Serum Zinc Levels in Newborns with Neural Tube Defects

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Neural tube defects (NTD) comprise of a group of congenital malformations that include spina bifida, anencephaly and encephalocele. Reports have implicated zinc deficiency as one of the causative factors of NTDs. We compared the serum zinc level of 23 newborns having neural tube defects with 35 healthy controls by spectrophotometery during 2003-2004. Zinc deficiency was documented in 43.5% of the cases and 8.6% of the controls (P = 0.002). Multivariate logistic regression analysis revealed a significant association between the presence of NTDs and zinc deficiency (OR = 8.2, 95% Cl: 1.9-34.7).

Key words: *Neural tube defects, Spina bifida, Zinc .*

NEURAL tube defects (NTD) are an important cause of perinatal morbidity and mortality(1,2). The incidence varies from 1/100 live births in certain regions of China to about 1/5000 live birth in Scandinavian countries(3). Etiology of NTD is considered multifactorial, with genetic, environmental and nutritional factors in all playing some role(4-6).

Maternal zinc deficiency may play a role in causation of NTD in the offspring(8). Studies have also documented low serum zinc levels in neonates born with neural tube defects(9). We conducted this study to look for an association of zinc deficiency and neural tube defects in North-East area of Iran, which has a high prevalence of neural tube defects.

Subjects and Methods

This hospital based case control study was conducted during 2003-04 at the Dezyani hospital in Gorgan located in the north of Iran. The sample population consisted of 23 newborns with NTD and 35 normal newborns selected at convenience. Data were collected regarding the maternal age, exposure to drug during pregnancy, history of abortions, and parity. Anthropometry of the newborn was recorded as per standard techniques. Peripheral blood sample was collected from all the newborns, serum was separated and analyzed for Zinc level by spectrophotometric method, using Randox Kit UR. Serum zinc level of less than 7.6 micro mol/L was used as the cut-off to label the individual as zinc-deficient. Parental consent was obtained for the study along with a clearance from Institutional ethical committee(10).

Categorical data were compared by Chi-square and Fisher's exact test. Mann Whitney U test and unpaired Student's 't' test were used for comparison of means. Presence of neural tube defect was considered as the dependent factor in multivariate logistics regression

analysis. Independent factors included in the analysis were parity, history of abortions, maternal drug exposure, and zinc deficiency as dichotomous variables. Data were analysed using SPSS 11.5 and STATA SE/8.

Results

Baseline characterstics of the two groups are depicted in *Table 1*. The groups were matched for parental age, parity, and obstetric history. However, control group babies were heavier and lengthy as compared to the study groups. The gestation of babies with NTD was less as compared to that of controls.

Serum zinc level (Mean ± SD) in NTD patients and normal newborns was 8 ± 3.9 micro mol per liter (μmol/L) and 12.3 ± 4.7 μmol/L, respectively. Overall 43.5% of patients and 8.6% of the controls in this study had zinc deficiency (P = 0.002). Multivariate logistic regression analysis showed an association between the presence of NTD and zinc deficiency (OR=8.2, 95% CI: 1.9-34.7) (*Table II*).

Discussion

The results from this study indicate that there is an association between NTD and zinc deficiency. These findings are similar with results from other researchers such as Velie et al in California(8), Groenen, *et al.*, in Netherland(11), Cengiz, *et al.*, in Turkey(12) and other studies(13,14). On other hand, Hombidgem, *et al.*(15), Nikolov, *et al*., in Sofiioi(16), Weekes, *et al.*(17) reported that there is no relation between zinc deficiency and NTD. Most studies reporting a relation between zinc level and NTD were based on the maternal zinc status; studies using newborn serum are limited. Some studies in Mexico(9), Netherland(11) and Turkey(18) have shown that serum and hair zinc status in newborns are associated with risk of NTD. Srinivas, *et al*., in India(19) reported that there is a relationship between low zinc levels in newborns hair with NTD, but no differences were found in the serum levels. It is possible that these differences are due to diverse methods of zinc analysis.

TABLE I–*Newborn Family History, Prenatal History and Newborn Charactristics*

	Cases (n = 23)	Control (n = 35)	P- value
Maternal age: Year (mean ± SD)	27.2 ± 6	25.7 ± 5.3	0.46§
Paternal age: Year (mean ± SD)	31.3 ± 6.3	29 ± 6	0.15§
Multiparity (*n*)	5 (20)	6 (16.2)	0.70¶
Pervious abortion (*n*)	4 (16)	5 (13.5)	0.79¶
History of other congenital malformations	4 (10.8)	1 (4.3)	0.64†
Newborn weight: gram (mean ± SD)	2865 ± 719	3439 ± 497	< 0.001*
Newborn height: cm (mean ± SD)	47 ± 4.6	50 ± 2.5	0.005*
Gestational age: week (mean ± SD)	36 ± 2. 5	38.5 ± 0.9	<0.0001§
Maternal exposure During 1st trimester (drug) (%)	7(28)	1(2.7)	0.006†

§: based on Mann-Wittney U test; ¶: based on Pearson's chi-square test; †: based on Fisher exact test; *: two independent sample 't' test.

