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Increased risk of metabolic bone disease in preterms born to preeclamptic mothers: A case-control study

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Abstract

Aim: To evaluate if there is an increased risk of metabolic bone disease associated with preeclampsia.

Materials and Methods: Preterm infants <32 weeks in gestation and <1500 gr at birth, who were born in our hospital, followed at least six weeks were enrolled. Metabolic bone disease cases were defined as elevated serum ALP concentration >500 IU/L and serum phosphate levels<4 mg/dl with radiological evidence of osteopenia. The control cases had serum ALP concentration ≤ 500 IU/L and serum phosphate levels >5.6 mg/dl. Maternal factors and clinical variables including postnatal drug use, presence of reduced physical activity, hypotiroidism, feeding intolerance and gastrointestinal patology were reviewed for anaylsis.

Results: The final analysis included 126 infants with 46 cases and 80 controls. Logistic regression showed birth weight, feeding intolerance, GIS pathology and preeclampsia were associated with the development of MBD. After the data adjusted for birth weight, preeclampsia showed an association with metabolic bone disease in preterms.

Conclusion: Our study identifies preeclampsia as a risk factor for MBD in premature infants. Individualized approach to postnatal nutritional support is warranted for infants born to mothers with severe preeclampsia.

Introduction

Despite significant advances in the diagnosis and treatment of metabolic bone disease (MBD) of prematurity, it remains a major cause of morbidity in premature infants with potentially long-term consequences. MBD refers to the insufficient mineralization of bone in preterm infants, resulting from inadequate levels of calcium and phosphate minerals, which can be influenced by a range of prenatal and postnatal factors [1]. Although there is a lack of a clear consensus on the definition of MBD, studies have shown that the incidence of MBD ranges from 15% to 40% in infants with a birth weight of <1500 grams [2,3].

Preterm infants face a significant risk of developing nutritional deficiencies owing to their incapacity to attain the maximal mineral accretion that typically occurs during the third trimester of gestation [4,5]. Furthermore, it is challenging for preterm infants to maintain a comparable mineral intake postnatally, increasing the risk of insufficient bone mineralization [6].

Although gestational age and birth weight are the most significant risk factors for MBD, its etiology is multifactorial and involves several other associated risk factors [7,8]. It is suggested that preeclampsia might cause a hypoxic-ischemic state in the intestine and/or its mucosa that disturbs enteral mineral accretion in the postnatal period [9]. However, despite being identified as a potential risk factor, there is limited evidence to suggest a direct link between preeclampsia and developing MBD [10].

Thus, this retrospective case-control study's objective was to investigate whether an increased risk of MBD is associated with preeclampsia. We also examined the other neonatal and maternal factors that increase the risk of MBD.

Materials and Methods

This retrospective case-control study was conducted between January 2016 and June 2017 in a single tertiary-level neonatal intensive care unit (NICU) at the Zekai Tahir Burak Women's Health and Children Hospital, Ankara, Turkey. The institutional ethical committee approved the study (Ankara City Hospital No. 2 Clinical Research Ethics Committee Presidency, number : E2-21-513).

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Preterm infants <32 weeks in gestation and <1500 gr at birth, born in our hospital, followed at least six weeks in NICU, were considered eligible for inclusion. Infants with congenital or chromosomal anomalies and missing data were excluded from the study.

At our institution, MBD is screened routinely in premature infants starting from the postnatal third week of life with laboratory analysis of calcium, phosphorus, and alkaline phosphatase (ALP). Due to the discrepancies in the definition of MBD in the literature, we chose the define MBD cases as elevated serum ALP concentration >500 IU/L and serum phosphate level <4 mg/dl with radiological evidence of osteopenia. Radiologic evidence of MBD was defined according to the criteria by Koo: the disappearance of the normal dense white line at the metaphysis with increased submetaphyseal lucency, increased submetaphyseal lucency, thinning of the cortex, fraying, splaying, or cupping of the metaphysis [11]. The controls were defined as patients who met the eligibility criteria and had serum ALP concentration ≤ 500 IU/L and serum phosphate levels >5.6 mg/dl. During the study period, 215 preterm infants were reviewed. A total of 93 infants were excluded from the study for various reasons. Among the exclusions, 28 infants died, eight infants had chromosomal or congenital anomalies, one infant had non-osteopenia fractures, 20 infants lacked radiological assessment or had missing prespecified data, and 36 infants were discharged or transferred before reaching postnatal six weeks. The final analysis included 126 infants with 46 cases and 80 controls.

Baseline infant and maternal demographic characteristics of the infant include gestational age, birth weight, gender, small for gestational age (SGA), the number of twin births, maternal history of weight during pregnancy, hypothyroidism, smoking, preeclampsia, prolonged rupture of membranes (PROM) (>18 h), and evidence of chorioamnionitis were recorded. Preeclampsia is defined as the new onset of hypertension and proteinuria or the new onset of hypertension and important end-organ dysfunction with or without proteinuria after the 20th pregnancy week or postpartum in a previously normotensive woman [12].

