Review Article

Neural Tube Defects, Patho-physiology and Relationship of Serum Zinc Level: A Review

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Introduction

Neural tube defects (NTD) account for most of the congenital anomalies of the central nervous system. These defects result from failure of the neural tube to close spontaneously at about 29th day post-conception. In the USA, the incidence of neural tube defect is estimated to be around 1 per 2000 deliveries[1].

In many of the cases, the defect is lethal or invalidating. NTD has a complex and imperfectly understood etiology in which genetic, environmental and nutritional factors appear to be involved.

Among the nutritional factors, abnormalities of folate metabolism has been shown to be crucial in the pathogenesis of NTDs and hence routine folate supplementation has been recommended by the Centers for Disease Control of the US Public Health Services as a measure of prevention of NTD since 1991[2]. Since this periconceptional folate supplementation reduces the NTD occurrence rate for 50% and the recurrence rate for 71%[3], studies have been revealing more nutritional factors like zinc, vitamin B12, magnasium and selenium. Deficiencies of which are found to be causally related to the development of NTD[4-7].

Among these, zinc deficiency has been documented by many authors[4,5,7,8]. Hence this article is meant to review the pathogenesis of NTD particularly its relation to serum zinc level.

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Pathophysiology

The central nervous system (CNS) appears at the beginning of the third week as a slipper-shaped plate of thickened ectoderm, the neural plate, in the mid-dorsal region in front of the primitive node. Its lateral edges soon elevate to form the neural folds[9].

Two distinct processes appear to be involved in the formation of the neural tube, primary neurulation and secondary neurulation, i.e., canalization.

The neural plate and the notochord are formed during early embryonic development. The neural groove develops by the third gestational week. Subsequently, the neural folds form bilaterally.

Primary neurulation: The neural folds elevate, approximate each other, and start closing thus forming the neural tube. The point of initial closure at the caudal rhombencephalon or cranial spinal cord. The cutaneous ectoderm fuses first, followed by neuroectoderm. The cranial neuropore closes during the fourth gestational week. The last area to close is the commissural plate. The caudal neuropore closes between T11 and S2.

Parallel to this process, the cutaneous ectoderm separates from the neuro-ectoderm to form the overlying skin, while the lateral mesoderm migrates between the two ectodermal layers to form the posterior vertebral arches[10].

Secondary neurulation (canalization): This comprises further neural development occurring caudal to the caudal neuropore after the termination of primary neurulation. This process includes formation of filum terminale and conus medullaris

from a poorly differentiated cell mass of the medial eminence. Because of differential growth between the vertebral column and the spinal cord, the conus become more rostral during the later developement.

Open neural tube defect (NTD) have been suggested to result from defective primary neurulation while defective secondary neurulation gives rise to close NTD. However, this issue is not settled. Another possible explanation is that, open NTDs (spina bifida in particular) results from defects in either primary or secondary neurulation depending on their site being cranial or caudal to the posterior neuropore (i.e., upper and lower spina bifida respectively)[10].

Frequency

The worldwide incidence of neural tube defects is estimated to be around 1 per 1000 live births[1]. However, there are remarkable variations in the incidence of NTD and other CNS defects. In certain regions of China, the incidence is 1 in 100, being the highest[11], whereas in the Scandinavian countries it is only 1 in 5000[12].

In general, neural tube defects has a female preponderance. In case of anencephaly, the ratio of female to male is 7:3 and for spina bifida the ratio is 55:45[13]. In a case control study it was found that about 70% of the children with anencephaly and 60% of spina bifida were female[14]. Another study revealed that 75% of the spina bifida defects at the thoracic level or higher was in females, while no such gender difference was found in more distal forms of neural tube defects[15].

The risk of recurrence in siblings following the birth of a baby with NTD is around 5% and may be related to the incidence in the area at a given time[14]. In some parts of the world the recurrence rate was found to be around 2.1%[16]. The recurrence rate of an NTD is about 10% of the mother who already had two or more affected cases. The risk to children of a parent who had spina bifida is of the same order as to siblings after a single affected case[14].

Aetiology

The causes of neural tube defects are difficult to study. Two children with similar defects may have developed through a completely different etiology. There are four major categories of known causes of NTD[17]:

1. Genetic disorders (either hereditary or arising during conception)
2. Exposure to environmental chemical (e.g., medications or solvents)
3. Maternal illness during pregnancy, exposing her baby to high temperatures and/or to viral or bacterial infections
4. Lack of nutrients

The stage of fetal development at the time of exposure to one of the latter three causes is critical. Because neural tube development takes place in the first month of pregnancy, exposure would have to occur during that period to give rise to a defect.

