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Maternal and Neonatal Vitamin D Deficiency Associated with an Increased Risk of Neonatal Hypoxic Ischemic Encephalopathy

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Abstract

Background: Neonatal Hypoxic-Ischemic Encephalopathy (HIE) remains a major cause of neonatal morbidity and mortality. Neonates are at a significantly high risk of vitamin D deficiency. Maternal and neonatal vitamin D deficiency is associated with multiple neonatal diseases including HIE. This study aims to explore the possible association between maternal and neonatal 25-hydroxy vitamin D (25-OHD) levels and HIE in full-term infants and it attempts to find whether there is any relationship between vitamin D level and the clinical severity of HIE.

Methods: This case-control study included 25 full-term neonates with HIE and their mothers along with 25 healthy neonates and their mothers. The level of serum (25-OHD) of the infants and their mothers was measured in the first 6 postnatal hours of the infants by isotope dilution ultra-performance liquid chromatography-tandem mass spectrometry. The severity of HIE was assessed depending on the clinical scoring system.

Results: Neonatal and maternal levels (25-OHD) were significantly lower in the study group compared with those of the control group. Neonatal (25-OHD) levels were significantly lower with increasing severity of HIE (p=0.005), but they did not follow the same order in the maternal (25-OHD) levels (p=0.96); i.e., a negative correlation was detected between neonatal (25-OHD) level and severity of HIE ($r = -0.66$, $P < 0.001$). A positive correlation was found between neonatal and maternal (25-OHD) levels in the study group ($r = 0.697$, $P < 0.001$).

Conclusion: Lower maternal and neonatal vitamin D levels were associated with HIE in full-term infants and the level of vitamin D was inversely associated with the clinical severity of HIE. Further studies are needed to examine the causal relationship between vitamin D deficiency and HIE in neonates.

Key Words: Hypoxic-Ischemic Encephalopathy, Maternal; Neonatal, Vitamin D Deficiency, 25-Hydroxyvitamin D.

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1- INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) in neonates is still a serious disease associated with significant neonatal deaths and long-term disability with the highest rates in developing countries (1).

Vitamin D deficiency is a global public health problem that affects more than 1 billion people. Even in Arabs sunny nations, maternal and neonatal vitamin D deficiencies are alarmingly high and significantly associated with each other (2).

Adequate vitamin D status is a vital component of normal brain development and functioning (3, 4). In the neonatal period, it may also play an important role in the brain's response to injury (5). The administration of vitamin D or its metabolites has been shown to reduce neurological injury and/or neurotoxicity in a variety of animal systems (6).

Maternal and neonatal vitamin D deficiency contributes to multiple neonatal disorders including HIE, transient tachypnea of the newborn and sepsis (7-9).

The aim of this study is to explore the possible association between maternal and neonatal (25-OHD) levels and HIE in full term infants and it attempts to find whether there is any relationship between vitamin D level and the clinical severity of HIE.

2- METHODS

2-1. Design and Participants

This case-control study was conducted between October 2018 to October 2019 at our Neonatal Intensive Care Unit (NICU). 25 full term neonates monitored for HIE and their mothers were enrolled as the study group; and 25 healthy neonates and their mothers were enrolled as the control group. All mothers in the control group were white mothers without racial/ethnical differences, and they were coming from the same region and all data were collected at the same period of time.

2-1-1. Inclusion and Exclusion criteria

The inclusion criteria encompassed all full term neonates with gestational age ≥37 weeks, Apgar score ≤ 5 at 10 minutes or need for resuscitation > 10 minutes after birth, pH ≤ 7.0 with base deficit ≥ −16 in cord blood or if not in the available blood gas within the first one hour after birth. If these criteria were met, all neonates underwent standardized modified Sarnat neurological examination by an expert physician within the first 6 hours of life classifying the degree of encephalopathy as mild, moderate, or severe (10).

Exclusion criteria included premature infants (gestational age < 37 weeks), over 6 hours of age at the time of admission, with central nervous system malformations, congenital lung diseases or congenital cyanotic heart diseases causing persistent hypoxia to the infant, maternal antiepileptic use, maternal treatment with narcotic analgesics, head trauma causing intracranial hemorrhage, severe intrauterine growth retardation and other conditions associated with early neonatal encephalopathy including metabolic disorders, sepsis and genetic diseases.