Data on clinical variables, including postnatal drug use (loop diuretics, caffeine, anticonvulsant, and steroids), presence of reduced physical activity (ventilation requirement >14 days), hypothyroidism, feeding intolerance, and gastrointestinal pathology (history of NEC, gut surgery and short bowel syndrome) were reviewed for analysis.

All neonates were administered parenteral nutrition until achieving 75% of the full enteral feeding, defined as a volume of 150 mL/kg/day, in accordance with the standard protocol of our neonatal intensive care unit (NICU). The human milk provided was fortified with Eoprotin, at 1 gram per 30 milliliters of milk, per the manufacturer's guidelines, whenever the enteral feeding volume reached 100 mL/kg/day. Vitamin D prophylaxis was initiated at a daily dosage of 400 international units (IU).

Statistical analysis

Statistical analyses were performed using SPSS 23.0 (SPSS for Windows, version 23.0; SPSS, Inc., Chicago, Ill, USA). Categorical variables were described as percentages and compared using Pearson's chi-squared and Fisher's exact tests when necessary. For continuous variables, mean and standard deviation (SD) or median (interquartile range [IQR]) were given as descriptive variables. Abnormally distributed data were evaluated with the Kolmogorov Smirnov test and analyzed with the Mann-Whitney U test when the data were not normally distributed. Multinomial logistic regression analysis was performed to determine independent risk factors for MBD. Another model was created by adjusting for birth weight to estimate the adjusted odds ratios (ORs) and measure the 95 % CI for whether preeclampsia is associated with an increased risk of MBD. Pearson correlation test was used where appropriate. A p-value <0.05 was considered significant.

Results

A total of 126 infants were analyzed, with 46 infants diagnosed with MBD of prematurity being classified as cases and 80 infants without constituting the control group. The two groups did not significantly differ for gestational age (27±1.88 vs. 27.9±1.73 weeks), but the MBD group had lower birth weight (896.7±235 vs. 1057±194g, p<0.01) compared to the other group. Furthermore, the MBD group had a significantly higher incidence of SGA, reduced

Table 1. Maternal and infant characteristics of study groups.

	MBD (n=46)	No MBD (n=80)	p value
Infant characteristics			
Gestational age, (weeks)(SD)	27.8 ±1.88	27.9±1.73	0.8
Gender (male), n (%)	20 (43.4)	46 (57.5)	0.54
Birth weight, (grams)(SD)	896.7 ± 235	1057 ±194	<0.01
Apgar, 5. Min (<5), n (%)	3 (6.5)	5 (6.2)	0.84
SGA	11 (23.9)	7 (8.8)	<0.01
Cesarian section, n (%)	36 (78)	60 (80)	0.56
Twin gestation, n (%)	12 (26)	18 (22.5)	0.64
Drug use, n (%)			
Caffein	44 (95.6)	77 (96.2)	1
Corticosteroid	14(30.4)	19 (23.8)	0.42
Anti-convulsants	3 (6.5)	0	0.03
Loop diuretics	17 (37)	15 (18.8)	0.03
Hypothyroidism,n (%)	6 (13)	5 (6.3)	0.22
Reduced physical activity, n (%)	14 (30.4)	9 (11.2)	0.01
Feeding intolerance, n (%)	19 (41.3)	4 (5)	<0.01
GIS pathology, n (%)	13 (28.3)	1 (1.3)	<0.01
Maternal characteristics			
Parity, median, IQR	2 (1-5)	2 (1-4)	0.83
Maternal weight gain, (grams)(SD)	8.76±3.73	8.92±4.08	0.88
Maternal smoking, n (%)	4 (8.7)	5 (6.3)	0.93
Hypothyroidism, n(%)	3 (6.5)	6 (7.5)	0.66
Preeclampsia, n (%)	17 (36.9)	11 (13.7)	<0.01
Chorioamnionitis, n (%)	4 (8.6)	6 (7.5)	0.82
PROM (>18 h), n (%)	7 (15.2)	9 (11.2)	0.62

*Plus-minus values are mean±standard deviation, SD: standard deviation, IQR: interquartile range p values<0.05 were considered as significant MBD= metabolic bone disease, SGA=small for gestational age, GIS=gastrointestinal, PROM= premature rupture of membranes.

Table 2. Logistic regression analysis of parameters associated with MBD.

	OR (95% CI)	p
Birth weight	0.71 (0.13-2.4)	0.03
SGA	1.19 (0.29-4.77)	0.81
Loop diuretics	1.60 (0.53-4.84)	0.4
Reduced physical activity	1.11 (0.29-4.12)	0.87
Feeding intolerance	4.62 (0.79-27.07)	0.09
GIS pathology	6.44 (0.42-42.66)	<0.01
Preeclampsia	3.34 (0.98-11.36)	0.04

CI, confidence interval; OR, Odds ratio; SGA, small for gestational age; GIS, gastrointestinal p values<0.05 were considered as significant.

Table 3. Independent risk factors of MBD adjusted for birth weight.