TABLE II–*Logistic Regression Analysis of the Variables Included in the Study*

Risk factor	Crude OR (CI 95%)	Adjusted OR (CI 95%)
Low levels of zinc	8.2 (1.9-34.7)	7 (1.5-32.7)
Multiparity	1.3 (0.4-4.8)	1.2 (0.2-7.4)
History of abortions	1.3 (0.6-2.9)	1(0.3-3.2)
Maternal drug exposure during 1st trimester	14 (1.6-122.7)	11.9 (1.2-118.2)

However, this study has certain limitation. Firstly, the study and control groups are not age and sex matched. Also, there are differences in anthropometry of the two groups which could have led to differences in zinc level. Also, maternal zinc status should also have been estimated. Some experts also feel that use of serum zinc as a measure of zinc nutriture itself in questionable. The selection of control is not random.

Despite these limitations, we are able to show that there is an association between neural tube defect and low serum zinc level in the newborns. This finding focuses attention once again to the importance of nutritional factor in the etiology of neural tube defects. Further studies should be carried out to verify or prove the cause - effect relationship of zinc deficiency with NTD.

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REFERENCES

1. Copp AJ, Brook FA, Estibeiro JP, Shum AS, Cockroft DL. The embryonic development of mammalian neural tube defects. Prog Neurobiol 1990; 35: 363-403.
2. Lary JM, Edmonds LD. Prevalence of spina bifida at birth–United States, 1983-1990: A comparison of two surveillance systems. MMWR CDC Surveill Summ 1996; 45: 15-26.
3. Botto LD, Yang Q. 5,10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: a HuGE review. Am J Epidemiol 2000; 151: 862-877.
4. Seller MJ. Risks in spina bifida. Dev Med Child Neurol 1994; 36: 1021-1025.
5. Van Loon K, Besseghir K, Eshkol A. Neural tube defects after infertility treatment: a review. Fertil Steril 1992; 58: 875-884.
6. Harris MJ, Juriloff DM. Mini-review: toward understanding mechanisms of genetic neural tube defects in mice.Teratology 1999; 60: 292-305.
7. Milunsky A, Morris JS, Jick H, Rothman KJ, Ulcickas M, Jick SS, *et al*. Maternal Zinc and fetal neural tube defects. Teratology 1992; 46: 341-348.
8. Velie EM, Block G, Shaw GM, Samuels SJ, Schaffer DM, Kulldorff M. Maternal supplemental and dietary zinc intake and the occurrence of neural tube defects in California. Am J Epidemiol 1999; 150: 605-616.
9. Carrillo-Ponce Mde L, Martinez-Ordaz VA, Velasco-Rodriguez VM, Hernandez-Garcia A,

Key Message

- Newborns having neural tube defects have lower serum zinc concentrations as compared to healthy controls.

Hernandez-Serrano MC, Sanmiguel F. Serum lead, cadmium, and zinc levels in newborns with neural tube defects from a polluted zone in Mexico. Reprod Toxicol 2004; 19: 149-154.

10. Makino T. A sensitive, direct colorimetric assay of serum Zinc using nitro-PAPS and microwell plates. Clin Chim Acta 1991; 197: 209-220.
11. Groenen PM, Peer PG, Wevers RA, Swinkels DW, Franke B, Mariman EC, *et al*. Maternal myo-inositol, glucose, and zinc status is associated with the risk of offspring with spina bifida. Am J Obstet Gynecol 2003; 189: 1713-1719.
12. Cengiz B, Soylemez F, Ozturk E, Cavdar AO. Serum zinc, selenium, copper, and lead levels in women with second-trimester induced abortion resulting from neural tube defects: a preliminary study. Biol Trace Elem Res 2004; 97: 225-235.
13. Shaw GM, Todoroff K, Schaffer DM, Selvin S.Periconceptional nutrient intake and risk for neural tube defect-affected pregnancies. Epidemiology 1999; 10: 711-716.
14. Groenen PM, Wevers RA, Janssen FS, Tuerlings JH, Merkus JM, Steegers-Theunissen RP. Are myoinositol, glucose and zinc concentrations in amniotic fluid of fetuses with spina bifida different from controls? Early Hum Dev 2003; 71: 1-8.
15. Hambidge M, Hackshaw A, Wald N. Neural tube defects and serum Zinc. Br J Obstet Gynaecol 1993; 100: 746-749.
16. Nikolov V, Tsachev K, Marinov B. The zinc concentration of the maternal serum and the amniotic fluid in pregnancies with fetal neural defects in the second trimester. Akush Ginekol (Sofiia) 1993; 32: 8-10.
17. Weekes EW, Tamura T, Davis RO, Birch R, Vaughn WH, Franklin JC, *et al*. Nutrient levels in amniotic fluid from women with normal and neural tube defect pregnancies. Biol Neonate 1992; 61: 226-231.
18. Cavdar AO, Bahceci M, Akar N, Erten J, Yavuz H. Effect of Zinc supplementation in a Turkish woman with two previous anencephalic infants. Gynecol Obstet Invest 1991; 32: 123-125.
19. Srinivas M, Gupta DK, Rathi SS, Grover JK, Vats V, Sharma JD, *et al*. Association between lower hair zinc levels and neural tube defects. Indian J Pediatr 2001; 68: 519-522.