Review Article

Neural tube defects: Different types and brief review of neurulation process and its clinical implication

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Abstract

Neural Tube Defects are the most typical congenital malformations, with almost 300,000 cases annually worldwide. The incidence varies amongst geographical ranges from 0.2 to up to 11 per 1000 live births. In India, incidence is reportedly higher in north than south and can be attributable to diet and genetic variances. Etiology is multifactorial. Severe forms of whitethorn are allied with syndromes. Primary neurulation and secondary neurulation are the most crucial steps in the formation and closure of the neural tube; any interruption can lead to mild to severe NTDs depending on the level of insult during embryogenesis. Various molecular and cellular events take place simultaneously for neural tube bending and closure of the neural tube. Neurological deficit in the newborn is contingent on the level of defect and severity of the structures affected. Survival of the newborn also depends on the severity of the lesion. Folic acid supplementation in all prospective mothers, preferably 4 weeks before conception and at least 12 weeks after conception, can prevent NTDs in folic responsive groups. But there is a significant number of other causes leading to neural tube defects apart from folic acid. Hydrocephalus is the commonest abnormality allied with NTDs in syndromic cases. **Conclusion:** NTDs are a frequent cause of stillbirths, infant mortality, and palsies in children. There are various reasons for NTDs, but the process of neurulation points towards some factors of NTC, which can be taken care of to lessen the burden of NTDs.

Keywords: Congenital malformations, neural tube defects, spina bifida aperta, spina bifida occulta

Introduction

Congenital deformities are the primary causes of infant mortality and morbidity in developed countries. The in-utero deaths caused by congenital anomalies sum up around 20% as therapeutic abortions or stillbirths.[1] Neural tube defects (NTDs) are affecting approximately 1 in every 1000 pregnancies globally and are the second most typical group of congenital deformities after congenital heart defects.[2,3] All congenital malformations of the central nervous system that arise during embryo development due to incomplete neural tube closure are grouped as neural tube defects.[3] Chromosomal aberrations linked with NTDs are 0.66–5.56% of anencephaly, 4.38–17.31% of spinal bifida, and 2.08–12.29% encephaloceles. Trisomy 13, trisomy 18 and triploidy are the most common chromosomal aberrations allied with NTDs. Spina bifida is the major NTD associated with chromosomal anomalies.[4] The infrequent types of NTDs include limb–body wall complex, amniotic band syndrome, cloacal exstrophy or OEIS complex, and other types of spinal abnormalities.[5] The spina bifida and anencephaly are the two

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commonest severely disabling types of NTDs, poignant at various levels of the spine and brain, generally reflecting alterations of the embryonic processes to facilitate these structures.[6]

NTDs are broadly divided into 'Open' NTDs and 'Closed' NTDs. Open NTDs occur due to disruption of primary neurulation resulting in anencephaly, myelomeningocele (open spina bifida), and craniorachischisis. Below the lesion level, there is a loss of neurological function due to the malformation of the open neural tube. 'Closed' NTDs are usually traceable to disruption of secondary neurulation process where lesions are covered by skin resulting in spina bifida occulta to extreme spinal cord tethering. Closed NTDs are generally asymptomatic and diagnosed incidentally.[7]

Neurulation is a process of formation and closure of the neural tube, leading to the formation of the spinal cord and brain.[6] Neurulation in vertebrates is a multifaceted process regulated at a genetic level by more than 300 genes and entails synchronizing various processes at molecular and cellular levels.[8] The sequence of events occurring during neurulation are as follows:

1. Formation of neural plate: Notochord induces the overlying ectoderm to form neuroectoderm which forms the neural plate. This process occurs under the influence of specific molecular signals released by the underlying notochord known as inductor proteins. The nucleus pulposus of the intervertebral disc is formed from the notochord.
2. Folding of neural plate: This neural plate (ectodermal cells) will results in formation of the neural tube by subsequent steps: elevation, juxtaposition, and fusion in the midline of the axis of body. These steps are known as primary neurulation (16–26 days of gestation). Resulting, the folding of the neural plate occurs into the neural tube, and this tube communicates with an amniotic cavity via two pores at both ends, known as the anterior and posterior neuropores.
3. Closure of anterior neuropores: Firstly, on day 25th (4th week), closure of anterior neuropore occurs, developing into the lamina terminalis. Failure of this process leads to neural tube defects at the cranial end. (e.g., anencephaly).
4. Closure of posterior neuropores: Secondary neurulation (45–53 days of gestation) occurs at the caudal region, which occurs in steps: cellular condensation and epithelial transition to mesenchymal tissue close the neural tube.[6] Successively, on day 27th (4 weeks), closure of posterior neuropore occurs—failure of this process leads to NTDs at the caudal end. (e.g., spinal bifida with myeloschisis).

