

# Neural Tube Defects: A Comprehensive Review

K Varinder<sup>1</sup>, S Jyoti<sup>2</sup>

<sup>1</sup>Lecturer, Obstetrics and Gynaecology Nursing, Maharishi Markandeshwar University, Mullana, Ambala

<sup>2</sup>Lecturer, Child Health Nursing, Maharishi Markandeshwar University, Mullana, Ambala

**Abstract:** Neural tube defects (NTDs) are common complex congenital malformations of the central nervous system resulting from failure of the neural tube closure. Early findings and management provides the best result. The neural tube defects result in physical and intellectual disability to paralysis, urinary and bowel control problems, lack of consciousness, and in many cases death or experience serious disability. Different diagnostics tests for Neural tube defects were invented to treat with this condition. Prenatal ultrasound imaging, fetal magnetic resonance imaging, maternal serum alpha fetoprotein and amniocentesis help to identify the neural tube defects. Surgical treatments usually help to correct abnormalities in the skull and face. A review contains the current practicing for identifying the NTDs.

**Keywords:** NTDs, Neurulation, Congenital Malformation, Folic acid.

## 1. Introduction

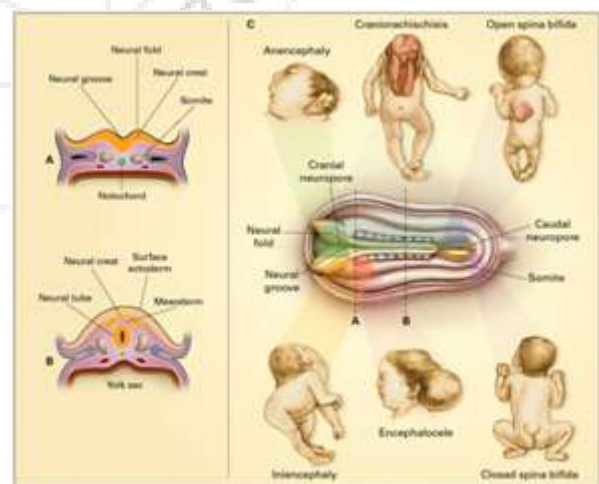
Neural tube defects (NTDs) are abnormalities that can occur in the brain, spine, or spinal column of a developing embryo and are present at birth. Very early in the development of an embryo, certain cells form a tube that will later become the spinal cord, the brain, and the nearby structures that protect them, including the spinal column or vertebra. As development progresses, the top of the tube becomes the brain and the remainder becomes the spinal cord. A neural tube defect occurs when this tube does not close completely somewhere along its length, resulting in a hole in the spinal column or another type of defect. These defects occur between 17 and 30 days after conception i.e. 4-6 weeks after the first day of a woman's last day of menstrual cycle, before a woman knows she is pregnant. They constitute a major cause of still birth, neonatal and infant death or significant lifelong handicaps. These are the debilitating structural birth defect, among newborn affecting 1 per 1000 births in all over the world population. Failure of the neural folds to fuse in the midline and form the neural tube will lead to secondary abnormal development of the mesoderm responsible for forming the skeletal and muscular structures that cover the underlying neural structures. [1] The human nervous system originates from the primitive ectoderm that also develops into the epidermis. The ectoderm, endoderm, and mesoderm form the three primary germ layers that are developed by the 3rd week. The endoderm, particularly the notochordal plate and the intraembryonic mesoderm, induces the overlying ectoderm to develop the neural plate in the 3rd wk of development. Failure of normal induction is responsible for most of the NTDs, as well as disorders of prosencephalic development. Neural tube defects (NTDs) account for the largest proportion of congenital anomalies of the CNS and result from failure of the neural tube to close spontaneously between the 3rd and 4th week of in utero development. [2]

## 2. Embryology

**Neurulation:** The neural tube development process is called neurulation and it is the fundamental embryonic activity. During foetal development process, neural tube is the

leading precursor for brain and spinal cord. The phenomena behind the building of neural tube is an extremely complex procedure where cell changes shape migrates, differentiates and form a hollow tube from a flat sheet of epithelial cells called neural plate. When the neurulation process fails at any stage, neural tube defects occur. The etiology behind NTDs is very complex and involves both genetic and environmental factors. Environmental factors that increases the possibility of NTDs includes geography, epidemic trends, socioeconomic factors, maternal age and maternal food habits, maternal disease conditions like diabetes, thyroid disorder and obesity and drug exposure mainly antiepileptic drugs.

