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Influence of selenium deficiency on neural tube defects

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ABSTRACT

Objective: As for the role of selenium on human fetal development, a little data is available in literature. The purpose of this manuscript was to study the influence of selenium on neural tube defects. This study will be helpful in planning strategies for prevention of neural tube defects. **Methodology:** After collection of the venous blood the same was immediately centrifuged and after immediate centrifugation, the clear serum was transferred to deionized plastic vials, stored and frozen at −20° C until determination of the analysis was carried out. The selenium levels as ng/ml were determined on GBC 932 spectrophotometer by fluorometery. **Results:** The mean maternal blood serum and cell mass concentrations in NTD group (306.4 ± 10.95 ng/ml, 192.44 ± 6.12 ng/ml, 165.8 ± 16.99 ng/g respectively) were significantly lower than those of control mothers (363.75 ± 17.1 ng/ml, 242.34 ± 15.7 ng/ml, 260.0 ± 20.57 respectively). A significant decrease in concentration of selenium in newborns with NTD (298.4 ± 12.3 ng/ml, 96.3 ± 7.15 ng/ml, 139.8 ± 27.5 ng/g respectively) as compared with healthy babies (358.1 ± 16.11 ng/ml, 122.44 ± 6.03 ng/ml, 268.6 ± 31.37 ng/g respectively). **Conclusion:** Selenium deficiency in mothers during pregnancy thought to be one of the factors responsible for NTDs. However, the lowered selenium concentrations in blood, serum and cell mass can be secondary cause of an abnormal pregnancy and didn't contribute to its production. More investigations on selenium status in mothers during antenatal period, especially in prenatal development and antenatal selenium status including normal babies and NTD babies are required.

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Key words: Neural Tube Defects, NTD, Selenium

INTRODUCTION

NTD is major congenital anatomy estimated 3-7% but actual number varies widely between countries.[1] Several genetic and environmental factors are known to have a role in the etiology of Neural tube defects (NTDs). Most of the cases of NTD appear to arise from the combined action of unknown factors.[2] The most important nutrients etiology of NTD is calories, fat, protein, folate, Zinc, Vitamins A, C, B_6, B_{12}.[1] Trace minerals are required by the body in minute quantities ranging from as little microgram to milligram per day. The trace elements known to be essential for humans and unquestionably associated with deficiency system.[3-4] Deficiencies of essential nutrients such as trace elements may be implicated in a multifactorial fashion in the production of developmental defects in humans.[5-6] Although, there is experimental evidences for the high rates of NTDs in some regions where zinc deficiency is common e.g. Turkey and the Near East[5] suggest that zinc deficiency may also be a human teratogenic and they may be the environmental factors contributing to the development of NTDs.[7]

In literature regarding selenium (Se) in human fetal development a very few data are available. Selenium (Se), an essential trace element, has evolved from its toxic properties after a series of researches over the past several decades. It was first recognized to be an essential trace element in 1957. Since its discovery about half a century ago, selenium has been a subject of intensive research. Deficiency of selenium produced experimentally in animals resulted in abnormalities such as defective growth, hepatic necrosis, myocardial degeneration and muscular dystrophy in sheep, cattle, chickens and horses.[8] Se deficiencies in ewes results in a high embryonic mortality around the time implantation, indicating an important role of this element

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in early gestation and a sodium selenite vitamin-E mixture injected into cows a month before calving completely prevented losses from the birth of premature, weak or dead calves.[9] In humans, it is well recognized that selenium plays a crucial role in various physiological processes and its altered level has a direct impact on health leading to the development of disease.[10]

The absence of clear signs of dysfunction or pathology among individuals of low Se status made the role of Se in human nutrition unclear for the almost two decades after the discovery of its nutritional essentiality in experimental animals. The present study was carried out to assess maternal and infant Se status in the NTDs by estimating whole blood, serum and packed cell mass in the newborns with NTD and their mothers.

MATERIALS AND METHODS

In the present study 287 newborns with NTD have been studied. All the newborns were alive. The obstetric history and socioeconomic status of the mothers were recorded and newborns with NTD examined carefully with the help of pediatrician. Ethical approval for the study was obtained from the departmental committee of our Institution. Patients who gave the consent were included in the study. The patients who did not agree and/or not given consent to answer the questionnaire were excluded from the study. The control groups were randomly selected with the same age group of the proband. The randomly selected control groups consisted of women aged 18 to 34 (mean 25.65) years, who had birth to normal baby.