Neural Tube Closure

The neural tube closure is a multifaceted process, which includes various cellular events like convergent extension, apical constriction, and interkinetic nuclear migration. In addition to this, specific molecular mechanism control via the non-canonical Wnt/planar cell polarity pathway, SHh/BMP signaling, and the transcription factors Grhl2/3, Pax3, Cdx2, and Zic2 are required.[9] Rad9b also has an exclusive and vital role in NTC. Members of the grainy head-like family of transcription factors are crucial at both cranial and spinal levels of the body axis in the closure of the neural tube.[10] Failure of NTC is associated with defects in the overlying bony structures: cranial vault and neural arches.[8,11,12]

Molecular mechanisms controlling CE (convergent extension)

Recent studies have shown that during the early stages of neural tube closure how the function of PCP signals takes place at the molecular level. Like NP bending also provides an indication that how interface between PCP and Wnt signals results in remodeling at cytoskeleton levels.[9] Hence, enough available evidence are there to the point that the PCP-dependent polarized protein localization is crucial for convergent extension, neural plate bending, and neural tube closure.

Bending of the NP (neural plate) and elevation of the neural folds

When the convergent extension is happening, the borders of the NP begin to uplift in the anteroposteriorly and mediolateral axis for forming the tentative CNS. So, these neural folds will ultimately meet in midline dorsally and join to form a neural tube. Similarly, the appearance of elevation of these neural varies between both regions, cranially and caudally.[9,13]

Mechanism of NP bending at cellular level

Cellular mechanism can be explained by following mechanism:

1. Apical constriction: During embryogenesis, there is a widespread decrease in the surface area of cells in the apical region as per the positions of the nucleus in the cells at various phases of differentiation. In mammals, cells of a neural plate are single pseudostratified columnar. Due to interkinetic nuclear migration (IKNM), every cell has a different position of nuclei due to apicobasal polarity, apical during the mitosis phase to basal during the S-phase of division.[14] The shape of the neuroepithelial cell depends on the position of the nucleoli. Although there is an arbitrary distribution of the different phases of the IKNM cycle, most parts of NP S-phased cells are more concentrated at the midline. Due to the basal location of nuclei in this phase of cells, these are wedge-shaped, which leads to local bending directly at MHP overlying the notochord.[15,16] Captivatingly, the lower part of NP does not show any association of NP bending with the position of nuclei in cells, pointing towards some other mechanism working at DLHPs.[15,17]
2. Actinomycin dynamics: There are actin filaments in between neuroepithelial cell junction apically, which can pull the folds in the neural plate by generating a force as a purse-string.[18-20] Signaling pathways Wnt/PCP is shown to play a vital role in the regulation of contractility of actinomycin as well as in cell movements.[21-23] Recent research revealed that ROCK-dependent disassembly of actin filaments is essential for spinal closure. If ROCK-dependent disassembly is inhibited, then NP becomes rigid to closure, and also actomyosin accumulates apically. Jasplakinolide, an inhibitor

of actin turnover, leads to a similar presentation of NTC failure and actomyosin accumulation.

Neural Tube Defects

Depending on whether the NTDs have epithelial coverings over neural structure or not, the NTDs have been broadly divided into two groups:

1. Open defects, like craniorachischisis, exencephaly-anencephaly, and myelomeningoceles, lipomyelomeningocele.
2. Closed defects include encephalocele, split cord malformation, spina bifida occulta, dermal sinus, or dermal nevus.[7,24,25]

Open defects, in general, are chiefly described by the external protrusion or exposure of neural tissue. An epithelial covering illustrates closed defects over the neural tissue entirely or partially (either complete or fractional skin thickness) without exposing neural tissues.[25] Biochemically, open defects are detectable due to the increased levels of α-fetoprotein and acetylcholinesterase in amniotic fluid. In contrast, closed defects do not have such biochemical abnormality. Clinically, closed defects have better neurological outcomes than open defects in children.[26]

Open Neural Tube Defects

a) Cranium bifida: It is a deformity of the skull in which the bony segment of the skull is not formed fully. Such a type of defect is most common in the occipital region of the skull.