2-2. Data Collection

Blood samples of the infants and their mothers were obtained in the first 6 postnatal hours of the infants. The level of serum (25-OHD) was measured by isotope dilution ultra-performance liquid chromatography tandem mass spectrometry.

2-3. Data Analysis

Statistical analyses were performed using SPSS for Windows statistical package, version 20. (SPSS, Inc., Chicago, IL, USA). Data were expressed as mean ± SD. Student's t-test, the Mann-Whitney U-test, and $\chi 2$ –test were used for comparing

mean values. A P-value<0.05 was considered statistically significant.

3- RESULTS

Twenty-five infants with HIE and their mothers along with 25 healthy controls and their mothers were included in this study. In the present study, there was no significant difference between the study and control groups regarding gender, gestational age, birth weight, mode of delivery and maternal demographic data. The study group showed significantly lower blood gas PH and Apgar scores at the 1st and 5th minutes, compared with the control group. Neonatal and maternal levels of (25-OHD) were significantly lower in the study group compared with those in the control group (Table 1). In the study group, the neonatal level of (25-OHD) was affected with the severity of the HIE clinical staging system to be the lowest with severe HIE (p=0.005) which did not occur with maternal (25-OHD) levels (p=0.96) (Table 2). A positive correction was found between neonatal and maternal 25-OHD levels in the study group ($r = 0.697$, $P < 0.001$). A negative correlation was detected between neonatal 25-OHD level and severity of HIE ($r = -0.66$, $P < 0.001$) (Table 3). The ROC curve analysis for serum vitamin D in neonates showed that at level ≤17.5 ng/mL had a sensitivity and specificity of 96% and 64%, respectively (P <0.001) (Fig. 1).

Table-1: Characteristics of the study and control group

Variable		HIE group (n=25)	Control group (n=25)	P-value
Gestational age (weeks)		37.84 ±0.89	38.08±0.9	0.32
Gender	Male	16 (64%)	14 (56%)	0.16
	Female	9 (36%)	11 (44%)	
Weight on delivery (kg)		3.03± 0.57	3.01 ± 0.30	0.696
Mode of delivery	CS	21 (84%)	19 (76%)	0.48
	Vaginal	4 (16%)	6 (24%)	0.48
Maternal demographic features	Age (years)	28.5 ±4	28 ±4	0.69
	Using Muslim religious cloths, n (%)	21 (84%)	20 (80%)	0.23
Vitamin D supplementation during pregnancy, n (%)	No usage	5	6	0.23
	Irregular usage	12	10	0.36
	Regular usage	8	9	0.23
Maternal education status	High school graduation	4	5	0.23
	University graduation	21	20	0.23
	Sun index	33.4 ± 12.8	35.0 ± 14.7	0.231
1st minute APGAR score		2.5±1.5	8.5±0.8	<0.001*
5th minute APGAR score		5.7±1.6	9.3±0.6	<0.001*
Blood gas PH		7±0.13	7.3±0.09	<0.001*
Neonatal 25(OH)D3 (ng/mL)		10.40±3.03	17.76±3.57	<0.001*
Maternal 25(OH)D3 (ng/mL)		13.32±3.05	18.32±3.91	<0.001*

* The P-values represent the statistical significance between two groups

Table-2: Relations between maternal/neonatal vitamin D level and severity of HIE

Variable	Mild HIE (n=10)	Moderate HIE (n=8)	Severe HIE (n=7)	p
Neonatal 25(OH)D3 (ng/mL)	12.18±2.86	9.80±2.4	7.0±0.82	0.005 *
Maternal 25(OH)D3 (ng/mL)	13.45±3.80	13.10±2.23	13.50±3.32	0.96 *

* The P-values represent the statistical significance between two groups

Table-3: Correlations between neonatal vitamin D level and other variables

Variables	Neonatal vitamin D level	
	R	P value
Maternal vitamin D level	0.697	0.001 *
Severity of HIE	− 0.66	0.001 *