	OR (95% CI)	p
Preeclampsia	2.82 (1.13-7.22)	0.03
GIS pathology	4.46 (0.89-22.77)	0.01

CI, confidence interval; OR,Odds ratio; GIS, gastrointestinal p values<0.05 were considered as significant.

physical activity, feeding intolerance, and GIS pathology. In addition, anti-convulsants and loop diuretics were used significantly more frequently in the MBD group. The incidence of preeclampsia was statistically higher in the MBD group (36.9% vs 13.7%, p<0.01). All clinical parameters are summarized in Table 1. Logistic regression showed that birth weight, feeding intolerance, GIS pathology, and preeclampsia were associated with the development of MBD (Table 2). After the data were adjusted for birth weight, nominal regression showed preeclampsia as an independent risk factor of MBD of prematurity (OR=2.82, 95% CI 1.13-7.22; p=0.03 in this cohort (Table 3). Moreover the incidence of preeclampsia was statistically associated with MBD of prematurity (r = 0.297, p = 0.001).

Discussion

This case-control study showed a statistically significant increase in the incidence of metabolic bone disease among preterm infants born to preeclamptic mothers. Previous systemic reviews have suggested that conditions such as preeclampsia impairing the placental blood flow and thereby interfering with nutritional transfer increase MBD's risk in preterms [8,13]. However, to our knowledge, our study is among the few to demonstrate a direct association between preeclampsia and metabolic bone disease. Additionally, our findings are in accordance with previous observations that demonstrated associations between MBD and lower birth weight and gastrointestinal pathologies.

Insufficient blood flow to the placenta, leading to a state of low oxygen and increased oxidative stress, is believed to be a significant contributing factor to the adverse outcomes of preeclampsia, including preterm birth and fetal growth restriction [14]. Additionally, given that the developing fetus relies on the placenta to adequately transfer nutrients such as calcium and phosphate, decreased transfer due to compromised placental function may further increase the risk of MBD. Contrary to our findings, several studies examining the risk factors of MBD have failed to identify an association between preeclampsia and MBD [15,16]. These findings may be attributed to variations in preeclampsia's severity and onset time and whether adequate treatment was administered to mothers in the studies. In our study, despite a similar mean gestational age, birth weight was significantly lower, and the incidence of SGA infants was higher in the MBD group. It has been suggested that neonatal outcomes in infants born to preeclamptic mothers are primarily associated with the severity of prematurity and SGA [14]. Birth weight was the most significant factor associated with decreased bone mineral density in DEXA analysis of preterm infants [17]. Our result might support this association and postulates that if preeclampsia is severe enough to cause significant growth restriction; the risk of MBD may increase.

MBD is caused by a decrease in mineral accretion during prenatal and postnatal development, particularly in preterm infants [1]. The criteria used to define MBD in clinical studies highly vary. Quantitative ultrasound (QUS) assessment has gained increasing popularity to monitor bone mineralization in preterm infants in recent years [18]. However, QUS was not in routine practice in our unit at the time of the study. Thus, biochemical criteria have been used as criteria for MBD. Nonetheless, several factors have consistently been associated with MBD across all studies, such as lower gestational age and birth weight, prolonged total parenteral nutrition (TPN) use, and feeding intolerance [8,13,15]. Our study further supports the common risk factors associated with MBD in preterm infants, including lower birth weight, feeding intolerance, reduced physical activity, SGA, and factors related to malabsorption. Our unit supports preterm infants with feeding intolerance with prolonged total parenteral nutrition (TPN) use. Therefore, we included prolonged TPN use as a subgroup of feeding intolerance in our analysis. Previous studies have found an association between preeclampsia, necrotizing enterocolitis (NEC), and feeding intolerance in preterm infants [19,20]. This association may contribute to the disruption of postnatal mineral accretion, increasing the risk of MBD in these infants.

This study is subject to certain inherent limitations attributable to its retrospective design. First, standard laboratory criteria were used to define MBD in our study; however, the radiological assessment of osteopenia was not conducted in all cases, with missing cases excluded from the study. Furthermore, clinicians did radiologic assessments rather than specialized pediatric radiologists. This may have had an impact on the incidence of diagnosed cases. Second, exposure to postnatal drugs, such as anti-convulsants and loop diuretics, differed between the groups, but these results did not reach statistical significance. Third, we did not specify the duration and severity of preeclampsia, which could have enabled a more precise prediction of the risk groups.

Conclusion

In conclusion, our study identifies preeclampsia as a significant risk factor for MBD in premature infants. Consequently, an individualized approach to postnatal nutritional support is warranted for infants born to mothers with severe preeclampsia. Further prospective investigations are necessary to evaluate the relationship between preeclampsia and the duration and severity of MBD.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions

HB had primary responsibility for protocol development and analytic framework of the study, outcome assessment, and manuscript preparation. HB and NBK participated in the development of the protocol and analytic framework of the study, had primary responsibility for review of the files, patient screening, enrollment, and data entry, and prepared the manuscript. HB,NBK and GKK contributed to preparation and revision of the manuscript.

Ethical approval

Ankara City Hospital No. 2 Clinical Research Ethics Committee Presidency (Number : E2-21-513).

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