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Etiology, Epidemiological Aspects and Preventive Strategies of Neural Tube Defects

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Abstract **Review Article**

Neural tube defect (NTD) is a defect in neurulation process of embryogenesis occuring during early human development. Failure of normal closure of neural tube causes NDT. Type and severity varies based on location of defect. NDT occurs predominantly at rostral and caudal ends. Folate is essential for DNA and RNA synthesis and for one carbon group transfer in methylation and nucleic acid synthesis. In folate deficiency, there is failure of post-translational methylation of the cytoskeleton leading to NTD. Some of the contributing factors for NTD include maternal illness, Low socio-economic status, Drugs, Food contamination and maternal Smoking. Folic acid supplementation reduces the prevalence of NTD by 70%. Multiple genes are associated with folate insensitive NTD. NTD can be classified based on the site of defect into Cranial and Spinal malformations and based on the presence or absence of exposed neural tissue into open or closed types. Some of the common factors to be considered in analysing NTD include Multiple Gestation, Dietary Factors, Sex, and Maternal obesity, Illness, Age, Socioeconomic Status, Parity, Occupational Exposure and Previous Pregnancy Wastage. Most popular strategy for prevention of NTD is folic acid supplementation for women of childbearing age. Other strategies for prevention of NTD include folate-rich diet, multivitamin supplementation, 6S- 5-MTHF, food fortification, combination of oral contraceptives and folate. With recent advances in genetics and diagnostic tools, genetic and syndromic causes of NTD can be prevented utilizing preimplantation genetic diagnosis or early detection by chorionic villous sampling and high resolution early antenatal ultrasound scan.

Keywords: Neural Tube Defect, Folate Supplementation, Homocysteine.

INTRODUCTION

Neural tube defects (NTD) are developmental defects which occur in early human development during 3rd week of pregnancy at the gastrulation stage [1]. It is a defect in neurulation process of embryogenesis [2]. Normally cells on dorsal side of embryo undergo change to form neural tube. Failure of normal closure of neural tube causes an opening in cranium or spine, which is called as NDT. Type and severity varies based on location of the defect. NDT occurs predominantly at rostral and caudal ends because during the process of neurulation, neuropore closure occurs at the last at rostral and caudal ends [3].

Etiology

Humans cannot produce folate. Dietary sources of folate include fresh and frozen green leafy vegetables, citrus fruits and juices, liver, wheat bread and legumes such as beans. Folate is essential for DNA and RNA synthesis. It is also important in one carbon group transfer in methylation and nucleic acid synthesis. In folate deficiency, there is failure of post-translational methylation of the cytoskeleton leading to poor differentiation which leads to NTD. Early human embryo is vulnerable to folate deficiency due to difference of the functional enzymes during embryogenesis along with high demand for post translational methylations of the cytoskeleton in neural cells during neural tube closure [4].

There are numerous genetic syndromes associated with NTD [5]. The specific genes involved are being studied. NTD have been identified in genetic syndromes with various modes of inheritance. Majority are Chromosomal disorders. Among single gene defects, most of genetic syndromes with NTD have autosomal recessive inheritance. Autosomal dominant and sex linked inheritance have also been noticed in some syndromes [6].