The venous blood (5.0 ml each) from all newborns and their mothers was drawn from an antecubital vein, using stainless steel needles (disposable syringes) and collected in plastic vials. All necessary precautions were taken to avoid contamination. After collection of the blood the same was immediately centrifuged and after immediate centrifugation, the clear serum was transferred to deionized plastic vials, stored and frozen at –20°C until determination of the analysis was carried out.

The blood from each case was divided into three groups. In group (I) whole blood, in group (II) blood serum and in group (III) packed cell mass was subjected for extraction of selenium. All the samples were digested in long necked round bottom flasks with triple acid (conc. HNO_3, 70% perchloric acid and conc. H_2So_4, 10:3:1). This process was executed by heating the contents till most of the triple acid mixture evaporated from the flask. The contents of each flask were then washed with triple distilled water and were stored in plastic vials at 4°C for further analysis.

The selenium levels as ng/ml were determined on GBC 932 spectrophotometer by fluorometery.[11,12]

A record of the following *viz*. age of the mother, consanguinity of parents, medical history, the number of pregnancies, abortions, history of previous NTD, use of medication, smoking, proximity to radiation during pregnancy was taken. The gestation period, birth weight and length were also recorded. Statistical analysis of the data was performed with SPSS Version 16.0. Differences in demographic data between the study group and control group were compared by t-test.[13] Statistical significance was defined for P values of less than 0.05. All the data were given as arithmetic means, SD, SEM and ranges. The 95% confidence intervals (CI) for the population means were also shown. t-test was used to compare the Se levels of the subjects.

RESULTS

The mean (± SEM) blood Se concentration measured in mothers with NTD newborns was 306.4 ± 10.95 ng/ml (Table I). This was significantly lower than those of the control (363.75 ±17.1 ng/ml, p <0.01) for the mothers with normal newborns. The mean serum and packed cell mass Se concentration was also significantly decreased in women with NTD infants as compared with those in the mothers with normal newborns. Comparison of the mean levels of the serum and packed cell mass Se between control groups showed significant difference (p< 0.01).

Table II indicates the mean values of blood, serum and packed cell Se concentration in the normal babies and those of NTD. The blood (2987.4 ± 12.3 ng/ml), serum (96.3 ± 7.15 ng/ml) and packed cell mass (139.8 ± 27.5 ng/g) of NTD babies had significantly lower Se concentrations than those of the normal babies (358.1 ± 16.11 ng/ml, p<0.01 for blood, 122.44 ± 6.03 ng/ml, p< 0.01 for serum and 268.6 ± 31.4 ng/g for packed cell mass, p< 0.01).

Table 1: Maternal Selenium status of Healthy and Newborns with NTD

Analysis	Mothers with NTD	Control Mother
Blood Se (ng/ml)		
Mean±SEM (SD)	306.4±10.95 (48.5)*	363.75±17.1 (76.4)*
95% CI	285.12 to 327.67	330.23 to 379.26
Range	139.12-412.75	255.25-548.62
Cell Mass Se (ng/g)		
Mean±SEM (SD)	165.8±16.99 (75.9)*	260.0±20.57 (91.8)*
95% CI	132.19 to 199.40	219.78 to 300.29
Range	21.93-325.2	82.35-539.54
Serum Se (ng/ml)		
Mean±SEM (SD)	192.44±6.12 (27.4)*	242.34±15.7 (70.3)*
95% CI	180.44 to 204.44	149.62 to 175.3
Range	115.29-189.00	161.42-369.32

CI - Confidence Interval; *p<0.05

Table III summarizes some characteristics of the subject compared age of the mother and parity and sex of the newborns. Although, a comparison of the mean ages of the mothers was not similar ($p< 0.05$). Parity was statistically insignificantly higher in NTD group.

