Early Human Development 112 (2017) 29–34

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Risk factors of metabolic bone disease of prematurity

Supamit Ukarapong[a,*], Sunil Kumar Batlahally Venkatarayappa[b], Cristina Navarrete[c], Gary Berkovitz[a]

[a] Pediatric Endocrinology, University of Miami, Miller School of Medicine, Miami, FL, USA
[b] Pediatrics, Jackson Memorial Hospital, Miami, FL, USA
[c] Neonatology, University of Miami, Miller School of Medicine, Miami, FL, USA

ARTICLE INFO

Keywords:
Bone
Preterm infant
Risk factor and comorbidities

ABSTRACT

Objective: To identify the factors that increase risk of metabolic bone disease of prematurity (MBD).
Study design: A retrospective case-control study of infants born between January 2013–April 2014 with gestation age < 30 weeks and birth weight < 1000 g. MBD was defined as serum alkaline phosphatase above 500 U/L and characteristic radiographic changes. Information was obtained on the presence of specific comorbidities.
Results: Of 76 infants evaluated, 40 met criteria for MBD. Median gestational age was 25 weeks in both groups ($p = 0.512$). Median birth weight of infants with MBD was significantly lower than that of controls (560 vs. 765 g, $p < 0.01$). Longer period of parenteral nutrition and dexamethasone use was observed in MBD group. Cholestasis was associated with the highest likelihood of MBD (OR 16.6, 95% CI 4.8–56.9). Seizures (OR 5.2, 95% CI 1.3–20.5) and the prolonged use of diuretics (OR 2.6, 95% CI 1.0–7.0) also significantly increased the likelihood of MBD. Only cholestasis remained significant (OR 9.6, 95% CI 2.1–45.3) after multiple regression analysis.
Conclusion: Cholestasis is a significant risk factor for the development of MBD. Our future studies will be directed towards determining the causal relationship between cholestasis and MBD.

1. Introduction

Metabolic Bone Disease (MBD) of prematurity is a condition characterized by deficiency in bone mineral content which can be recognized by radiographic changes in bone and elevated serum alkaline phosphatase [1]. MBD of prematurity poses significant risk for both fracture and subnormal growth in the first year of life. The MBD results in large part from the lack of normal transfer of calcium and phosphorus from the mother to the fetus, a process occurring most significantly in the last trimester of gestation. As such, MBD of prematurity is most common among infants born at less than thirty weeks of gestation and in particular with extremely low birth weight (< 1000 g) [1,2].

The development of MBD should be considered especially at the peak onset of around 4–8 weeks of postnatal age [1,2]. The combination of radiographic and biochemical studies will identify preterm infants with MBD. Biochemical studies include serum calcium, phosphorus, alkaline phosphatase, urine calcium to creatinine ratio, tubular reabsorption of phosphorus (TRP) and PTH. In a study by Lee et al., elevated alkaline phosphatase level at 4 and 5 postnatal weeks and subnormal serum phosphorus at 2 and 3 postnatal weeks are associated with decreased bone mineral density [3]. Figueras-Aloy et al. reported that serum alkaline phosphatase above 500 U/L gives the highest sensitivity and specificity for MBD [4]. Elevated serum PTH has also been shown to be a good predictor of decreased bone mineral content in preterm infants [5].

Even with the availability of breast milk fortifiers and preterm formulas with higher amounts of minerals, the prevalence of MBD of prematurity continues to be high with estimates of between 23 and 55% [6]. The purpose of our study was to investigate the role of mineral delivery and the potential role of other comorbidities on the development of MBD of prematurity. Identification of the specific factors that negatively affect bone health in premature infants is key to development for specific therapeutic intervention.

2. Materials and methods

We performed a retrospective review of the medical records of preterm infants admitted to the Neonatal Intensive Care Unit (NICU) at Holtz Children's Hospital between January 2013 and April 2014. The

Abbreviations: MBD, metabolic bone disease of prematurity; PDA, Patent Ductus Arteriosus; TPN, total parenteral nutrition; DB, direct bilirubin

* Corresponding author at: 1601 NW 12th Avenue #3044A, Miami, FL 33136, USA.
E-mail address: s.ukarapong@med.miami.edu (S. Ukarapong).

http://dx.doi.org/10.1016/j.earlhumdev.2017.06.010
Received 25 April 2017; Received in revised form 27 June 2017; Accepted 27 June 2017

study was approved by the Institutional Review Board of the University of Miami. We studied patients born at gestational less than thirty weeks and with a birth weight < 1000 g. We chose a gestational age of 30 weeks and a cutoff weight of 1000 g to identify a group most likely to develop MBD. Infants were considered to have MBD if peak serum ALP was > 500 U/L and characteristic radiographic changes of long bones were present. The ALP cutoff level of > 500 U/L was used as this level gives the highest sensitivity and specificity [4]. Characteristic radiographic changes include loss of dense white line (zone of provisional calcification) at metaphyses, increased submetaphyseal lucency, thinning of cortex, fraying, splaying or cupping of metaphyses as previously described [7]. We reviewed radiographic studies of long bones, with confirmation by radiologist, performed after 6 weeks of life as these changes usually occur after this period [7]. For purposes of the study, we included only infants who survived more than three months and who had a complete data set in their charts.