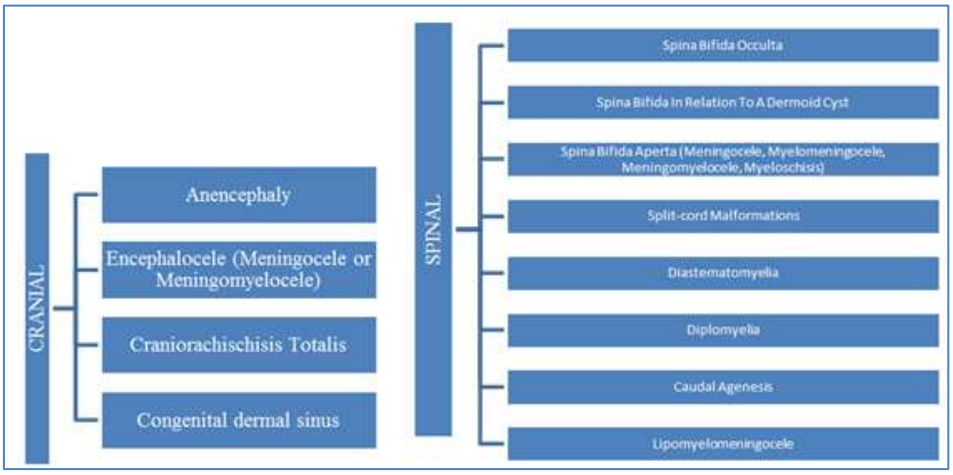
There are many contributing factors of NTD which include

Folate Deficiency	Maternal Diabetes	Low Socio-Economic Status
Drugs	Maternal Hyperthermia	
	Maternal Stress	Food contaminated with Fumonisins (Myocotoxins)
Pesticides	Maternal Smoking	
Hazardous waste	Maternal Diarrhea	Electromagnetic fields
	Maternal Dieting Behavior	
Chlorination disinfection by-products in drinking water	Maternal intake of foods with high Glycemic Index	UV Radiation-induced Folate Photolysis

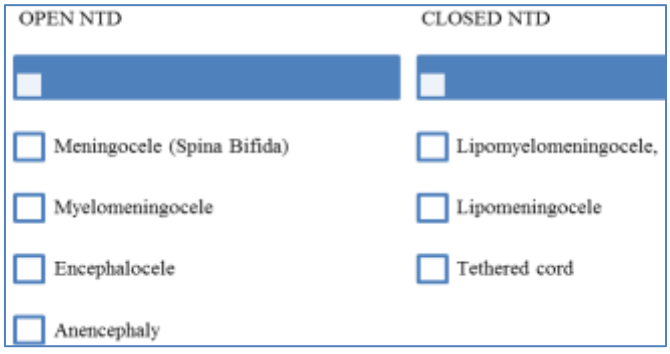
Some of the drugs which are suspected to cause NTD include antihistamines, sulphonamides, anticonvulsants, carbamazepine, valproate, methotrexate and aminopterin, recently research has suggested association between NTD and Maternal myo-inositol, zinc and glucose levels. Folic acid supplementation has shown to have reduced the prevalence of NTD by 70% [7]. However there are some NTD which occur independent of folate levels. Multiple genes are found to be associated with folate insensitive NTD. Meckel syndrome and Triploid Syndrome have NTD which is suspected to be unrelated to folate metabolism [5].

Types of NTD

NTD can be classified based on the site of defect and based on the presence or absence of exposed neural tissue. Based on the site of defect there can be Cranial and Spinal malformations [8].



Based on the presence or absence of exposed neural tissue, NTD can be classified as “open” or “closed” types.



Open NTD are the commonest and they constitute about 80% of all NTD. Open NTD occur due to failure of primary neurulation. Neural tissue is exposed or covered by a membrane. There may be cerebrospinal fluid (CSF) leakage [9]. They are associated with presence of Hydrocephalus and Chiari II malformation. In contrast, Closed NTD are localized and confined to spine. They occur due to failure in secondary neurulation. There is no neural tissue exposure and defect is fully covered by epithelium [10].

Epidemiological Aspects of Neural Tube Defects

Prevalence of NTD is dependent on epidemiological, demographic and social factors. Some of the common factors to be considered in analysing NTD include.

Variations in Birth Incidence	Multiple Gestation	Dietary Factors
Sex	Obesity	Recurrence of NTD
Age of Presentation	Maternal Illness	Family Recurrence Risks
Maternal Age	Socioeconomic Status	Folate and NTD
Parity	Occupational Exposure	Genetics and NTD
Previous Pregnancy Wastage		

Variations in Birth Incidence

There is seasonal and secular variations noted in the trend of prevalence of NTD. Some of the etiological factors leading to NTD are common at specific prenatal age. According to Indian data, the estimated prevalence of NTD varies between 0.5 to 11 per 1000 births [1]. Studies from the time before in-utero diagnosis and termination of affected pregnancies has established two trends. Initially there were epidemics of NTD followed by a general decline over several decades. Racial data suggest significance of genetic component in occurence of NTD [11].