DISCUSSION

Our results showed that Se was significantly lower in women with neural tube defect pregnancies than in those with unaffected pregnancies. Se thought to play a role in normal metabolism and it has become obvious that the greatest health risk of this element is to be found among newborns and children. The absence of clear signs of dysfunction or pathology among humans of low Se status made the role of Se in human nutrition unclear for the almost two decades after the discovery of its nutritional essentiality in experimental animals. Although, Se deficiency of such magnitude as to compromise health is not common, the circumstances that predispose a patient to low Se status are important to understand for diagnostic purposes.

In the present investigation it was observed that level of Se in blood, cell mass and serum was lower in mothers' and NTD neonates. All the values were statistically significant. Present findings supports the earlier observations, who reported that women with NTD had

Table 2: Selenium status in normal Newborns and those with NTD

Analysis	Newborns with Neural Tube Defect	Normal Newborns
Blood Se (ng/ml)		
Mean±SEM (SD)	298.4±12.3 (55.03)*	358.1±16.11 (72.05)*
95% CI	274.31 to 322.54	326.50 to 389.66
Range	206.11-410.23	247.06-512.4
Cell Mass Se (ng/g)		
Mean±SEM (SD)	139.8±27.5 (122.7)*	268.6±31.37 (140.6)*
95% CI	86.05 to 193.66	206.99 to 330.24
Range	27.75-333.60	13.08-402.00
Serum Se (ng/ml)		
Mean±SEM (SD)	96.3±7.15 (32.14)*	122.44±6.03 (26.99)*
95% CI	82.20 to 110.39	110.4 to 134.45
Range	19.46-118.02	26.34-138.65

Table 3: Characteristics of control Mothers, Newborns & those with NTD

	NTD group (n=287)	Control group (n=110)	p
Mothers' age			
Mean±SEM (SD)	24.52±0.22 (3.8)	25.65±0.39 (4.1)	<0.05
Range	18 to 31	18 to 34	
Parity			
Mean±SEM (SD)	1.68±0.06 (0.8)	1.64±0.07 (0.74)	>0.05
Range	0 to 4	0 to 3	

significantly lower mean Se concentration of both serum and hair at delivery than women with normal pregnancies and non-pregnant controls.[15,16] Hinks *et al.*, 1989 also demonstrated that Se level in plasma and leukocytes were low in mothers with NTD. Another interesting new finding is the significantly low concentrations of Se in the serum and blood of newborns with NTD, compared with normal newborns. This is possibly because the serum and blood Se concentration were decreased because of the intake of Se had fallen below the requirement at sometime during early weeks of gestation.[15,16] Even a transient Se deficiency might have contributed to the development of a NTD, if it occurred at a critical time before the closure of neural tube,[2] which is completed at around 25 days after conception.[17] An estimated safe and adequate dietary intake for adults has been defined as 50 to 200 mg per day by National Research Council, 1980.[18]

The majority of the mothers of infants with NTD in this study were found socio-economically poor. No history of known teratogenic agents was observed due to poor socio-economic status alcoholism did not found within this group of Indian women. Diet was largely comprised of chapati, vegetables and negligible amount of animal proteins. The best sources of dietary selenium are more expensive foods containing animal protein such as meat, eggs etc.[19,20] In addition the Se intake from normal diet may be marginally low during pregnancy. Therefore, the possibility of the postulated Se deficiency would be dietary inadequacy.[20-23] A relationship between poor diet and NTD recurrence has already been reported.[24] The widely observed socio-economic status factors in the prevalence of NTD suggest the possibility of a nutritional contribution to its cause.[20,25]

The combined actions of environmental and genetic factors such as multifactorial defects may be responsible for a group of birth disorders such as NTDs.[21] It is possible that Se deficiency in mother interacts with the genetic, environmental or other maternal factors to cause this developmental anomaly during early pregnancy. Another lurking possibility for the observation is that the lower Se concentration in blood, serum and cell mass may only secondary manifestations of an abnormal pregnancy and did not contribute in its causation. However, a detailed study needs to be undertaken to establish whether the observed fall in the Se concentration was an outcome of an underling abnormality. There is a need for further investigations on the importance of Se in pregnancy and NTDs as it is of fundamental importance to human health. As a constituent of selenoproteins, selenium has structural and enzymic roles and having antioxidant and catalytic properties.

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