

Neural Tube Defects: A Neglected Problem

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Neural tube defects (NTDs) are the most common congenital malformations affecting the brain and spinal cord. They assume significance by virtue of their morbidity, mortality, health care expenditure, and human suffering. The incidence of NTDs ranges from 0.5-11/1000 births in different regions of India(1). The true incidence of NTDs is difficult to ascertain as affected pregnancies may end up in spontaneous abortions, or may be medically terminated. Neural tube formation (neurulation) is a highly complicated biological process controlled by a number of genes, growth factors, adhesion molecules and receptors(2). By third week of postconceptional age, human embryo has three distinct primary germ layers- ectoderm, mesoderm and endoderm which subsequently develop into various tissues and organs. The formation of neural tube begins during third week when midline ectoderm, under the inductive influence of the underlying mesoderm, becomes the neural plate that further develops into the neural groove, then the neural tube. Neural tube closes during the fourth week, and failure to do so results in NTDs(3).

The main NTDs are anencephaly, encephalocele, and spina bifida (including meningocele and meningomyelocele).

The incidence of NTDs shows wide variation, being influenced by race, ethnicity, nutritional status, geographic location, and socioeconomic conditions(3). The exact cause of NTDs is not clear in most cases. Both genetic and environmental factors have been implicated in the etiopathogenesis of NTDs. Polymorphism of genes involved in folic

acid metabolism significantly increase the risk(2). Other well described factors associated with NTDs include folic acid deficiency, prenatal exposure to drugs including antiepileptics, maternal hyperthermia and maternal diabetes. There are also single gene disorders and chromosomal abnormalities associated with NTDs. However, they constitute only a minority of cases. The risk of NTDs after exposure to valproate during early pregnancy is 1-2%. The risk of recurrence of NTDs after one affected pregnancy is 2-3% and may approach 10% with two previous abnormal pregnancies.

Nutritional status of pregnant women may influence their vulnerability to NTDs. Folate deficiency is a well known cause of NTDs. The search for other etiological factors, particularly nutritional factors, continues. In recent years, zinc and vitamin B₁₂ have attracted the attention of researchers. Zinc is essential for fetal growth and development and plays a critical role in many cellular reactions including gene transcription, cell division and differentiation. Inadequate zinc intake is associated with NTDs in both animals and humans(4). The essentiality of zinc in neural tube formation is further supported by the observation that women with acrodermatitis enteropathica, a disorder of impaired zinc absorption from the intestine, are at high risk for babies with NTDs(5).

In this issue of *Indian Pediatrics*, Zeyrek, *et al.*(6) report that low maternal zinc and high copper during pregnancy may be responsible for NTDs. However, the case-control design of the present study precludes such a conclusion. What

this study shows is that NTD-affected pregnancies are associated with low zinc and high copper levels. It is not possible to conclude from this study that the observed association is causal in nature. Only a randomized controlled trial of zinc supplementation in periconceptual period can settle the issue of causative link between zinc and NTDs. The authors assessed micronutrient status of pregnant women during the third trimester or at delivery and then correlated this with the occurrence of NTDs. They assumed that similar state of micronutrient status must have prevailed at the time of formation of neural tube, *i.e.* during third and fourth weeks of postconceptional age. This assumption is not valid.

Nutrient status changes with the stage of pregnancy, and may be influenced by a number of factors, including nutrient-nutrient interactions. Zinc levels are known to decline with advancing pregnancy. Another confounding variable to be considered is the prenatal iron supplementation which can reduce zinc bioavailability(7). Generally pregnant women are given iron in the later part of pregnancy. The present study does not provide any information on this important aspect. Thus low zinc levels observed in later part of pregnancy does not necessarily mean that similar state existed in the beginning of pregnancy. In the present study, case and control mothers also differed with regard to age, the former being of higher age group. Older mothers tend to have lower zinc levels than the younger age group. Thus difference in zinc levels in cases and controls in this study has to confront many confounding variables. In the discussion, the authors make a contradictory statement that low zinc and high copper levels were due to NTD-induced inflammation. In the remaining text they maintain that low zinc and high copper possibly resulted in NTDs. One is left wondering what came first: NTD, or low zinc and high copper levels.

NTDs constitute the most disabling birth defect in humans. Therapeutic options are limited in resource poor settings. Therefore, high priority should be accorded to preventive strategies. The role of folate in preventing NTDs is well established by several prospective trials. Periconceptual folate supplementation reduces the incidence of NTDs significantly (relative risk 0.28, 95%

confidence interval 0.13 to 0.58)(8). It is recommended that all women capable of becoming pregnant consume 0.4 mg of folic acid daily on an ongoing basis to prevent NTDs (primary prevention). For high risk (previous NTD-affected pregnancy) women planning a pregnancy, the recommended intake of folic acid is 4 mg daily beginning at least one month before conception and continuing through the first trimester (secondary prevention). The timing of folate supplementation is critical. As NTDs arise very early in embryonic life (third or fourth weeks of gestation), before many women realize they are pregnant, supplementation needs to be started even before conception to ensure adequate blood and tissue folate levels at the time of neural tube formation. Given that most of the pregnancies in India are not planned, timely supplementation presents a formidable challenge to health professionals and policy planners. Another approach is the fortification of food with folate as is being done in western countries. There is a need for public awareness campaign on a large scale to reach out to the eligible women. Professional organizations like FOGSI, IAP, and NNF can play a vital role on this front. We also need a public health agency similar to the US Public Health Service (USPHS) which can act as a nodal centre to frame and disseminate guidelines to professionals and general public on issues of public health significance.

Folate-NTD connection illustrates the best example where a debilitating birth defect can be easily prevented by simple means. The birth of babies with NTDs in present scenario is a greatly missed opportunity. In view of wide prevalence and high social costs of these defects, there is an urgent need to have a national neural tube defects prevention program in India.

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