Anencephaly [Figure 1.1] is a type of upper NTDs (cranial anomaly) in which cranial neuropore doesn't close during neural tube closure in the fourth week of embryogenesis. This type of anomaly leads to failure in the development of the brain, lamina terminalis, and bony cranium. These are not compatible with survival after birth. Usually, these fetuses are stillborn, or if they are live-born, they can sustain for a few hours or days. Fortunately, these defects can be diagnosed antenatally by ultrasonography so that abortion can be done. Human anencephaly has been divided into two types: meroacrania (in which mainly rostral brain is affected) and holoacrania (in which posterior brain and skull are affected).[27-29] Rarely, anencephaly and spinal bifida may coexist, termed as craniorachischisis (a most severe type of NTDs) [Figure 1.2]. The estimated incidence of anencephaly of 3 pregnancies per 10,000 births per year has been reported by CDC.[27]

Cranium bifida with meningocele [Figure 1.3]: this anomaly results due to protrusion of CSF-filled sac of meninges through cranial vault.

Cranium Bifida with meningoencephalocele [Figures 1.4 and 1.5] this anomaly results from protrusion of brain tissue covered with meninges via cranial vault. It is usually diagnosed early in postnatal period. The outcome is poor, with 75% infant mortality, or severe mental retardation if they survive.

Cranium bifida with meningohydroencep halocele [Figures 1.6a and 1.5 b]: this anomaly results due to protrusion

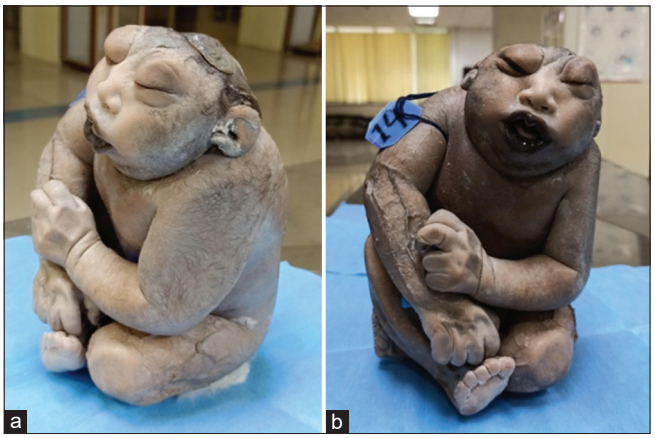

Figure 1.1: The photograph in Figure 1.1 (a and b) shows a newborn infant with anencephaly, showing folded ears, bulging eyes, and protruded tongue

Figure 1.2: Illustration showing craniorachischisis with the extension of the defect into the cervical region

Figure 1.3: The photograph in Figure 1.3 shows a fetus with an occipital meningocele

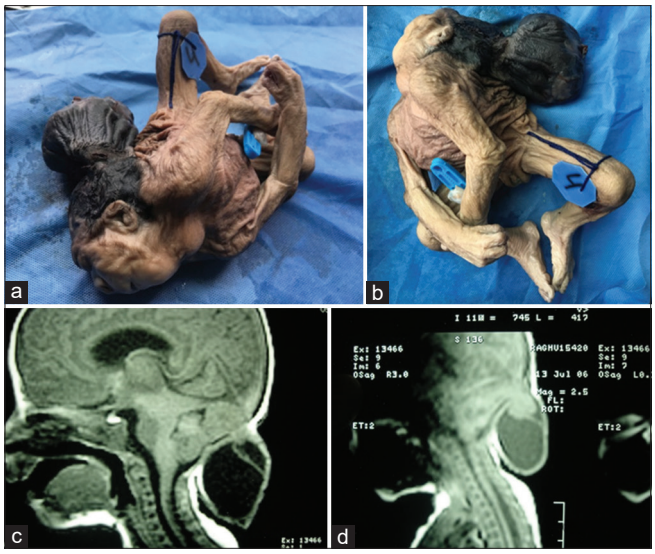

Figure 1.4: The photograph in Figure 1.4 shows (a and b) newborn infant with an occipital meningoencephalocele (c and d) MRI showing occipital meningoencephalocele

