Editorial

Neural tube defects: A need for population-based prevention program

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Neural tube defect (NTD) is one of the commonest malformations with worldwide prevalence of 1-3/1000 live births. They are caused by failure of neural tube to close during neurulation in 21-28 embryonic days. The most common types of NTD are anencephaly and spina bifida, which are caused by failure of closure of cranial pore and spinal part of neural tube, respectively. Another classification of spina bifida may be open or closed depending upon whether the spinal defect is covered by skin or not.[1]

The phenotypic spectrum of NTDs are widely varied, which can range from lethal conditions like anencephaly and craniospinal rachiasis to closed spina bifida with minimal or no symptoms. On the other hand, open spina bifida (meningocele or meningomyelocele) may have varied outcome depending upon the extent of lesion, associated Arnold-Chiari II malformation and ventriculomegaly. Though surgery can lead to normal outcome in some, majority of the operated cases of meningomyelocele have residual neurological deficit of lower limbs and bladder bowel involvement with or without cognitive involvement. Meningocele, meningomyelocele, lipomeningocele are the names that are given on the basis of content of herniated sac through spinal defect and histopathological findings.[2] Majority of NTDs are isolated/non-syndromic and are not associated with other congenital malformations. However in about 10% of the cases, NTD can be a part of genetic syndrome hence may follow Mendelian inheritance. The syndromes associated with neural tube defects include Walker-Warburg syndrome, Jarcho-Levin syndrome, Robert syndrome and Meckel-Gruber syndrome. Rarely, NTD can be associated with chromosomal abnormalities including trisomy 13 and 18, triploidy and other chromosomal rearrangement.[2] Association of these genetic syndromes are important to assess as final outcome and risk of recurrence in these families depends upon the individual syndrome. In syndromes with autosomal recessive inheritance, risk of recurrence in the siblings of affected individual is 25% while isolated NTD follow multifactorial inheritance pattern. Risk of recurrence in the siblings of isolated cases of NTD is 2%-5% after one affected child and 10% after the birth of two affected children.

Various environmental risk factors that have been suggested for isolated NTD are maternal diabetes, maternal intake of anticonvulsant drugs, other drugs with folate antagonist effects (Methotrexate), family history of NTDs, maternal obesity, hyperthermia and lower socioeconomic status.[1] Genetic mechanisms behind neural tube defect are complex and follow multifactorial inheritance governed by interplay of multiple genes and environment factors. Despite a number of studies, exact pathophysiological pathways and cellular mechanisms causing NTD remains unidentified. Various mouse models like loop tail mutants and curly tail mutants have

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provided important insights into the genetic pathways involved in NTD.[3] More than hundred genes have been studied for association with NTD. Periconceptional use of folic acid is known to be associated with definite decrease in prevalence of NTDs by 50%-70%.[4] Folic acid is an essential vitamin that cannot be synthesized by human body and have to be provided by diet only. The efficacy of folic acid in prevention of NTD had prompted studies into genes involved in folic acid pathways. The metabolically active form of folate is 5-methyl tetrahydrofolate (5-THF), which is required for various methyl donation/one carbon reaction, DNA and RNA synthesis, DNA methylation and homocysteine metabolism. Conversion of dietary folate to 5-THF requires activity of multiple enzyme and cofactors including vitamin B12.[5] Each of these enzymes and cofactors has been studied to elucidate the possible association with folate pathways to NTDs. However, the exact mechanism by which consumption of folate reduces the risk of NTD still remains the matter of research even now. Major genes found to be associated are Methylene tetrahydrofolate reductase inhibitor (MTHFR, 677T variant), Methionine synthase (MTR), methionine synthase reductase (MTRR) and Cystathionine synthase. But association studies with occurrence of NTDs are inconsistent with the majority of studies showing no significant association.[3] MTHFR is most extensively studied gene in this context and presence of a thermolabile 677T variant in heterozygous/homozygous state with or without raised serum homocysteine levels confers no or minimal increased risk for the development of NTD. At present, offering the genetic test for this polymorphism is not indicated in clinical settings.[3] With new tools of genome-wide association studies and exome sequencing better insight into genetic etiologies of NTDs are expected.