- **Primary neurulation** is associated with open NTDs including Anencephaly, open Spina bifida and Craniorachischisis.
- **Secondary neurulation** is associated with closed NTDs like spina bifida occulta. [3]



**Figure 1:** Features of Neural-Tube Development and Neural-Tube Defects

Panel A shows a cross section of the rostral end of the embryo at approximately three weeks after conception, showing the neural groove in the process of closing, overlying the notochord. The neural folds are the rising margins of the neural tube, topped by the neural crest, and demarcate the neural groove centrally.

Volume 7 Issue 4, April 2018

[www.ijsr.net](http://www.ijsr.net)

Licensed Under Creative Commons Attribution CC BY

Panel B shows a cross section of the middle portion of the embryo after the neural tube has closed. The neural tube, which will ultimately develop into the spinal cord, is now covered by surface ectoderm (later, the skin). The intervening mesoderm will form the bony spine. The notochord is regressing.

Panel C shows the developmental and clinical features of the main types of neural-tube defects. The diagram in the center is a dorsal view of a developing embryo, showing a neural tube that is closed in the center but still open at the cranial and caudal ends. The dotted lines marked A and B refer to the cross sections shown in Panels A and B. Shaded bars point to the region of the neural tube relevant to each defect. [4]

In anencephaly, the absence of the brain and calvaria can be total or partial. Craniorachischisis is characterized by anencephaly accompanied by a contiguous bony defect of the spine and exposure of neural tissue. In open spina bifida, a bony defect of the posterior vertebral arches is accompanied by herniation of neural tissue and meninges and is not covered by skin. In anencephaly, dysgraphia in the occipital region is accompanied by severe retro flexion of the neck and trunk. In encephalocele, the brain and meninges herniate through a defect in the calvaria. In closed spina bifida, unlike open spina bifida, the bony defect of the posterior vertebral arches, the herniated meninges, and neural tissue are covered by skin.

Primary neurulation has four distinct anatomical closure sites, which forms multiple site neural tube fusion.

- 1) First closure is at hindbrain/ cervical spine, and progresses both rostrally and caudally.
- 2) Caudally it proceeds to the end of the neural groove until the caudal neuropore.
- 3) Second closure is at forebrain / midbrain boundary extends both rostrally and caudally and completes the roof of telencephalon and metencephalon.
- 4) Third closure site is at the end of forebrain and closes the rostral end of the neural groove closing the cranial neuropore.
- 5) The fourth site appears at the caudal end of the neural groove and extends rostrally to meet the fusion extending back from site one. Phenotype of NTD will vary depending on the involvement of site of fusion. [5]

### 3. Classification

Neural tube defects (NTDs) refer to the inability of the neural tube to close properly, resulting defects of the brain and spinal cord. When the neural tube fails to close properly, this can result in two different types of defects – spina bifida and anencephaly

Neural tube defects (NTDs) are classified as ‘Open’ NTDs, Closed NTDs and Herniation NTDs.

**Open NTDs** result from failure of primary neurulation as seen in anencephaly, myelomeningocele (open spina bifida) and craniorachischisis.

‘Closed’ NTDs are skin-covered disorders of spinal cord structure, ranging from asymptomatic spina bifida occulta to severe spinal cord tethering.

‘Herniation’ NTDs are those in which meninges, with or without brain or spinal cord tissue, become exteriorised through a pathological opening in the skull or vertebral column (e.g. encephalocele or meningocele).