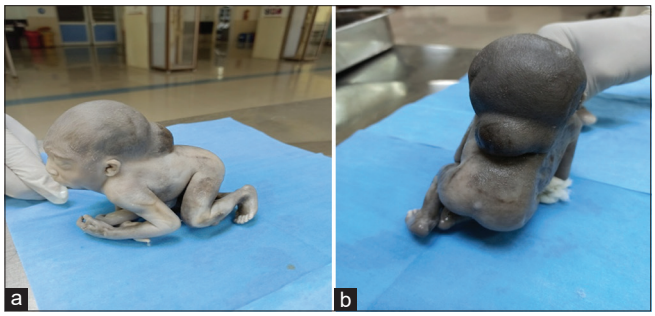

Figure 1.6: The photograph in Figure 1.6 (a and b) shows a newborn infant with cranium bifida with meningohydroencephalocele

of part of the brain besides the ventricular system covered with meninges through cranial vault.

b) Spina bifida [Figures 1.7 and 1.8]: This anomaly occurs when cartilaginous arches of vertebral bodies do not fuse completely. The most common site of this type of defect is in the lumbosacral.

Variations of Spina Bifida

Spina bifida occulta [Figure 1.9] -"mildest type of spina bifida," which is seen as a tuft of hair, a small dimple, vascular nevus, and dermal sinus in the lumbosacral region. It happens in the L5 or S1 vertebra in approximately 10% of population. An overlying lipoma, dermal sinus, or other birthmarks may also occur. It connotes the presence of underlying malformation, in most cases, which may be split cord malformations or lipoma, or tethered cord syndrome.[30]

Spina bifida cystica: This abnormality results due to the protrusion of the cyst-like sac of meninges or spinal cord through defects in the vertebral arches. It is a severe type of spina

Figure 1.5: The photograph in Figure 1.5 shows a newborn infant with frontonasal encephalocele

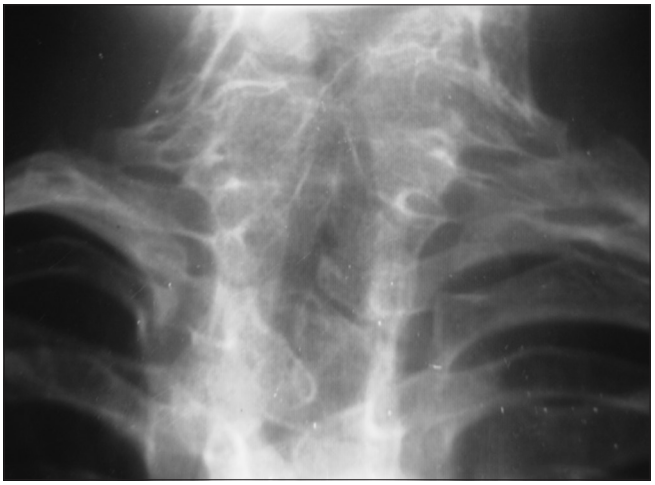

Figure 1.7: X-ray showing deficient fusion of spinal arches in the cervical region. Defect is apparent

bifida, as there is direct exposure of neural tissue to amniotic fluid leading to neural malformation.[30]

Spina bifida with meningocele occurs when the cyst contains meninges and CSF (cerebrospinal fluid) via a defect in the vertebral column, the defect is referred to as a spina bifida with meningocele. The spinal cord and spinal roots remain in their normal position. This sac principally contains CSF.

Spina bifida with meningomyelocele [Figures 1.10 and 1.11]-occurs when the cysts containing the spinal cord or nerve roots protrude across the defect in the vertebral arch. Meningomyelocele is a more common and more severe malformation than meningocele. It shows varying degrees of neurologic deficit, contingent on the position and extent of the deformity as neural tissue is directly exposed to the amniotic fluid.