Genetic disorders

While some neural tube defects may arise as a result of gene-environment interaction, there are a number of identified syndromes that also can give rise to neural tube defects. Some sixty syndromes that have a component of NTD together with other birth defects been identified. Each of the different types of NTD may arise as a result of one or more of these syndromes. There is also evidence that non-syndrome neural tube defects may sometimes also have a genetic source, based on familial and twin studies[18].

Environmental exposures

Since neural tube defects are relatively rare birth defects, it is hard to definitively associate an environmental exposure to a specific NTD. However, a number of studies[17] have identified exposures that may cause neural tube defects. A selection of these is listed in Table-I, which gives an idea of the range of exposures in the first trimester of pregnancy that may give rise to neural tube defects. Occupational exposures to glycol ether, pesticides, drinking water containing high concentration of nitrates and lead are among the important exposures found to be associated with NTD[19-22]. Maternal tea consumption has also been described in the etiology of NTD[23].

Table-I

Environmental exposures associated with increased risk of NTD

Exposure	Type of NTD	Exposure type	Odds ratio (95% confidence interval)	Reference
Glycol ethers	All combined	Occupational	1.94 (1.16, 3.24)	19
Nitrates	Anencephaly	Drinking water nitrates >45mg/L	4.0 (1.0, 3.24)	21
Lead	All combined	Drinking water lead >10µg/L	1.25	20
Trihalomethane	Isolated NTDs	Highest tertile of drinking water	2.1 (1.1, 15.4)	24
Valproic acid	Spina bifida	Anti-seizure medication	5.7 (2.9, 10.9)	25
Tea	Spina bifida	Maternal consumption	2.3 (1.2, 4.4)	23
Oxytetracycline (antibiotic)	All combined	Treatment during 2nd month of pregnancy	9.7 (2.0-47.1)	26
Pesticides (Paternal)	Spina bifida	Paternal spraying in orchards and green houses	2.76 (1.07, 7.13)	27
Pesticide (Maternal)	All combined	Professionally applied to home living within ¼ mile of an agricultural plot	1.6 (1.1, 2.5) 1.5 (1.1, 2.1)	22
Landfill sites	All combined	Living within 3 km of landfill sites	1.86 (1.24, 2.79)	28
Heat	All combined	Hot tub use	2.8 (1.2, 6.5)	29

Maternal factors

1. General conditions: There are a number of maternal conditions that may contribute to an increased risk of an NTD-affected pregnancy. It was found that the incidence of NTD among infants of women who had a fever in the first trimester to be higher than control afebrile women. Though it was not clear whether the exposure to high temperature or to the bacteria or virus is the cause of the mal-development of the neural tube[30]. Women with diabetes were found to be four times associated with the pregnancies involving neural tube defects (95% CI [3.1, 5.1]) in comparison to the non-diabetics. However the investigators found a much smaller odds ratio of 1.3 (95%CI [1.0, 1.6]) of neural tube defect pregnancies among women of with gestational diabetes[31]. Obese women were found to be 3.5 times more affected by NTD in comparison to non obese[32]. Maternal psychological stress may increase the risk of neural tube defects. It was reported that woman who experienced death of someone close, job loss, separation or divorce either themselves or someone close to them in the very early stages of pregnancy had an odds ratio of 1.5 (95% CI [1.1, 2.1])[33]. Another study counted job changes, residential moves and major injuries as stressful events in the year prior to conception in Mexican America[34]. Women with at least one such event had almost three times the risk of an NTD-affected pregnancy (odds ratio 2.9, 95% CI [1.8, 4.7]). Women with low levels of emotional support also had an increased risk of an NTD-affected pregnancy (odds ratio 4.6, 95% CI [2.2, 9.7]). A

number of medications also can give rise to neural tube defects. Several are listed in Table-I. However, sometimes the consequences of not taking such medications also may be grave for mothers and pregnancy outcomes[26].