❖ Cranial NTDs	❖ Spinal NTDs
<ul style="list-style-type: none"> <li>• Meningocele</li> <li>• Meningomyelocele</li> <li>• Anencephaly</li> <li>• Encephalocele</li> <li>• Iniencephaly</li> </ul>	<ul style="list-style-type: none"> <li>• Spina bifida cystica</li> <li>• Spina bifida occulta</li> <li>• Myelomeningocele</li> <li>• Meningocele</li> </ul>

The resulting abnormalities of NTDs of the spinal cord may involve the meninges, vertebrae, muscles and skin. When the neural folds remain open, the sclerotome unable to open the neuro epithelium and bifid vertebral column is the secondary result. The spina bifida is a general term affecting the spinal region, consists of two different types. Spina bifida closed and spina bifida open. [6]

#### Spina Bifida

Spina bifida is the most common type of neural tube defect. It occurs when the neural tube does not close completely. An infant born with spina bifida usually has paralysis of the nerves below the affected area of the spine, which can cause lifelong problems with walking and other difficulties. Because bladder and bowel control are controlled by the lowest spinal nerves, bowel and urinary dysfunction are common. Many infants who are born with spina bifida will have normal intelligence, but some will have learning or intellectual disabilities. [21]

#### There are several common types of spina bifida:

Spina bifida occulta is the mildest form, and most experts do not consider it to be a true neural tube defect. There is a small gap in the spine but no opening or sac on the back. The nerves and spinal cord are not damaged, and the defect usually does not cause any disability. Consequently, spina bifida occulta sometimes is called “hidden” spina bifida. [22]

Closed neural tube defect is a malformation of the fat, bone, or membranes. In some persons, it causes few or no symptoms, but other people might experience partial paralysis or other symptoms. In some cases, the only outward sign might be a dimple or tuft of hair on the spine. [23]

**Spina bifida occulta :** In spina bifida occulta (closed) the defect is in the non-fusion of vertebral arches covered by skin and hairs does not involve underlying neural tissue and occurs mainly in lumbosacral region, seen in 10% of people.

#### Spina bifida cystica

Spina bifida cystica is severe type of NTDs where there is a protrusion of nervous tissue through the defect of vertebral arches, covered by meningeal sac. The spina bifida cystica are meningocele or meningomyelocele.

### **Meningocele**

It includes a sac of fluid that protrudes through an opening in the back, but the spinal cord is not involved. Some people will have no symptoms, and some people will have more severe problems. [22]

### **Myelomeningocele**

It is the most severe and also the most common form of spina bifida. In this condition, the bones of the spinal column do not form completely, which causes some of the spinal cord and tissues covering the spinal cord to bulge out of the opening. A person with this condition usually has partial or complete paralysis in the parts of the body below the spinal column abnormality. Bowel and urinary dysfunction are common. Children with myelomeningocele may develop hydrocephalus is excess fluid on the brain. Hydrocephalus can lead to intellectual and learning disabilities. Some infants born with myelomeningocele have severe intellectual disabilities.[22]

### **Anencephaly**

Anencephaly is a more severe, but less common, type of neural tube defect. This condition occurs when the neural tube fails to close at the top. The fetus has little or no brain matter and also may be lacking part of its skull. Infants born with this condition are usually unconscious as well as deaf and blind and unable to feel pain. They may have reflex actions, such as breathing and responding to touch. All infants with anencephaly are stillborn or die soon after birth. [24, 25]

There are three types of anencephaly described:

- 1) Meroanencephaly, where there is rudimentary brain tissue and partial formation of the
- 2) Cranium
- 3) Holoanencephaly, the most common type, in which the brain is completely absent.
- 4) Craniorachischisis, the most severe, where the defect extends beyond the cranium [8]

### **Encephalocele**

Encephalocele another rare type of neural tube defect occurs when the tube fails to close near the brain and there is an opening in the skull. The brain and membranes that cover it can protrude through the skull, forming a sac-like bulge. In some cases, there is only a small opening in the nasal or forehead area that is not noticeable. The infant may have other problems as well, such as hydrocephalus, paralysis of the arms and legs, developmental delays, intellectual disabilities, seizures, vision problems, a small head, facial and skull abnormalities, and uncoordinated movements (ataxia). Despite the various disabilities and developmental effects, some children with this condition have normal intelligence. [26]