Other CNS anomalies associated with myelomeningocele include cerebral ventricle abnormalities in >90%, syringomyelia (88%),

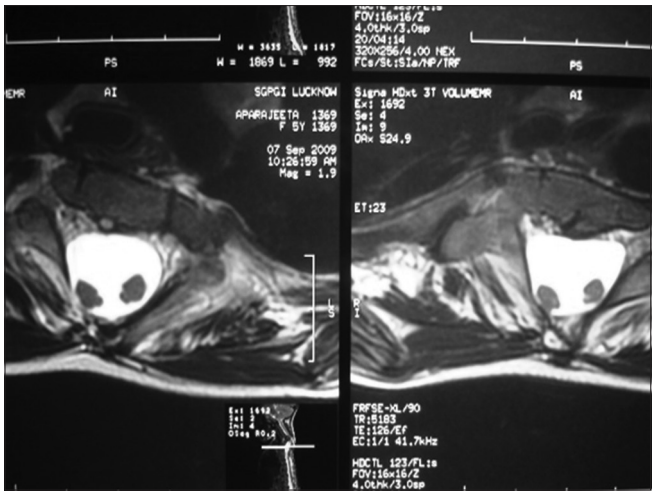

Figure 1.8: Split cord syndrome because of split cord (diastematomyelia, two cords are seen)

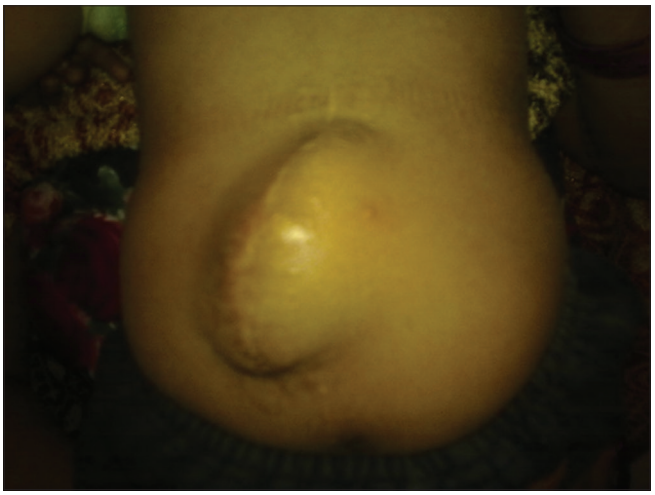

Figure 1.9: Showing spina bifida occulta with lipomyelomeningocele

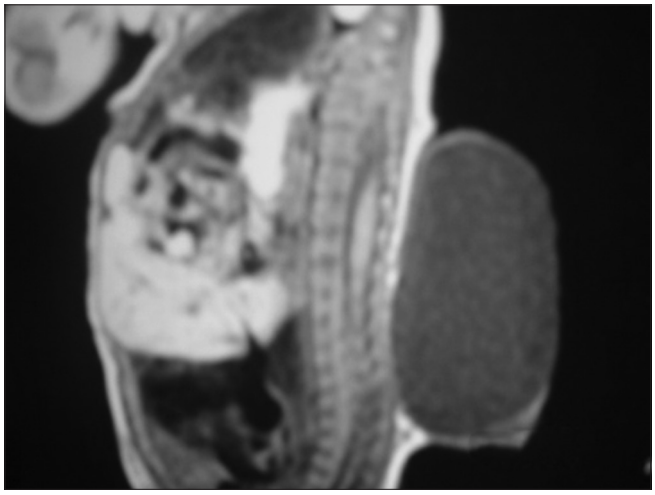

Figure 1.10: Spina bifida with lumbosacral meningomyelocele

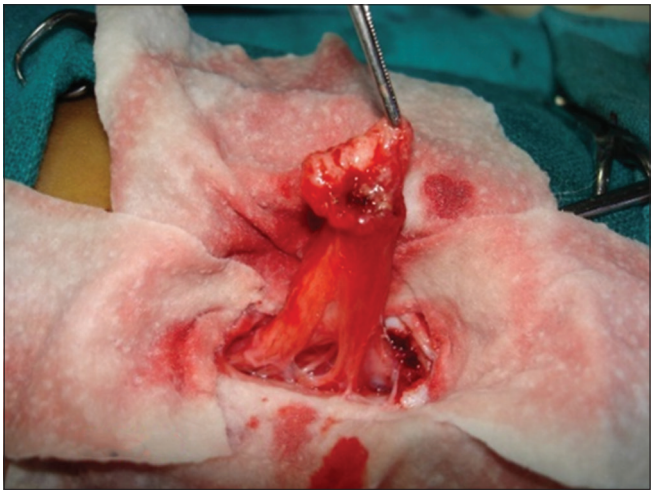

Figure 1.11: Spina bifida with meningomyelocele with adhered nerve roots and placode (intraoperative pic)

brainstem malformations (75%), cerebral heterotopias (40%), polymicrogyria (15–30%), Chiari malformations (80–9%), and agenesis of the corpus callosum (12%).[31]

