis if direct bilirubin concentration is higher than 2 mg/dL or more than 20% of the total bilirubin. Term and preterm neonates with FGR were identified and screened for a diagnosis of cholestasis. Institutional Review Board approval was obtained to review the records of all the patients.

Results

A total of 2,850 infants were admitted to the NICU during the 2-year period. Of these infants, 42 had a birth weight of less than 10th percentile and categorized as infants with FGR. Of the 42 neonates, 19 developed cholestasis (45%). 12 of these 19 infants were preterm infants (born <37 weeks gestation) and 7 were term infants. Ethnicity, maternal factors such as pregnancy induced hypertension, chronic hypertension, and admitting diagnoses in both the groups were similar. The average gestational age at birth was 31.6 weeks with a range of 25.1 to 40.6 weeks. Maximum direct bilirubin levels ranged from 2 to13 mg/d, with an average of 5.2 mg/dL, and 95% confidence interval of 4.1 to 8.6 mg/dL. The average length of stay was 54 days with a range of 12 to 124 days. Of the 19 infants who developed cholestasis, 8 were discharged on ursodiol and followed up in gastroenterology clinic. 17 showed resolution of cholestasis within 6 months of discharge. Most infants had resolution of their cholestasis either prior to discharge or within 6 months of discharge; one infant died from pulmonary disease and one infant was lost to follow-up.

In our population, cholestasis was prevalent in more than 45% of the neonates with FGR. Some of the infants underwent extensive work-up including multiple abdominal ultrasound, HIDA scan, genetic cholestasis panel and tests to rule out congenital infections. Costs for the work-up added up to an average of $8,920 with a range of $842 to $31,428 Treatments included ursodiol, formula changes, vitamin supplementation, intravenous fish oil-based lipid administration.

Discussion

Intrauterine growth is an important indicator of fetal well being. Disruption of growth can lead to significant consequences on fetal growth and development. FGR is a pathological condition with utero-placental insufficiency due to various etiologies, whereby the placenta does not meet metabolic requirements of the fetus leading to reduced growth and decreased cell size in select organs [6]. The 'organ-sparing' effect leads to relative increase in supply of the resources to vital organs, resulting in low birth weight and impaired organ function of other organs, such as the liver [7]. This leads to alteration in metabolic and physiologic variables in the fetus and likely affect the hepatocyte function and feeding tolerance in the growth restricted infants [8,9]. These infants undergo rapid catch-up growth in early postnatal life, and the undernourished liver stands to gain the most relative to other organs [10,11].This is evident in SGA infants who undergo hypersomatotropism by postnatal day four, which occurs due to increased levels of insulin growth factor 1 (IGF-1) in the liver and blood [12]. Barker's 'thrifty phenotype' hypothesis states that fetal programming will adapt in anticipation of a similar postnatal environment, and hence this rapid weight gain is detrimental to hepatic function [13]. In fact, preterm infants undergo catch-up growth following consumption of nutrient-dense formula, leading to high ratios of LDL to high density lipoprotein (HDL) [14]. The liver is highly subjected to oxidative stress given that it is abundant in mitochondria, due to its critical role in nutrient metabolism. Numerous studies have found evidence of hepatic oxidative and mitochondrial stress in growth-restricted offspring .These studies also provide evidence for pancreatic and skeletal muscle mitochondrial dysfunction [15-17].

Previously published data suggest that hepatocellular and gastrointestinal function is most likely influenced by factors that induce IUGR such as uteroplacental insufficiency. This could result in a reduced liver metabolic capacity, and hence a higher incidence of NC in SGA-extremely lowbirth weight infants(ELBW) who received total parenteral nutrition(TPN) [16]. Another study by Beserga et al. shows that preterm infants with IUGR had increased incidence of cholestasis compared to their appropriate for gestational age (AGA) counterparts when they received >1 week of TPN (56% vs 27%) [18]. Yet another study reported that the SGA-ELBW infants had an increased incidence and earlier onset of cholestasis when compared to AGA-ELBW patients [19]. This supports the theory that some of the FGR infants, particularly those born preterm require proplnged TPN support and hence have multiple contributors for developing cholestasis.

In our study population, cholestasis was prevalent in 45% of neonates born with FGR. This is similar to the other reports of prevalence 50-56% [1,2,6]. The investigations done in our unit were more extensive for term infants than preterm infants, likey due to concerns of biliary atresia. Preterm infants more often received prolonged parenteral nutrition administration and had long hospital stay and hence stepwise investigations were possible compared to term infants. 89.5% of patient data was available for followup and all of them showed full resolution of cholestasis. As menitioned earlier one patient was lost for followup and another died of pulmonary disease during the initial admission.

Like other reported studies, we also observed that 12 of the 19 infants also had severe hypoglycemia requiring a higher concentration of dextrose and caloric requirement. 3 of the 19 infants were discharged home on Diazoxide for hypoglycemia, which was discontinued within 3 months of discharge by an endocrinologist. Its likely that similar insult to the pancreas and the elevated IGF can lead to transient hyperinsulinism in this population. A published

case series report demonstrated premature infants with IUGR are also predisposed to transient hyper-insulinemic hypoglycemia related to perinatal stress [20].