Sex

Among NTD, cranial defects are more common in female. For example, Anencephaly has a female-to-male ratio of 3:1. Likewise other NTD which arise from regions above thoracolumbar junction show female preponderance [12]. However in case of distal forms of spina bifida, there is no such gender bias. The explanation for such female predisposition is that the requirement of human chorionic gonadotropin is more in female fetus as compared to male. This hormone deficiency can increase the risk of NTD [13].

Age of presentation

The time at which the NTD are detected varies based on the type. Since there is exposed neural tissue along with CSF leak sometimes, open NTD are immediately diagnosed at birth. In fact antenatal scans can pick some of such defects. Moreover presence of associated Hydrocephalus or Chiari II malformation helps in early diagnosis. In contrast, closed NTD may remain undiagnosed even for decades. This is more possible in the absence of cutaneous markers. However, one or more cutaneous lesions are present in nearly 70% of asymptomatic patients with closed NTD.

Maternal age

Per se maternal age does not directly affect incidence of NTD. However in presence of other risk factors, risk for NTD increases in older and very young mothers [14].

Parity

Compared to maternal age, parity has a stronger association with NTD risk. Primiparous mothers are at increased risk and there is a modest risk in mothers of parity three or more [15].However there is no association between the risk of NTD and infertility treatment [16].

Previous Pregnancy Wastage

Previous spontaneous abortions increase the risk of subsequent development of NTD [17]. Short interval between pregnancies also contributes to occurrence of NTD [18].

Multiple Gestations

Association between NTD and multiple gestations is complex. Twinning itself has been associated with a higher risk for NTD [19].

Obesity

Increase in Maternal weight and elevated body mass index have been associated with increased risk for NTD. When the Body mass index is more than 29, the risk for NTD doubles [20].

Maternal illness

Maternal health affects the fetus. In case of NTD also maternal illnesses, maternal diabetes, maternal hyperthermia have been associated with increased risk for NTD. First trimester of pregnancy is very important. A flu or cold syndrome, febrile illness or Hot-tub use in the first trimester has been associated with a 2-3 fold higher risk for occurrence of NTD [21]. The combination of hottub use, febrile illness and sauna use increases the risk of NTD six fold.

Parental Socioeconomic Status

The socio-economic status of the family determines the nutrition and wellbeing of the family. Lower socio-economic status is associated with higher incidence of NTD [22].

Parental Occupational Exposures

Some parental occupations have increased risk for NTD. For example increased risk of NTD is associated with both paternal and maternal occupations like welding, transport, painting, cleaning, healthcare occupations and agriculture [23].

Dietary Factors and Other Exposures

Proper diet during pregnancy is very important for a healthy baby. Excessive intake of Tea during the first trimester has a twofold increased risk of NTD [24]. Excess vitamin A, Lead exposure, Zinc deficiency and high levels of organic matter in drinking water are associated with higher NTD occurrence [25]. Cigarette smoking causes elevations of homocysteine levels and increased risk of NTD [26].

Recurrence of NTD

Recurrence rate of NTD triples with each subsequent pregnancy after the first affected pregnancy. The recurrence risk of NTD after one affected pregnancy is around 4%, whereas it is 11.1% after two affected pregnancies and about 28.6% after three affected pregnancies [15].

Family Recurrence Risks

Consanguinity increases the occurrence of many diseases and genetic disorders. For first-degree relatives of affected individuals the risk of NTD is approximately 1 in 30. For second-degree relatives, the risk is approximately 1 in 220 [27].