Since 1990s in various parts of the world, national programs for food fortification by folic acid had started, which had led to significant reduction (20-50%) in births of infants with NTD.[5] The recommended daily dose of folic acid in the females of childbearing age group without prior risk factor for the child with NTD is 400 microgram per day at least 1 month before conception. Females with higher risk of having a child with NTD like maternal diabetes, maternal consumption of anticonvulsant drug, personal or family history of NTD and previous child affected with NTD should take 4 mg of folic acid daily. The same dose of folate should be continued up to 3 months of pregnancy.[6] In India most of the pregnancies are unplanned and most of the pregnant women get themselves registered in an antenatal clinic only after they missed their first period (after 28 days of last menstrual period) when process of primary neurulation is already complete. Ideally all women should start taking folic acid as soon as they stop using any method of contraception. A well-implemented public health program for regular food fortification may further reduce the prevalence of NTDs. These will include various strategies regarding target food for fortification, the optimum and maximum level of fortification. There are few recent reports of other possible consequences of higher blood folate levels, which are not desirable including cancer.[5] These speculations remain unproven as of now and areas under research.

Another approach for identification of the candidate genes in pathogenesis of NTD is animal models, mainly mouse models in which neural tube formation is strikingly similar to humans. Many mutant models like curly tail have been created in an effort to identify the probable candidate genes so that human paralogs can be identified. These are the genes mainly involved in cell signaling pathways (Wnt signaling) and pathways of cellular development and differentiation.[3] Out of the few genes in planar cell, polarity pathway genes have shown some hope in probable association with the development of NTD. Other genes being studied are p53, genes in glucose metabolism pathway, oxidative stress and obesity. However, none of these individual genes have been proven to contribute significantly to the occurrence of NTD.[7] Study on association of NTD with p53 gene polymorphism is published in current issue as well.

The mainstay of diagnosis of NTD remains antenatal ultrasound (USG) done at 18-20 weeks of pregnancy. Severe defects like anencephaly can be picked by USG as early as 11-12 weeks of pregnancy. In the past, screening test like maternal serum alfa-feto protein had been used to identify pregnant women at high risk of having babies with neural tube defect. If the risk was found to be high then they were offered amniocentesis and estimation of alfa-feto protein and/or acetyl

cholinesterase in the amniotic fluid. But in the modern era due to greatly improved resolution of ultrasonographic machines invasive test is only of historical value and detection rate of NTD in second trimester antenatal USG is 90%-95%.[8] Recently described obliterated or diminished intranuchal translucency is now been used as a sensitive ultrasonographic marker for the detection of open neural tube defect in 11-13 weeks of gestational age.[9]

Treatment of NTD is mainly prevention of occurrence and recurrence in the family by universal periconceptional folic acid, control of maternal diabetes and early diagnosis. If severe defect is identified early in the pregnancy, then termination of pregnancy can be offered. If diagnosed late then child can be surgically treated after birth with developmental disabilities of various degrees and overall outcome cannot be predicted. There are few recent reports of fetal surgery in open spina bifida to prevent neurological damage to exposed neural tissues thus reducing the need of shunt replacement and improved motor function after birth but these options are available on research basis only.[10]

To conclude, NTD remains an important health burden for the society in all ethnic and geographical areas. Precise genetic mechanisms remain unidentified even after decades of research studies. Analysis of multiple pathways and their simultaneous interaction in affected individuals or recent advanced molecular techniques like exome sequencing may provide some clues to underlying pathogenesis. Being a very common malformation, population-based preventive method by way of periconceptional folic acid and integrated screening tests need to be implemented nationwide. In India attempts need to be made for providing information to all women of reproductive age group about the use of periconceptional folic acid and it is high time that India considers compulsory food fortification with folate. Pre-existing programs for anemia prevention in adolescent girls and women can be used for NTD prevention program by providing folic acid to them.

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