### **Iniencephaly**

Iniencephaly another rare but severe type of neural tube defect, is diagnosed when the infant's head is bent severely backward. The spine is exceptionally distorted. Often, the infant lacks a neck, with the skin of the face connected to the chest and the scalp connected to the back. Other abnormalities may exist as well, such as a cleft lip and palate, cardiovascular irregularities, anencephaly, and

malformed intestines. Infants born with this condition usually do not live longer than a few hours. [25]

### **Risk Factors**

- Family history of NTDs
- Certain syndromes and chromosomal disorders.
- Low dietary folic acid.
- Administration of sodium valproate and folic acid antagonists, e.g. some anti-epileptics, trimethoprim.
- Hyperthermia
- Malnutrition
- Low red cell foliate levels
- Chemicals, Radiation and maternal obesity or diabetes
- Genetic determinants (mutations in foliate-responsive or foliate-dependent enzyme pathways) [9]

### **Causes**

Although the precise cause of NTDs remains unknown. Approximately 85 % of NTDs may be the result of a combined influence of environmental and genetic factors, indicating a multifactorial aetiology (Copp and Bernfield 1994). Over the past few decades there has been a worldwide decline in the number of NTD births, due mainly to the introduction of ultrasound screening as part of routine prenatal care, followed by therapeutic termination of pregnancies. The three causes believed to result in neural tube defects are the insufficient intake of folic acid, lifestyle habits and maternal illnesses.

#### **1) Insufficient intake of folic acid in the first trimester of pregnancy**

In the first trimester of pregnancy, organs like the brain, nerves and heart are made from the neural tube. Folic acid helps to promote the production of DNA, which is used to make cells. When there is insufficient intake of folic acid, inability of the maternal body to absorb folic acid, or intake of large amounts of alcohol which blocks the absorption of folic acid, the formation of cells might slow down and increase the risk of a neural tube defect appearing. [10]

#### **2) Lifestyle habits and maternal illnesses**

Expectant mothers who have diabetes, are obese, are taking antiepileptic drugs, have a high fever in the first trimester of pregnancy, are exposed to radiation, or take too much vitamin A are at the risk of having babies with neural tube defects. Neural tube defects can also happen because of genetic defects. [11]

### **Symptoms of Neural Tube Defects**

The symptoms associated with neural tube defects vary widely depending on the type of defect. Symptoms range from physical and intellectual disability to paralysis, urinary and bowel control problems, blindness, deafness, lack of consciousness, and in many cases, death. Most children with neural tube defects die or experience serious disability.

## **4. Diagnostic Evaluation**

Diagnostic evaluation can be done non-invasively and invasively.

### **Non-invasive NTD screening techniques**



- **Ultrasound screening:**

Ultrasound is the non invasive screening choice for the detection of fetal anomalies including NTD's because of its safety, cost efficiency and detection sensitivity. The current generation of ultrasound machines allow for highly detailed fetal imaging. The detection of congenital anomalies from 18 to 22 weeks gestation and avoiding the need for a second trimester Maternal serum alpha fetoprotein screening test. It is recommended routinely in all 2<sup>nd</sup> trimester pregnancies and is a more effective screen for open/closed neural tube defects than maternal serum alpha fetoprotein screening. Preliminary research has been reported for 1<sup>st</sup> trimester ultrasound screening for NTD at 11-13 week gestation, assessing structural development variation, such as the absence of intracranial translucency, decreased front maxillary facial angle, partial or complete cisterna magna obliteration and decreased intracranial CSF volume.

