

## Primary Prevention of Neural Tube Defects

Nasib C. Digra MS, Mch

Neural tube defects (NTDs) are one of the commonest malformations seen in pediatric surgical practice. They form a spectrum of disease ranging from anencephaly to spina bifida occulta. NTDs are devastating conditions as most of the lesions (myelomeningoceles, myelocele etc.) are always associated with neurological deficits producing varying degree of limb paresis/paralysis, bladder and anorectal incontinence. A significant number also have or later on develop hydrocephalus with its attendant complications following shunt surgery. Thus NTDs offer a tremendous challenge in management, that requires the co-ordination and co-operation of many specialists with an aim to rehabilitate and integrate these handicapped patients with a satisfying life in to the society. This may be an ideal and true situation in the West but in a developing country like India, it is a difficult task as most of the patients are poor and their number is so large requiring huge resources for their treatment and rehabilitation. In the given scenario, the emphasis should on antenatal prevention, diagnosis and treatment and in postnatal period on selective management.

### Incidence and Etiology

The prevalence of NTDs has been reported at ~ 5 per 1,000 births in the UK, 3 per 1,000 in Hungary, 1 per 1,000 in USA, France, Australia, and Japan (1). The rate of recurrence in the sibling was 5, 3 and 1 per 1,000 in these countries, respectively. In India, one study from Karnataka has reported a prevalence rate of 11.4 per 1,000

(2). The risk of NTD recurrence is sometimes 10 times higher than that of occurrence suggests that NTD-or some major part of NTD may have a genetic basis. Chromosomal aberrations (eg., trisomy-18), gene mutations (eg., Meckel syndrome) and teratogenic factors (eg., valproic acid) were identified in 2%, 2% and 4% of cases respectively. However, most of these cases belong to the group of multiple or syndromic NTDs- i.e., NTD associated with non-NTD defects. The other 92% of cases (nearly all of which are isolated NTDs) may have multifactorial origins such as polygenic liability triggered by environmental factors. It has been demonstrated that there are five separate closures, or "zippers," in normal neural tube fusion (3). Different closures may be determined by different genes and therefore may be susceptible to different environmental factors.

Among triggering environmental factors, undernutrition has been found to be a factor in the well known association between NTDs and poverty, seasonality and rapid secular changes in the birth prevalence of NTDs. Smithells et al. have convincingly reported lower levels of red cell folate and vitamin C during the first trimester of pregnancy in women who later gave birth to an infant with an NTD than in matched controls (4). This fact was confirmed by other workers also in prospective studies where all recurrences of NTDs were in mothers with poor diets (5).

**From the Postgraduate Department of Surgery, Government Medical College, Jammu (J&K), India.**

**Correspondence to :** Dr. Nasib C. Digra, Asstt. Prof. & Consultant Pediatric Surgeon, Government Medical College, Jammu (J&K), India.

### **Folic Acid in Prevention of NTDs**

Humans are not able to synthesize folate and are thus dependent entirely on exogenous sources. As mentioned earlier, folic acid plays an important and critical role in closure of neural tube (neurulation). There are two general and important biological effects of folate. First folate acts as a cofactor for enzymes involved in DNA and RNA biosynthesis. Folate provides one-carbon units for the de-novo synthesis of DNA bases (guanine, adenine, and thymine). Folate requirements increase dramatically during the periods of rapid growth of fetus. Thus with folate deficiency, DNA synthesis is inhibited and cells are unable to manufacture enough DNA for mitosis, leading to limited and/or imbalanced cell growth, followed by cell death. Second, folate is involved in the supply of methyl groups to the methylation cycle. The methyl group is used by methionine synthetase, which is a vitamin B12-dependent enzyme to recycle homocysteine back to methionine. A disturbance in this process causes hyperhomocysteinemia and shortage of methionine; therefore cells are not able to methylate important compounds like proteins, lipids and myelin. Thus, folate deficiency or genetically rooted error in folate metabolism can cause developmental defects through disturbances of DNA biosynthesis and/or the methylation cycle (1, 3-9).

The nervous system becomes evident on post-ovulation day 18, and neural tube closure occurs during days 22-28. Thus, NTDs occur so early that most women are unaware of their pregnancy. Therefore, any advice regarding dietary modification, supplementation, and food fortification should be in the periconceptional period i.e. beginning at least 1 month before conception and continuing through the first trimester. The dosage of folic acid recommended are: to avoid occurrence of NTDs- 0.4 mg/day and to avoid recurrence of NTDs- 4 mg/ day (1-9). It has been observed that by these folate supplementation dosage, the NTDs occurrence rate has decreased by 58% and the recurrence rate by 95% (5).

The principal dietary sources of folate are leafy green vegetables, legumes (beans, peas), citrus fruits (juices), liver and whole bread. The folate content of these natural sources is variable with less bioavailability as folate in these is present as polyglutamates and it needs to be converted to monoglutamates for its utilization. All synthetic forms of folic acid contain only monoglutamates. Furthermore, persuading women to consume adequate amounts of folate through the diet is difficult. It has been shown that folate intake from food sources was 0.4 mg of folic acid daily in 8% of adult women only (6). In addition, folate poor diets, related to lack of education in nutrition, poverty, poor eating habits, prolonged cooking of vegetables and cultural factors (food-fads) are also frequent. Women on anticonvulsants, antimetabolites, and oral contraceptives have suboptimal folate status. Thus, diet alone as a measure of preventing NTDs may not be of much help. Therefore, the use of folate supplements seems to be a better option than folate rich diet (1). But it is also prone to problem of ensuring compliance on a widespread population. In addition, it has been seen that women who know that periconceptional folic acid can prevent the majority of NTDs, compliance is still poor.

Many women, even if they plan to become pregnant, do not comply since concept of taking a daily tablet when they are feeling completely healthy is not accepted. Furthermore, even in developed countries like US and Hungary, more than 50% of pregnancies are unplanned posing a major practical problem in folate supplementation program. Thus, food fortification seems to be the most practical means of supplementation (7) and would be comparable to prevention of goiter by the iodised salt. In Ireland, the addition of vit B12 in 1981 and folic acid in 1987 to fortified breakfast cereals, have caused a fall in the prevalence of NTDs in Dublin since 1980 from 4.7 to 1.3 per 1,000 births (8). Some breads and fruit juices are also fortified. It was hoped that women who did not feel inclined to take a tablet would elect to increase their intake via this means. However, the problems remain of unplanned pregnancies, knowledge



and compliance that were encountered with not taking supplements. An alternative within the fortification option is mandatory fortification by legislation or in agreement with the industry, folic acid is added to a staple diet at agreed concentration, e.g. wheat flour. All these food fortification measures are currently in use in US , UK and other European countries (1, 7, 9).

So at present, there are three possibilities- consumption of a folate rich and other vitamin rich diet, supplementation and/or food fortification to provide multivitamin and folic acid consumption for women of childbearing age who are capable of becoming pregnant. All three possibilities should be pursued in parallel to provide options for women planning their pregnancies. It is a real hope that this primary preventive method would not only reduce NTDs and some other congenital anomalies but also ensure better health for all infants, mothers and adult people.

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