Folate and NTD

Normally during protein metabolism, amino acids like methionine are released. Methionine is converted to a toxic metabolite. Remethylation of homocysteine to methionine is catalyzed by methionine synthase enzyme which requires vitamin B12 as a cofactor and 5-Methyl-tetra-hydro-folate (5-MTHF) as methyl donor. Hence folate deficiency can lead to accumulation of toxic homocysteine and thereby leads to defects like NTD.

Genetics and NTD

Genetic polymorphism of MTHFR – (Methyl-tetra-hydro-folate reductase) gene is the important cause of hyperhomocysteinemia and/or lack of methionine. MTHFR: c.677C 1 T mutation reduces activity of MTHFR enzyme which causes decreased 5-MTHF production [28]. Since 5-MTHFis the methyl donor for remethylation of homocysteine to methionine, its deficiency leads to increased homocysteine level and decreased methionine levels [29]. These cause delay in the neural tube closure and NTD.

Prevention of NTD

NTD are defects that occur in early human development. Hence prevention of NTD revolves mainly in the antenatal period. Most popular strategy is folic acid supplementation for women of childbearing age. The following are some of the strategies for prevention of NTD

Consumption of Folate-Rich Diet

About 3.5 fold increase in daily folate intake (0.16–0.20 mg/ day) is required prior to conception. Moreover Cooking reduces some part of dietary folate. Hence folate rich diet is important for NTD prevention but cannot alone neutralize genetic predisposition [30].

Periconceptional Folate Supplementation

Since dietary supplementation is difficult, all women of childbearing age should take 400 mcg of folic acid daily atleast three months prior to anticipate pregnancy. Those with previous child with NTD should increase dose to 4.0 mg daily [31]. If maternal intake of folic acid can be increased around the time of conception, the risk of the occurrence of NTD may be reduced by 60–70% [7].

Multivitamin Supplementation

Folic acid supplementation can reduce the prevalence of NTD by 70%. However there are some NTD which occur independent of folate levels. They occur due to defects in folate-homocysteine metabolism for homocysteine detoxication due to deficiency of cofactors like vitamins B12, B2 and B6. Hence folate and Vitamin B12, B2 and B6 containing multivitamins are more effective in prevention of NTD [32].

6S- 5-MTHF

6S-5-MTHF is a nature-identical folate .Thus inspite of being a synthetic product, it is equivalent to the natural form [33].

Food Fortification

Since majority of pregnancies are unplanned, food fortification is the most practical means of folate supplementation. Food fortification with folic acid of cereals about 0.14 mg/100 g adds only 0.1 mg folic acid to daily folate intake, however there was around 26% decreased in total (birth + fetal) prevalence of NTD [34].

Combination of Oral Contraceptives and Folate

There is now a FDA approved drug combining drospirenone and ethinyl estradiol as contraceptive components and levomefolate calcium as folate component [35].

Managing Pre-Existing Health Conditions

Since maternal illness and premorbid conditions are a risk factor for occurence of NTD, preventing diabetes by monitoring blood sugar levels and preventing Obesity can help in prevention of NTD. Expectant mothers must be protected against infections, fever should be treated promptly and any environmental exposures that increase core body temperature should be limited as hyperthermia is a risk factor for occurrence of NTD. Medications like antihistamines, sulphonamides, anticonvulsants, carbamazepine, valproate, methotrexate and aminopterin should be avoided during pregnancy [36]. With recent advances in genetics and diagnostic tools, genetic and syndromic causes of NTD can be prevented utilizing preimplantation genetic diagnosis (PGD) or early detection by chorionic villous sampling and high resolution early antenatal ultrasound scan.

CONCLUSION

Neural tube defect is a defect of early human development. Understanding the etiological factors and contributing epidemiological factors will help in reducing the prevalence of NTD. Inspite of advances in diagnosis, even though defects in fetus can be diagnosed early and termination can be done, preventing NTD by judicious folate supplementation

and avoiding risk factors can really reduce prevalence of NTD. As always prevention is better than cure.

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