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Maternal And Neonatal Serum Magnesium Concentrations In Neural Tube Defects Pregnancies In Gorgan (North Of Iran) - A Case Control Study

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ABSTRACT

Objective: Neural tube defects (NTD) comprise a group of congenital malformations that include spinabifida, anencephaly and encephalocele. Previous studies have reported the embryotoxic and teratogenic effects of Magnesium deficiency in animal models. Therefore, this study was conducted to determine an association between Magnesium deficiency and neural tube defects in Northern Iran, which was reported to have a high prevalence of neural tube defects.

Methods: This hospital based case control study was conducted on 13 mothers with newborns having neural tube defects and 35 healthy mothers as controls in Northern Iran during 2005-2006. Serum Magnesium was measured by spectrophotometery.

Results: Serum Magnesium levels in mothers with NTD affected newborns and in mothers with healthy newborns were 1.5±0.6 and 1.32±0.3 micromol/litter, respectively. Overall, 46.2% mothers in the case group and 48.6 % mothers in the control group had Magnesium deficiency. Logistic regression analysis showed no association between the presence of NTD and Magnesium deficiency (OR =0.9, 95% CI: 0.2-3.9, p=0.88).
Serum Magnesium levels in newborns with NTD and healthy normal newborns were 1.4±0.6 micromol/litter and 1.3±0.4 micromol/litter, respectively. Overall, 30.8% newborns in the case group and 37.1 % newborns in the control group had Magnesium deficiency. Logistic regression analysis showed no association between the presence of NTD and Magnesium deficiency (OR =0.8, 95% CI: 0.1-3.4 p=0.68).
Conclusion: The present study did not find any association between the occurrence of NTD and Magnesium deficiency.

[**Key words]** Neural tube defects, Spina bifida, Anencephaly, Magnesium deficiency, Iran

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Introduction:

Pregnancy is a period of increased metabolic requirement for the growing foetus [1-3]. Mineral element nutrition disorders and the metabolism in embryos are potentially mutagenic and teratogenic and can lead to miscarriage and various types of malformations [4-6]. Magnesium is a trace element and is needed for proper bone formation in humans and in various intracellular enzymatic processes. It is an essential element which is required for foetal health [7]. The deficiency of magnesium may possibly be associated with pre-term delivery and possibly, with low

birth weight. It has been reported that magnesium deficiency during the embryonic period, significantly increase neonatal mortality and morbidity [8-12].

Although there are many reports regarding the effect of Magnesium in the outcome of pregnancy and some other diseases, there are only few studies on the teratogenicity of Magnesium deficiency. Two previous studies have reported the embryotoxic and teratogenic effects of Magnesium deficiency in animal models [13-14].

Neural tube defects (NTD) are important causes of infant mortality and childhood morbidity [15-16]. Several studies have revealed a high incidence of NTDs (28-32 per 10000) in Iran [17-18]. The aetiology of NTD is considered to be multifactorial, with genetic, environmental and nutritional factors in all, playing some role or the other [19-20]. Therefore, we conducted this study to determine whether there is an association between serum Magnesium levels and neural tube defects in Northern Iran.

Materials And Methods

This hospital based case control study was conducted during 2005-2006 at the Dezyani hospital in Gorgan, which is located in the north of Iran. The study was approved by the Human Research Review Committee at the Gorgan University of Medical Sciences. Dezyani hospital is the largest hospital with a labour facility in Gorgan, a capital city in the Golestan province in northern Iran. This hospital is a referral hospital with an annual rate of more than 6000 deliveries, accounting for 20% of the annual birth in the Golestan province of Iran and the largest portion of deliveries (80%) in the city. Other deliveries (20%) in Gorgan city are carried out in three private medical centers. The patients are usually from the moderate to low socioeconomic class families.

Subjects:

All babies delivered in this hospital during the investigation period (2005–2006) were screened after delivery for NTD by a gynaecologist and later, the diagnosis was confirmed by a paediatrician. 13 NTD affected newborns with their mothers were chosen consecutively as the case group. Immediately after the birth of every NTD affected newborn, two normal newborns were chosen from the hospital delivery list as controls and in this way, 35 healthy newborns with their mothers were chosen as the control group. The healthy newborns in the control group were assessed clinically by a gynaecologist and a paediatrician before these newborns and their mothers entered the study as controls. The control to case ratio was almost 3:1. The mother's consent was obtained for the study, along with a clearance from the institution's ethical committee.

A questionnaire covering all relevant clinical and demographic factors was filled out for each case and control infant by the paediatrician and was then completed by a nurse during an interview with the mothers. The data included: birth date, sex, birth weight, birth height, gestational age and type of NTD. Also recorded were: mother's age, and mother's history of exposure to drugs during the 1st trimester.Anthropometry of the newborn was recorded as per standard techniques.

Serum collections and Magnesium measurements: Peripheral blood samples were collected from the case and control groups, a maximum two hours after the delivery. Serum was separated and analyzed for estimating the Magnesium levels by a spectrophotometric method, by using the Randox Kit UR. Magnesium levels between 1.5-2.5 meq /litres in mothers and 1.2-2.6 meq /litres in newborns were used as the normal and serum Magnesium levels of less than 1.5 meq /litres in mothers and serum Magnesium level of less than 1.2 meq /litter in newborns was used as the cut-off to label the individual as Magnesium deficient.