2. Maternal age: The literatures report associations between maternal age and the incidence of neural tube defects. Prevalence of NTD-affected pregnancies was found to be decreased with increasing maternal age[16]. Meanwhile some authors found a U-shaped distribution of neural tube defects in relation to maternal age[14,15].
3. Maternal diet: Folic acid is a nutrient that is clearly needed for proper neural tube development. In 1992, the US centers for Disease Control and Prevention recommended that all women of child bearing age consume 0.4 mg of folic acid daily[2]. This routine supplementation prevents the occurrence of NTD by more than 50% when it is taken before conception and continued throughout the first trimester of pregnancy. Women who have had a child with an NTD, the recommendation for daily consumption of folic acid is 4000 µg. This supplementation in addition to folate in the diet before and during early pregnancy resulted in 71% reduction of recurrence of NTDs[35]. The recommendation originated in research indicating that inadequate levels of folic acid in the first weeks of pregnancy inceased the risk of having a baby with neural tube defect[3]. In 1996, the US Food and Drug Administration agreed that enriched cereal grain products must be fortified with folic acid, as a means to reduce the rate of neural tube defects in the United States[2].

There is evidence to suggest that excess lead (Pb) is causally related to NTD especially anencephaly[20,36].

Besides, deficiencies of zinc, selenium and vitamin B12 have been described to be associated with increased incidence of NTD[6,7]. Among these zinc deficiency is described by many authors.

Zinc and Neural Tube Defects

Zinc is an essential trace element, necessary for sustaining life. In the human body three hundred of proteins contain zinc prosthetic group, one of which is called the so called zinc finger[37]. Zinc is an activator of certain enzymes, such as carbonic anhydrase. Carbonic anhydrase is important in the transport of carbon dioxide in the vertebrate blood.

The US recommended dietary allowance of zinc from puberty onwards is 11mg for males and 8 mg for females, with higher recommended during pregnancy and lactation[37]. In children the daily requirement is 2.5 mg/kg/day[13].

Zinc deficiency has been described to be associated with neural tube defects by authors from different part of the world[7,8,38]. Low level of serum zinc in the babies was associated with increased occurrence of NTD which was independent of serum folate level. Maternal zinc deficiency may play role in the causation of NTD in the offspring[4]. Population based case control studies conducted in California, showed that the risk of NTD in infants and foetuses decreased with increasing maternal preconceptional zinc intake[4,5]. Mothers taking zinc supplementation starting from few months before conception and continued into the first trimester had significantly lower incidence of NTD in these studies. However, it remains unclear whether increased zinc intake, or another nutrient or combination of nutrients highly correlated with zinc intake in the diet, is causally associated with reduced NTD risk.

A case of a nutritionally zinc deficient young Turkish woman was reported who had previously delivered two anencephalic stillborn infants. After zinc supplementation she delivered a normal full term child[41].

A recent survey in two county of Shanxi province of China where there is high incidence of congenital malformations, found that there was markedly insufficient intake of nutrients like folate, zinc, vitamin B12, vitamin A by the mothers of the newborn with congenital malformations including NTD.

There was a positive correlation between NTD and zinc deficiency in a study conducted in Mexico, that means the less was the serum zinc level, the more was the occurrence of NTD and vice versa[38].

Reports concerning maternal plasma zinc concentrations after an oral zinc tolerance test in pregnancies associated with NTDs in Turkey showed that some of the affected women had defective zinc absorption due to chronic zinc deficiency, which returned to normal after zinc supplementation[42]. Four affected women gave birth to normal infants; only one infant had closed spina bifida[43].

Another case control study conducted in Boston, USA revealed a significant association between increased

toe-nail zinc in the second trimester of pregnancy and the risk of having a child with an NTD[8]. The author predicted the possible sequestration of zinc resulted in relative zinc deficiency at the site of neural tube closure.

Maternal zinc and selenium status were examined in a study where both these micronutrients were found to be deficient in NTD affected mothers[7]. Similar report is also available describing low maternal serum zinc level in relation to foetal neural tube defects[8]. Another study carried out in India revealed an association between NTD and decreased hair zinc level[39]. In this case the authors predicted that long term zinc deficiency in the blood resulted into decreased hair zinc level.

A recent study in Turkey revealed, high maternal serum levels of copper and lower level of zinc during pregnancy associated with NTD in newborn[44].

However, contrary results are also evident where no association been serum zinc level and neural tube defect has been found[40]. Here the authors found normal serum zinc level in the mothers of NTD affected babies.

Conclusion

Neural tube defects, the commonest congenital malformation of the central nervous system results from multifactorial etiology. Among the nutritional factors, folic acid deficiency or abnormal folate metabolism is an established mechanism. However, deficiency of some other nutrients is also found to be associated with its pathogenesis. Low serum zinc level in the mother and in the babies is described by authors from different parts of the world as an association of neural tube defects. Though the investigation reports are not uniform in all the reports, zinc deficiency is increasingly found to be related to NTD. Hence, routine supplementation of zinc may come out as a measure to prevent neural tube defects like folic acid.

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