There is usually a corresponding dermatomal loss of sensation along with partial or complete paralysis of skeletal muscle. Bladder or anal sphincter paralysis is familiar with lumbosacral meningomyelocele, which can lead to saddle anesthesia too. The defect causes incontinence of urine and feces, paralysis of legs, anesthesia of skin, and deformities of the hips, knees, and feet. Few cases of meningomyelocele are associated craniolacunia, which is non-ossified regions at inner surfaces of skull.[32] More than 90% of cases have associated hydrocephalus due to the coexistence of an Arnold-Chiari malformation. Most patients require surgical diversion of CSF to avoid high intracranial pressure-related complications.

Meningomyelocele may be associated with split cord malformation (SCM), found to be 41% in a study by Kumar *et al*.[33] Prognosis is also poorer than pure SCM. Such patients warrant MRI scanning of the skull and spine for identifying SCM and hydrocephalus both. The term "Spina Bifida Multiplex" has been coined where tethering of cord is also present at more than two sites along with MMC.

According to the CDC, Spina bifida aperta is the commonest type in humans, with an average incidence of 1.8 per 10,000 live births in the United States.

Children born with a meningomyelocele need multiple surgeries and invasive procedures. Surgery is required within 24 to 48 h after birth to repair an open defect to lessen the menace of infection. Without this surgery, only 20% of these infants survive to age two years.[30] Most affected individuals have an associated deformity at the base of the brain, the Arnold-Chiari type II malformation, which probably accounts for the well-established hydrocephalus present at birth in approximately 80% of cases.[34]

Spina bifida with rachischisis [Figure 1.12] It is the utmost severe type of spinal bifida, which presents as an open neural tube defect at the back. It results when the posterior neuropore of the neural

tube fails to close in the fourth week of embryogenesis. It usually presents in the lumbosacral region. This defect generally leads to permanent paralysis or weakness of the lower limbs. In this defect, the spinal cord in the affected area is open because the neural folds failed to fuse, so there is a mass of nervous tissue at the defect level. Myeloschisis usually results in permanent paralysis or weakness of the lower limbs. The finding that C677T homozygosity in the mother but not in the father is allied with an augmented risk for spina bifida in the infant suggests that the mother's genotype might independently contribute to her child's risk of disease.[35,36]

Hydrocephalus[Figures 1.13, 1.14 and 1.15]

Hydrocephalus and Chiari malformation was seen to be associated with 58% and 50.6% in patients with spinal dysraphism.[33] The defect lies in developing the posterior fossa of the brain and the brain stem, which leads to the slogging of brain stem and cerebellar tonsils downward. CSF circulation is blocked, which leads to obstructive hydrocephalus.[24,37] [Figure 1.14]. Tethering of cord where open neural tube is tethered to adjacent skin and surrounding structures can also be associated[38] [Figure 1.15]. It leads to pulling off neural tube downward, resulting in the brain stem and tonsillar descend.

Factors for Prevention of Neural Tube Defects

Approximately 75% prevention of neural tube defects is possible prenatally if the prospective mothers can be provided with folic acid supplementation.[39,40] A daily dose of 0.4 mg of folic acid should be given to all those women. A dose of 4 mg of folic acid per day should be started in all high-risk pregnancies one month prior to conception and should be continued until the 12th week of conception.[24] Folate deficiency causes a substantial rise in cranial NTDs among Sp2H embryos, showing a gene-environment interaction.[41] Reduced Serum Folate, SerumVitB12, and elevated levels of serum homocysteine have been observed. The estimated level of red blood cell folate of 900–1000 nmol/L in the mother is safe for decreased development of NTDs.[24] Supply of inositol is also requisite for cranial neural tube closure.[42] Micronutrients like zinc are essential for neural tube closure so that zinc deficiency can lead