Some factors that may affect ultrasound screening for NTDs include gestational age, amniotic fluid volume, position and number of fetus and maternal BMI. Other factors to consider are maternal medication use, maternal diabetic status and personal, pregnancy and family histories. [12]

- **Fetal MRI:**

Fetal MRIs are usually conducted between the late second and early 3<sup>rd</sup> trimesters, between 23 and 32 weeks gestational age allows for optimal imaging of the entire fetal brain and subarachnoid space. The use of fetal MRI primarily for its superior brain imaging capabilities has been expanded to detect non-CNS abnormalities. It mainly emphasizes the importance of correct imaging methods and radiologist interpretation of the MRI requires a thorough knowledge of normal and abnormal fetal anatomy. As the option of fetal NTD surgery becomes available in prenatal medicine, the use of MRI could significantly enhance CNS evaluation. [13]

- **Maternal serum AFP:**

Maternal serum alpha fetoprotein has been used for the detection of open neural tube defects. Its levels rise early in the pregnancy and open neural tube defects screening was optimised to find out normal from abnormal maternal serum alpha fetoprotein results in the 2<sup>nd</sup> trimester between 15 and 18 weeks gestation. Maternal serum alpha fetoprotein levels are measured in multiples of the median, using unaffected pregnancies of the same gestational age as the control value. It helps in interpreting results, it is important to correctly identify the gestational age, number of foetuses, maternal history and maternal weight. First trimester maternal serum alpha fetoprotein levels in normal pregnancies are affected by maternal race, weight, smoking status and method of contraception. [14]

#### **Invasive prenatal diagnostic methods (NTD screening/testing)**

- **Amniocentesis :**

It is mostly performed for the detection of chromosomal aneuploidy or genetic mutation but the amniotic fluid can also be used for the detection of NTDs. The procedure is usually conducted between the 15<sup>th</sup> and 20<sup>th</sup> gestational week. Amniotic fluid can be analysed for fetal karyotype, chromosomal microarray and amniotic fluid alpha fetoprotein and AFAChe levels will assist with the specific type of NTD diagnosis and counselling regarding prognosis.

Risks associated with amniocentesis include spontaneous abortion (estimated procedural risk of 0.5% to 1.0% added to the no-procedure background spontaneous risk of pregnancy loss), post-procedure spotting, infections, rupture of membranes and fetal damage or loss. Amniocentesis for genetic testing is especially important when considering prenatal or postnatal repair of congenital anomalies including open and closed NTDs. Identification of additional fetal genetic factors is important as these factors may interfere with the neonatal outcomes. Although an amniocentesis is an important diagnostic option for high risk pregnancies in the detection of chromosomal abnormalities and open NTDs, amniocentesis should not be used as a method for laboratory NTD (amniotic fluid alpha fetoprotein and AFAChe) screening because of the risks and cost associated with the test. [15]

#### **Complications**

- Infections
- Associated motor and sensory problems, particularly lower limb
- Associated learning disability, developmental delay and hearing impairment
- Bladder and bowel dysfunction [16]

#### **Management**

Multidisciplinary approach - to address any associated physical, developmental, hearing, visual and learning difficulties

- Keep baby warm and the defect covered with sterile saline dressing
- Position baby in prone position to avoid pressure on the defect
- Defect should be closed promptly
- Treatment of hydrocephalus [17]

### **5. Treatments for Neural Tube Defects**

Encephalocele are sometimes treated with surgery. During the surgery, the bulge of tissue is placed back into the skull. Surgery also may help to correct abnormalities in the skull and face.

Treatment for spina bifida depends on the severity of the condition and the presence of complications. For some people, treatment needs may change over time depending on the severity or complications. [19]

- **Open spina bifida.** An infant with myelomeningocele, in which the spinal cord is exposed, can have surgery to close the hole in the back before birth or within the first few days after birth.
- **Hydrocephalus.** If an infant with spina bifida has hydrocephalus (water on the brain), a surgeon can implant a shunt—a small hollow tube to drain fluid—to relieve pressure on the brain. Treating hydrocephalus can prevent problems such as blindness.
- **Tethered spinal cord.** Surgery can separate the spinal cord from surrounding tissue. [19]

- **Paralysis and limitations in mobility.** People with spina bifida use different means to get around, including braces, crutches, walkers, and wheelchairs.
- **Urinary tract infections; lack of bladder and bowel control.** People with myelomeningocele often have nerve damage that prevents the bladder from completely emptying, a condition that can cause urinary tract infections and kidney damage. Health care providers may address this problem by regularly inserting a catheter into the bladder to allow it to empty fully. Medications, injections, and surgery also can help correct incontinence and preserve kidney and bladder function for the long term.