* P-values represent the statistical significance of the correlations

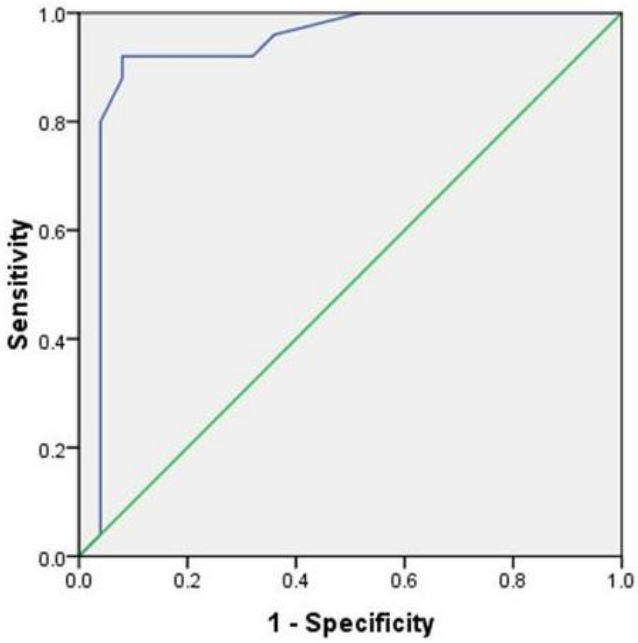

Fig. 1: ROC curve analysis for serum vitamin D in neonates

4- DISCUSSION

Vitamin D is an important neurosteroid with anti-inflammatory, neuroprotective, immunomodulatory, and antioxidant properties which play a vital role in normal neuronal development. Vitamin D deficiency has been linked to both increased vulnerability to neurologic injury and abnormal brain development (5). Very few studies have investigated the possible relation between maternal and neonatal vitamin D status and the development of neonatal HIE.

In pregnancy, sufficient levels of vitamin D are required as a unique source of vitamin D for the fetus, and several neonatal adverse outcomes occur from maternal vitamin D deficiency (11). In the Saudi population which is very close to our population, Fouda et al., reported that

almost 85% of mothers and 88% of neonates have vitamin D deficiency (2).

We observed in our study that maternal 25-OHD in the study group (13.32±3.05 ng/mL) was significantly lower than that in the control group (18.32±3.91 ng/mL). Mutlu et al. also reported significantly lower maternal 25-OHD levels of neonates with HIE compared to the control group (7).

This can be explained by a recent report on the importance of maternal circulating vitamin D concentrations in determining neonatal vitamin D status (11).

In the present study, neonates with HIE showed significantly lower vitamin D levels compared to their healthy counterparts. Other studies have also reported similar results (7,12-14); e.g., Lowe et al. observed that urinary losses and increased degradation may contribute to low or decreasing serum 25-OHD concentrations in HIE infants (12).

We also found that vitamin D level is inversely correlated with the clinical severity of HIE staging. McGinn very recently reported that there is a significant association between low vitamin D concentrations at birth and more extensive brain injury on MRI in infants with HIE but not with clinical staging (14). Further studies are needed to explore these findings.

Recently Hagag et al. found that Vitamin D could be used for adjuvant therapy in neonatal hypoxia (13).

In lipopolysaccharide-sensitized hypoxic ischemic rat model, combined uses of vitamin D and hypothermia are found to have synergistic effects in improving cellular redox status, thus preventing secondary oxidative stress and augmenting the neuroprotective effect of therapeutic hypothermia (15).

4-1. Limitations of the Study

The main limitation of our study was the small sample size for each group. Furthermore, the severity of HIE was mainly measured based on clinical assessment.

5- CONCLUSION

The present study revealed that lower maternal and neonatal vitamin D levels were associated with HIE in full term infants, and the level of vitamin D was inversely associated with the clinical severity of HIE.

6- CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

7- ETHICAL CONSIDERATIONS

This study was approved by the institutional Ethics Committee of our Faculty of Medicine, and informed consent was obtained from the parents of all the neonates throughout the study.

8- FUNDING

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