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IP Indian Journal of Neurosciences

Journal homepage: https://www.ijnonline.org/

Editorial

Neural tube defects: Current status

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ARTICLE INFO

Article history:
Received 08-11-2024
Accepted 19-11-2024
Available online 20-11-2024

1. Introduction

Neural tube defects (NTDs) are the second most common congenital malformations in humans. Although NTD pathogenesis has not yet been fully understood, many risk factors, both genetic and environmental, have been extensively reported. Classically divided in two main sub-groups (open and closed defects) NTDs present extremely variable prognosis mainly depending on the site of the lesion.

Neural Tube Defects (NTDs) arise secondary to abnormal embryonic development of the future central nervous system. The two most common types of NTDs are spina bifida and anencephaly, affecting different levels of the brain and spine, normally reflecting alterations of the embryonic processes that form these structures. Birth defects such as NTDs are relatively uncommon, with a global prevalence among live births of 1 in 1200, and a worldwide prevalence ranging from 1 in 1,000 (in Europe and the Middle East) to 3–5 in 1,000 (in northern China).[1,2]

The central nervous system (brain and spinal cord) is formed in vertebrates during a process known as neurulation. This process occurs in human embryos between days 17 and 28 post-fertilisation. In the previous developmental phase (gastrulation), the ectoderm is formed, which will thicken in response to specific molecular signals released by the underlying notochord, giving rise to the neural plate. This plate of ectodermal cells will form the neural tube by elevating, juxtaposing and fusing along the midline (primary neurulation) of the body axis. In the caudal region, neurulation (secondary) involves cellular condensation and mesenchymal-to-epithelial transition to close the neural tube . In mammals, primary neurulation is a multi-site process and recent evidence suggest that in humans two closure sites are recognisable (one at the prospective cervical region and one over the mesencephalon-rombencephalic boundary. Mammalian neurulation is tightly regulated and energetically highly demanding, involving the formation of an anterior and posterior neuropore. These neuropores or openings will progressively reduce in size until final fusion completes the process of neural tube closure.

Different types of NTDs reflect the site of the interrupted neurulation. For example, craniorachischisis, which affects the brain and spinal cord, results from a failure of the initial closure site resulting in an open brain and spine, while anencephaly arises from abnormalities in the cranial neurulation process, and spina bifida results from incomplete caudal neurulation.[3]

Chromosomal anomalies such as trisomy 13, trisomy 18 and triploidy represent less than 10% of all NTDs cases, while non-syndromic isolated cases represent the vast majority of NTDs, exhibiting a sporadic pattern of occurrence. The prevalence of the different types of

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https://doi.org/10.18231/j.ijn.2024.039

NTDs is not always reported in publications, given the difficulties in data ascertainment following legal pregnancy terminations and spontaneous abortions. The prevalence of NTDs in miscarriage or stillbirths appears higher than in term pregnancies, and the estimated prevalence reflects temporal, regional and ethnic variations. Interestingly, the different prevalence of NTD cases between ethnic groups persists after migration of the racial groups to other geographical areas, indicating a genetic contribution to NTD susceptibility.

In terms of genetic predisposition, women who have had an affected foetus have an empirical recurrence risk of 3% in any subsequent pregnancy, yet this risk only rises to approximately 10% after conceiving a second NTD embryo. This underscores the fact that while genetic factors are important, one cannot ignore the impact of the environment on the development of the NTD phenotype. In twins, the NTDs' concordance rates among monozygotics is reported to be 7.7%, significantly higher than the rate for dizygotic twins (4.4%). gender predisposition has been reported for some types of NTDs, a female excess has been reported for neural tube defects, possibly due to a sex-related genetic or epigenetic effect.

Many factors, both genetic and non-genetic, are involved in the abnormal closure of the neural tube, suggesting that multi-factorial causes lead to the development of NTDs. However, together these genetic and non-genetic factors produce synergistic effects leading to failed neural tube closure and the abnormal embryonic phenotype. This working hypothesis represents the so-called "multifactorial threshold model". Non-genetic factors are maternal diabetes, maternal obesity, maternal hyperthermia, air pollution, drugs(e.g. valproate) and maternal nutritional status.[4]

NTDs have been classically divided into open defects such as craniorachischisis, exencephaly-anencephaly and myelomeningoceles, and closed defects, including encephalocele, meningocele and spina bifida occulta. In general, open defects are characterized by the external protrusion and/or exposure of neural tissue. Closed defects have an epithelial covering (either full or partial skin thickness) without exposure of neural tissue. Biochemically, during pregnancy open defects are detectable due to the high levels of amniotic fluid α-fetoprotein and amniotic fluid acetylcholinesterase, whereas closed defects do not deviate from normal levels of amniotic fluid α-fetoprotein or acetylcholinesterase. Clinically, open defects trend towards having worse functional neurological outcomes in children, compared to closed defects.

Different types of neural tube defects are classified as given below-

2. Craniorachischisis

Craniorachischisis is a defect of neural tube closure that involves both the cranial and spinal portions of the neural tube. It is the most severe expression of an open NTD.[5]

3. Anencephaly

When the primary defect involves failure to close just the cranial portion of the neural tube, the defect is referred to as exencephaly (anencephaly). The degeneration of the cerebral-neural tissues due to the destructive exposure of the brain to the intra-amniotic environment converts the exencephaly defect to anencephaly.