There is no treatment for anencephaly or iniencephaly. [20] These conditions are usually fatal shortly after birth.

### Cure for neural tube defects

There is no cure for neural tube defects, and any nerve damage or loss of function present at birth is usually permanent. However, a variety of treatments can sometimes prevent further damage and help with related conditions. Infants born with anencephaly or iniencephaly are usually stillborn or die soon after birth. Preventing neural tube defects is the best cure.

## 6. Prevention

- Pre-conceptual foliate supplementation
- Food fortification with the addition of foliate

**Folic acid:** Folic acid is a known environmental factor for neural tube defects. Studies have shown that women who take folic acid prior to getting pregnant and through the first trimester reduce the chance of having a child with an NTD by 50-70%. Folic acid does not prevent all cases of NTDs. And, despite taking folic acid in the recommended dose during the recommended time period, it is still possible to have a child with an NTD. Unfortunately, it is not yet understood how folic acid works to decrease the chance of having a child with an NTD.

Prevention of NTDs by pre-conceptual folic acid supplementation has only been studied in women who have had a previous pregnancy or child with an NTD, Spina bifida, encephalocele, or anencephaly. Therefore, there are no specific recommendations for taking high doses of folic acid for women who have an NTD themselves, for other relatives, such as sisters, aunts, or cousins of someone with an NTD, or for the female partners of men who have an NTD. In addition, there are no specific recommendations or studies to determine if folic acid reduces the change of having a child with one of the more rare neural tube defects, such as lipomyelomeningocele, lipoma, etc.

Getting enough folic acid means that the risk of a neural tube defect in the fetus is decreased by 70 to 80%. It's recommended that expectant women actively take in more than 600 µg of folic acid a day. However, as neural tube defects are genetic abnormalities, there are no 100% foolproof ways of actually preventing them from happening. [18]

### Pregnancy Management

Following the detection of an isolated open/closed neural tube defect, families should be offered a choice of 3 obstetrical care management options after diagnostic and genetic testing results are available. Options should include information about prenatal myelomeningocele repair and prognosis (if there are no maternal or fetal contraindications for prenatal repair at 20-26 weeks gestation), postnatal myelomeningocele surgical repair and prognosis, and pregnancy termination with autopsy. Because anencephaly is a lethal condition, pregnancy with anencephaly may be interrupted at any gestational age on the woman's request. For an encephalocele, individualized counselling is recommended because of the possibly unique circumstances of the anomaly.

Caesarean section is the most common method of delivery for a fetus with a myelomeningocele in either vertex or breech presentation, but it is mandatory for breech presentation. Vaginal delivery with intrapartum fetal heart rate monitoring can be considered in selected myelomeningocele vertex presentation cases that have no macrocephaly related to gestational age and a small or no myelomeningocele sac. [19]

## References

- [1] Articles R. Classification, clinical features, and genetics of neural tube defects. 2014; 35(5):5-14.
- [2] Himabindu N, Anjum A, Saritha S, Nagajyothi D, Gayathri P. COMPREHENSIVE STUDY OF NEURAL TUBE DEFECTS IN 1000 FOETUSES WITH CLINICAL SPECTRUM. 2015; 3(4):1-7.
- [3] Sadler TW. Embryology of Neural Tube Development. 2005; 8:2-8.
- [4] Defects B, Disabilities D, Americans M, Office SAR, Framework RS, Defects PB, et al. Neural Tube Defects. 2012;
- [5] Programmes S. Neural tube defects (NTDs): open spina bifida (also called spina bifida cystica). 2013 ;(April):105-9.
- [6] Imbard A, Benoist J, Blom HJ. Neural Tube Defects , Folic Acid and Methylation. 2013;4352-89.
- [7] Rana M, Bisht SS, Rana AJ, Upadhyay J. Neural Tube Defects , Its Etiology: Environmental Exposures and Genes , Possible Risk Factors. 2017;9(2):131-8.
- [8] Code RA. Neuroembryology of Neural Tube Defects Congenital Anomalies of the Spinal Cord.
- [9] Donkelaar HJ, Mullaart RA, Hori A, Shiota K. Neurulation and Neural Tube Defects. 2001;
- [10] Crane JMG, Sun C, Crowley M, Rn I. Newfoundland and Labrador. 2001;(June).
- [11] Edition SI. News about ... NEURAL TUBE DEFECT Research An Introduction to Genetics. 2004;(November 2002):1-8.
- [12] Gagnon A, Bc V, Dodds L, Ns H. Pre-conception Folic Acid and Multivitamin Supplementation for the Primary and Secondary Prevention of Neural Tube Defects and Other Folic Acid-Sensitive Congenital Anomalies. 2015;2015(324).
- [13] Bifida TS. Pregnancy and Nutrition: Folate and Preventing Neural Tube Defects. 2017;(38).