Statistical analysis:

Categorical data were compared by the Chi-square and the Fisher's exact tests. Mann Whitney U test and unpaired Student's-t test were used for the comparison of means. The presence of neural tube defects was considered to be the dependent factor in the multivariable logistics regression analysis. The independent factors included in the analysis were parity, history of abortions, maternal drug exposure and Magnesium deficiency, as dichotomous variables. The data were analyzed by using SPSS 11.5 and STATA SE/8. P values < 0.05 was the criterion for a significant difference.

Results

The baseline characteristics of the two groups are depicted in Tables 1and 2.

The control group babies were heavier and lengthy as compared to those in the study group. The gestation of babies with NTD was less as compared to those in the control group.

Serum Magnesium levels in mothers with NTD affected newborns and mothers with normal healthy newborns were 1.5±0.6 micromol/litre and 1.32±0.3 micromol/litre, respectively and this difference was not significant. Overall, 46.2% mothers in case group and 48.6 % mothers in the control group had Magnesium deficiency. Logistic regression analysis showed no association between the presence of NTD and Magnesium deficiency (OR =0.9, 95% Cl: 0.2-3.9, p=0.88).

Serum Magnesium levels in newborns with NTD and in healthy normal newborns were 1.4±0.6 micromol/litre and 1.3±0.4 micromol/litre , respectively. Overall, 30.8% newborns in the case group and 37.1 % newborns in the control group had Magnesium deficiency. Logistic regression analysis showed no association between the presence of NTD and Magnesium deficiency (OR =0.8, 95% Cl: 0.1-3.4 p=0.68).

[Table/Fig:] 1 Maternal and neonatal characteristics in case and control groups.

	Cases (n=13)	Controls (n=35)	P-value
Maternal age: year (mean±SD)	24.3±5.8	25.4±5	0.56 †
Newborn weight: gr (mean±SD)	2217±1013	3167±678	0.001 *
Newborn height: cm (mean±SD)	43.5±7.9	48.7±2.8	0.07 †
Gestational age: week (mean±SD)	34.7±5.3	38.1±1.5	0.048 †
Maternal exposure during 1st trimester (drug) (%)	2 (15.4)	2 (5.7)	0.294 ‡

† based on Mann-Wittney U test, ¶ based on Pearson's chi-square test
‡ based on Fisher exact test, *two independent samples 't' test

	Cases (n=13)	Controls (n=35)	P-value
Maternal age: year	24.5(7.25)	25 (7.5)	0.56 †
Newborn weight: gram	2350(1312)	3125(670)	0.001 *
Newborn height: cm	46.5(12.5)	50(3)	0.07 †
Gestational age: week	36(5.75)	38 (1)	0.048 †

† based on Mann-Wittney U test

[Table/Fig 2]: Median and interquartile range of Maternal and neonatal characteristics in case and control groups

Discussion

The present study did not find any association between the occurrence of NTD and Magnesium deficiency. The results of this study contradict the two pervious investigations [13-14]. Hurley et al [13] reported that when pregnant female rats were fed a magnesium deficient diet only between days 6 and 14 of gestation, a high incidence of resorptions and gross malformations were seen in full term foetuses. She concluded that the rapidity of the effects of severe magnesium deficiency in pregnant rats and indicated the importance of the element for embryonic development.

Also in other study, Gunther et al showed that when pregnant rats (between days 1and 20 of gestation) and pregnant mice (between days 3 and 19 of gestation) received a magnesium deficient diet, at the end of gestation, the Mg concentration in the maternal serum was found to have decreased by up to 0.3 mmole/liter, depending on the Mg content of the food. Mg-dose-dependent embryotoxic effects including resorptions, retardations, disturbed bone development and skeletal malformations were observed only below a threshold value of 0.7 mmole/liter of the maternal serum Mg concentration [14].

The possible Mechanism behind the teratogenic effect of Mg can be due to the

important role of Mg in ATP metabolism and the transfer reaction with phosphate. It also reacts with Ca ++, Na+, K+. Also, Mg participates in the formation of the ribosome structure and ultimate binds to it [13-21]. Bone development disorder may be caused due to the inhibition of the synthesis of a mature mineralizable matrix [14]. Studies have been shown that Mg depletion or deficiency causes foetus damage, severe IUGR, foetus body temperature disorder and sudden death syndrome [22-24].

In our study, although we did not find any relationship between Mg and NTD, there were differences regarding the neonatal characteristics including weight, height and gestational age in the cases and controls, which were not related directly to Mg, but were mostly related to the birth defects themselves. Studies have shown that in newborns with neural tube defects, neonatal characteristics such as weight, height and gestational age are reduced .

However, this study has certain limitations. Firstly, the neonatal cases and the control groups were not gestational age matched and secondly, this study had sample size limitation which made the statistical tests less significant. . In addition, to explore the relationship between Mg deficiency and NTD with high accuracy, it is advisable to collect maternal blood in early pregnancy, which can be considered as one of limitations of our study. We recommend conducting a cohort study for assessing the relationship between serum Magnesium with a larger sample size at the prenatal and antenatal intervals. Despite our limitations in this study, we were able to show that there was no association between neural tube defects and serum Mg deficiency in the newborns and their mothers.

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