Baseline characteristics of infants with and without MBD were collected. Data gathered included gestational age, birth weight, sex, rate of weight gain, length of parenteral nutrition and duration of steroid (dexamethasone) use. Rate of weight gain (g/kg/day) was calculated using a method described by Patel et al. [8]. We collected data for both enteral and parenteral nutrition over the first 3 months of life by reviewing the data on nutrition on the last day of every 2-week- period. The amount of mineral and vitamin D intake per day was calculated depending on the constituents of TPN and the type of formula. The Neonatal Intensive Care Unit at Holtz Children's Hospital starts with parenteral nutrition in the initial phase and introduces enteral feeding with breast milk as soon as the patient is able to tolerate. The amount increases gradually and liquid human milk fortification (Mead Johnson, IL, USA) is added when the amount of breast milk feed reaches 60 mL/kg/day. Parenteral nutrition is discontinued when a patient can tolerate up to 120 mL/kg/d of milk. Premature formula (Enfamil, Mead Johnson, IL, USA) is also used if the amount of breast milk is insufficient. We combined both parenteral and enteral intake data during the transition period to full enteral feedings in the analysis of total mineral and vitamin D intake. Mineral and vitamin composition of breast milk and formula were based on the average composition of breast milk and the manufacturer's product information. We also analyzed the intake of mineral and vitamin D from TPN separately. Serum calcium, phosphorus and alkaline phosphatase levels were obtained weekly as per unit protocol. The data were then compared between the two groups. The analyses were performed with Vitros 5600 integrated automated system (Ortho Clinical Diagnostics, NJ, USA). The monthly average of serum calcium and phosphorus levels were calculated and compared in a similar manner.

We also collected the information on the presence of comorbidities such as:

1. Bronchopulmonary dysplasia defined as the requirement of oxygen > 28 days,
2. Prolonged use of diuretics (> 2 weeks)
3. Anemia requiring blood transfusion
4. Retinopathy of prematurity
5. PDA requiring medical or surgical management
6. Hyperbilirubinemia requiring phototherapy
7. Cholestasis defined by serum direct bilirubin (DB) > 2 mg/dL and persisted for > 2 weeks
8. Sepsis (positive blood culture)
9. Acute kidney injury defined by modified pediatric RIFLE criteria (estimated creatinine clearance decreased by 50%) [9]
10. Seizures that required anti-epileptic drugs
11. The use of vasopressors
12. Neutropenia requiring G-CSF therapy
13. Thrombocytopenia requiring platelet transfusion
14. Necrotizing Enterocolitis above grade 2 Bell's criteria [10]

2.1. Statistical analysis

Mann-Whitney *U* test was used for data that did not have normal distribution. These data included gestational age, birth weight, length of parenteral nutrition, and rate of weight gain.

Two-way repeated measures ANOVA was used to analyze serial data of serum calcium, phosphorus, mineral and vitamin D intake. We analyzed the interaction between group and time for these parameters.

The odds ratio (OR) of MBD and comorbidities was first analyzed using univariate logistic regression analysis. We then used multivariate logistic regression analysis to adjust OR of co-morbidity that reached the significant level on the univariate model. Birth weight, rate of and duration of parenteral nutrition were also included as independent risk factors in the univariate model.

The data were analyzed using IBM SPSS software version 22. The difference between groups is considered significant when p value is < 0.05.

3. Results

3.1. Patient population

During the period January 2013 to April 2014, 114 infants with gestational age < 30 weeks and birth weight < 1000 g were admitted to the NICU at Holtz Children's Hospital. Among all of these patients, records of 76 infants (67%) contained all data needed for our analyses. Among those 76 infants, 40 subjects (52%) met criteria for MBD. The remaining 36 patients constituted a control group. The average age at the diagnosis was 6 weeks (range 6–10 weeks).

3.2. Patient characteristics

Data comparing subjects with MBD and controls are shown in Table 1. The median gestational age in MBD group (25 weeks, IQR 24–27) was similar to that of control group (25 weeks, IQR 23.5–26.5). Gender distribution among patients with MBD (male 62.5%) and among those without MBD (male 55.6%) was also similar ($p = 0.53$). However, there was a statically lower median birth weight ($p < 0.01$) in MBD (560 g, IQR 466–654) than in control (765 g, IQR 657–873) group. Median duration of parenteral nutrition in subjects with MBD (49 days, IQR 29–69) was significantly longer ($p < 0.01$) compared to those in the control (26 days, IQR 16–38). The average duration of

Table 1
Patient characteristics, length of TPN, duration of steroid use and rate of weight gain.

	MBD ($N = 40$)	Control ($N = 36$)	
Median Gestation age, (IQR)	25 weeks [24–27]	25 weeks [23–26]	$p = 0.30$
Median Birth Weight, (IQR)	560 g (466–654)	765 g (657–873)	$p < 0.01$
Male sex, n	25 (62.5%)	20 (55.6%)	$p = 0.53$
Median Length of TPN, (IQR)	49 days (29–69)	27 days (16–38)	$p < 0.01$
Dexamethasone use (Mean ± S.D.)	5.62 ± 7.85 days	1.13 ± 2.56 days	$p < 0.01$
Median weight gain, first 3 months (IQR)	12.11 g/kg/day (11.25–12.97)	12.05 g/kg/day (11.03–13.07)	$p = 0.95$