- [14] Clinical S, Guideline P. Prenatal Screening , Diagnosis , and Pregnancy Management of Fetal Neural Tube Defects. 2014;2014(314):927–39.
- [15] Radouani MA, Chahid N, Benmiloud L, Ammari L El, Kharbach A, Rjimati L, et al. Prevalence of Neural Tube Defects : Moroccan Study 2008-2011. 2015;(September):248–55.
- [16] Northrup H, Volcik KA. Spina Bifida and Other Neural Tube Defects. 2000;(December):317–32.
- [17] The New England Journal of Medicine Downloaded from nejm.org on December 29, 2017. For personal use only. No other uses without permission. Copyright © 1992 Massachusetts Medical Society. All rights reserved. 1992;
- [18] Ray JG, Blom HJ. Vitamin B12 insufficiency and the risk of fetal neural tube defects. 2017;12(December):289–95. Registry A, Defects NT. World Birth Defects Day 2016 – Neural Tube Defects. 2016;1–5.
- [19] National Institute for Neurological Disorders and Stroke. (2007). Spina bifida fact sheet. Retrieved July 24, 2012, from [http://www.ninds.nih.gov/disorders/spina\\_bifida/detail\\_spina\\_bifida.htm#203463258](http://www.ninds.nih.gov/disorders/spina_bifida/detail_spina_bifida.htm#203463258) [top]
- [20] Centers for Disease Control and Prevention. (2001). Facts about anencephaly. Retrieved on July 23, 2012, from <http://www.cdc.gov/ncbddd/birthdefects/Anencephaly.html> [top]
- [21] Centers for Disease Control and Prevention. (2011). Spina bifida. Retrieved July 23, 2012, from <http://www.cdc.gov/ncbddd/spinabifida/facts.html> [top]
- [22] National Institute of Neurological Disorders and Stroke. Spina bifida fact sheet. (2012). Retrieved July 23, 2012, from [http://www.ninds.nih.gov/disorders/spina\\_bifida/detail\\_spina\\_bifida.htm](http://www.ninds.nih.gov/disorders/spina_bifida/detail_spina_bifida.htm) [top]
- [23] McComb, J. G., & Chen, T. C. (1996). Closed spinal neural tube defects. In: G. T. Tindall, P. R. Cooper, & D. L. Barrow (Eds.), *The practice of neurosurgery* (pp. 2754–2777). Baltimore: Williams & Wilkins. [top]
- [24] National Institute of Neurological Disorders and Stroke. (2010). NINDS Anencephaly Information Page. Accessed July 23, 2012, from <http://www.ninds.nih.gov/disorders/anencephaly/anencephaly.htm> [top]
- [25] National Institute of Neurological Disorders and Stroke. (2012). Cephalic disorders fact sheet. Accessed July 23, 2012, from [http://www.ninds.nih.gov/disorders/cephalic\\_disorders/detail\\_cephalic\\_disorders.htm](http://www.ninds.nih.gov/disorders/cephalic_disorders/detail_cephalic_disorders.htm) [top]
- [26] National Institute of Neurological Disorders and Stroke. (2007). NINDS encephaloceles information page. Retrieved on July 23, 2012, from <http://www.ninds.nih.gov/disorders/encephaloceles/encephaloceles.htm> [top]