Conclusion

The prognosis for NC in the FGR neonates appears to be good with resolution in all available data, in our study population within the first year of life. Hence, it may be safe to monitor these neonates with outpatient followup with early limited evaluation until complete resolution of cholestasis. If warranted, inpatient work up maybe limited to treatable and time sensitive conditions like bacterial sepsis, galactosemia, tyrosinemia, panhypopituitarism, anatomic obstruction and biliary atresia. However most of these patients except those with biliary atresia are generally more sick appearing and may warrant more workup in the first place. To determine true incidence and long term health implication of NC in the FGR population, a prospective study over a longer period is needed.

Conflict of Interest

There is no conflict of interest to report by all three authors.

References

1. Moyer V, Freese DK, Whitington PF, Olson AD, Brewer F, Colletti RB, et al. Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Journal of Pediatric Gastroenterology and Nutrition. 2004 Aug 1;39(2):115-28.
2. Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, 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. Journal of Pediatric Gastroenterology and Nutrition. 2017 Jan 1;64(1):154-68.
3. Hoerning A, Raub S, Dechêne A, Brosch MN, Kathemann S, Hoyer PF, et al. Diversity of disorders causing neonatal cholestasis–the experience of a tertiary pediatric center in Germany. Frontiers in Pediatrics. 2014 Jun 23;2:65.
4. Mieli-Vergani G, Portman B, Howard ER, Mowat A. Late referral for biliary atresia—missed opportunities for effective surgery. The Lancet. 1989 Feb 25;333(8635):421-3.
5. Sharma D, Shastri S, Sharma P. Intrauterine growth restriction: antenatal and postnatal aspects. Clinical Medicine Insights: Pediatrics. 2016 Jul 14;10:67-83.
6. Baschat AA. Pathophysiology of fetal growth restriction: implications for diagnosis and surveillance. Obstetrical & Gynecological Survey. 2004 Aug 1;59(8):617-27.
7. Barker DJ, Martyn CN, Osmond C, Hales CN, Fall CH. Growth in utero and serum cholesterol concentrations in adult life. British Medical Journal. 1993 Dec 11;307(6918):1524-7.
8. Boehm G, Müller DM, Teichmann B, Krumbiegel P. Influence of intrauterine growth retardation on parameters of liver function in low birth weight infants. European Journal of Pediatrics. 1990 Mar;149:396-8.
9. Boehm G, Senger H, Braun W, Beyreiss K, RÄIMÄ N. Metabolic Differences between AGA-and SGA-Infants of Very Low Birthweight: I. Relationship to Intrauterine Growth Retardation. Acta Pædiatrica. 1988 Jan;77(1):19-23.
10. Valsamakis G, KANAKA-GANTENBEIN CH, MALAMITSI-PUCHNER AR, Mastorakos G. Causes of intrauterine growth restriction and the postnatal development of the metabolic syndrome. Annals of The New York Academy of Sciences. 2006 Dec;1092(1):138-47.
11. Neerhof MG. Causes of intrauterine growth restriction. Clinics in Perinatology. 1995 Jun 1;22(2):375-85.
12. Deiber M, Chatelain P, Naville D, Putet G, Salle B. Functional hypersomatotropism in small for gestational age (SGA) newborn infants. The Journal of Clinical Endocrinology & Metabolism. 1989 Jan 1;68(1):232-4.
13. Hales CN, Barker DJ. The thrifty phenotype hypothesis: Type 2 diabetes. British Medical Bulletin. 2001 Nov 1;60(1):5-20.
14. Singhal A, Cole TJ, Fewtrell M, Lucas A. Breastmilk feeding and lipoprotein profile in adolescents born preterm: follow-up of a prospective randomised study. The Lancet. 2004 May 15;363(9421):1571-8.
15. Theys N, Bouckenooghe T, Ahn MT, Remacle C, Reusens B. Maternal low-protein diet alters pancreatic islet mitochondrial function in a sex-specific manner in the adult rat. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2009 Nov;297(5):R1516-25.
16. Lane RH, Chandorkar AK, Flozak AS, Simmons RA. Intrauterine growth retardation alters mitochondrial gene expression and function in fetal and juvenile rat skeletal muscle. Pediatric Research. 1998 May;43(5):563-70.
17. Selak MA, Storey BT, Peterside I, Simmons RA. Impaired oxidative phosphorylation in skeletal muscle of intrauterine growth-retarded rats. American Journal of Physiology-Endocrinology and Metabolism. 2003 Jul;285(1):E130-7.
18. Baserga MC, Sola A. Intrauterine growth restriction impacts tolerance to total parenteral nutrition in extremely low birth weight infants. Journal of Perinatology. 2004 Aug;24(8):476-81.
19. Champion V, Carbajal R, Lozar J, Girard I, Mitanchez D. Risk factors for developing transient neonatal cholestasis. Journal of Pediatric Gastroenterology and Nutrition. 2012 Nov 1;55(5):592-8.
20. Rana P, Rodrigues M, Mahajan CN, Nyp MF, Vishal P. A Case Series of Four Preterm Intrauterine Growth Restricted Babies With Transient Hyper-Insulinemic Hypoglycemia and Cholestasis. Journal of the Endocrine Society. 2021 May 5;5(Suppl 1):A693.