Figure 1.12: The photograph in Figure 1.12-shows a newborn infant with rachischisis

Figure 1.13: The photograph in Figure 1.13 shows a newborn infant with hydrocephalus

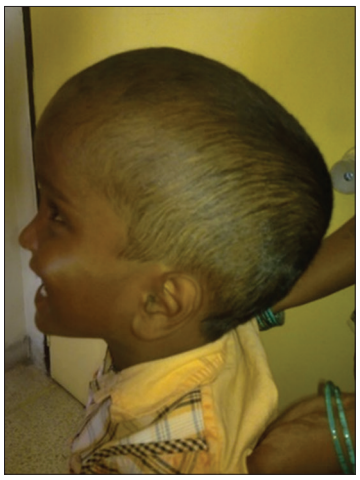

Figure 1.14: The photograph in Figure 1.14 shows a head enlargement in hydrocephalus in a child

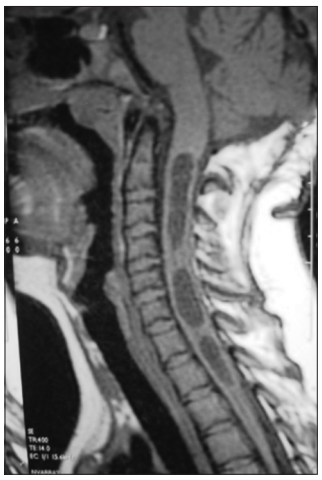

Figure 1.15: The photograph in Figure 1.15 shows an MRI film with Arnold Chiari Malformation with cervicodorsal syrinx

to neural tube defects. It disrupts neural tube closure through decreased p53 ubiquitylation, increased p53 stabilization, and excess apoptosis.[43] Recently, obesity has also been found to be associated with increased incidence of NTDs.[44] Even, all physicians should be aware of missing possible NTDs in obese patients due to inability to detect it precisely in ultrasonography. Primary care physicians can help in counselling of all prosective mothers for weight reduction and folic acid supplementation before conception. A parent with already having an NTD baby, should also receive pre-conception counselling during next pregnancy. These parents may be referred to specialist for the need of genetic testing.[45]

Although the incidence of spina bifida is thought to be multifactorial, advances in genetic and molecular biology studies have pointed to polymorphisms in C677T of the MTHFR gene leading to reduced activity of 5,10 Methyl TetraHydrofolate reductase (MTHFR) enzyme.

Conclusions

Neural tube defects are owing to persistent non-closure or reopening after the closure of the neural tube. Neural tube forms due to the fusion of neural plate edge called neural folds by around 25 and 27 days of IU life for cranial/upper and caudal/lower ends, respectively. Failure of primary neurulation leads to 'Open' NTDs as comprehended in anencephaly, myelomeningocele (open spina bifida), and craniorachischisis. There is a loss or impairment of functional neurological function below the lesion level due to the malformation of persistently opened neural tissues in utero. Failure of secondary neurulation leads to 'Closed' NTDs, covered with overlying epithelium, resulting in either asymptomatic spina bifida occulta or severe spinal cord tethering. NTDs have various causes, where genetic besides environmental factors interact to conclude the individual risk of malformation. The embryonic development of NTDs is multifaceted, with various cellular and molecular mechanisms functioning at different levels of the body axis. Folate deficiency, anti-folate, anti-epileptic drugs, maternal obesity or extremes of maternal age are perceived to be associated with NTDs. Folate supplementation before conception and continuing so throughout pregnancy is beneficial in preventing NTDs by 70%. Rest is conferred to as the folate-resistant NTDs. Pre-conception maintenance of adequate BMI should also be suggested. Surgical correction is necessary for spinal NTDs (spina bifida, myelomeningocele) to prevent neurological handicaps.

Key Messages

- NTDs are preventable cause of neurological handicap in most of the cases.
- Reproductive age females should be screened and treated for anemia, micronutrient deficiencies and obesity.
- Folic acid supplementation should be given to all prospective and antenatal mothers.
- Pre-conception counselling should be offered to all high-risk pregnancies.

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Conflicts of interest

There are no conflicts of interest.

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