4. Myelomeningocele

In myelomeningocele, the developmental defect involves the failure to close the posterior spinal portion of the neural tube, more frequently the lumbar portion is the region which fails to fuse. In this defect, the meningeal sac herniates through a bony defect of the vertebral arch. In some cases, a clear open defect that involves the spinal cord, but without a protruding meningeal sac, is defined as a myelocele. Therefore, a myelocele is an open defect without the cystic component.[6]

4.1. Encephalocele

Encephalocele is a herniation such as a sac-like protrusion of the brain and/or the meninges through an opening in the skull. According to the type of tissue involved in the herniation, cephaloceles are classified as meningocele (herniation of meninges), encephalomeningocele (herniation of meninges and brain), and encephalomeningocystocele (herniation of meninges, brain and ventricle).

5. Meningocele

Although macroscopically similar to a myeolomeningocele meningocele is a closed spina bifida, comparable to encephalocele, whereby the defect consists in herniation of meninges through the vertebral column. Although the herniation of the meninges through the vertebral arch defect, the spinal cord resides within the spinal canal.[7]

6. Prevention of Neural Tube Defects

NTDs are known as one of the few birth defects in which primary preventive strategies are available and effective. Supplementation with 4 mg folic acid per day resulted in a threefold reduction in NTD recurrence risk. Together

with several non-randomised trials, this data indicate that folic acid supplementation during pregnancy in a dose range of ~0.4–5 mg per day prevents NTD births. The biological and molecular mechanisms of this prevention are yet to be elucidated, despite the large number of studies conducted using animal studies to test various hypotheses mechanistically, as folate plays a pivotal role in numerous cellular reactions, including purines and thymidylate production and SAM synthesis (S-adenosyl-methionine), which is the cellular methyl donor used in methylation reactions for DNA, proteins including histones and lipids. One potential adjunct therapy that has arisen from the mouse studies is the use of inositol, which is effective in preventing a large proportion of spinal NTDs in the Grhl3 (curly tail mutant) mouse, where FA is ineffective. Uniquely among vitamins, inositol deficiency leads to NTDs in rodent embryos. A randomised clinical trial to evaluate inositol for prevention of human NTD recurrence is currently underway in the UK. [8]

6.1. Folate related genes

Most recently, genes that encode enzymes functioning in mitochondrial one-carbon metabolism have also been implicated in NTD aetiology. An intronic polymorphism in MTHFD1L, the gene for mitochondrial 10-formyl-THF synthetase, is associated with increased risk of NTD, while two genes encoding enzymes of the glycine cleavage system, AMT and GLDC, have been found to harbour a number of missense (i.e. amino acid-changing) genomic alterations in NTD cases, but not in unaffected controls. In the case of GLDC, these variants diminish enzyme activity indicating a functional effect on folate metabolism. Each of these enzymes markedly affects flux of formate from the mitochondrion into the cytoplasm, which accounts for approximately 75% of one-carbon units entering folate metabolism. At the molecular level, convergent extension cell movements are dependent on non-canonical Wnt signalling: the planar cell polarity (PCP) pathway, which signals via frizzled membrane receptors and cytoplasmic dishevelled, but does not involve downstream stabilisation of beta-catenin. Indications of a possible involvement of the PCP pathway in human NTDs came from the discovery of PCP gene involvement underlying severe NTDs in several mouse mutants. Mutations in the trans-membrane proteins Vangl2, Celsr1, Ptk7 and Fzd3/6 (double mutant), and the cytoplasmic proteins Dvl1/2/3 and Scrib, all result in craniorachischisis, a severe NTD. [9]

7. Surgical Management of Neural Tube Defects

Neural tube defects are closed by standard multilayer technique under general anaesthesia and antibiotic covering. Microscope and neurological monitoring are used intra-operatively. Myelomeningocele repair should be done within the first 72 hours of birth. Cardiopulmonary and genitourinary system should be evaluated. Cranial ultrasonography should be done to evaluate size of ventricle. Goals of meningomyelocele repair are-protecting functional spinal cord tissue, minimize loss of cerebrospinal fluid and to decrease the risk of meningitis. The surgical goal is to free the neural placode from epidermis circumferentially. We should preserve abnormal vascular supply to the neural placode. Associated congenital lesions like dermoid lipoma neuroenteric cysts should be managed. To reform neural placode into a tube, pia is closed. For the skin defect closure we should use skin flaps. [10]

8. Recent Advancements

In utero repair of neural tube defects have significantly improved outcome related to hydrocephalous. In utero repair techniques include, open in utero repair, fetoscopic repair and endoscopic repair. Though these closure techniques improved outcome, they are technically demanding and widespread use is limited due to resource constraints and ethical issues.

9. Conflict of Interest

None.

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Cite this article: Singh DK, Yadav K, Singh N. Neural tube defects: Current status. *IP Indian J Neurosci* 2024;10(4):178-181.