International Journal of Anatomy and Research,
Int J Anat Res 2015, Vol 3(4):1456-62. ISSN 2321- 4287
DOI: http://dx.doi.org/10.16965/ijar.2015.255

Original Research Article

COMPREHENSIVE STUDY OF NEURAL TUBE DEFECTS IN 1000 FOETUSES WITH CLINICAL SPECTRUM

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ABSTRACT

Introduction: A variety of malformations are included under the description of Neural tube defects (NTDs). These are abnormalities of the embryonic neuralization process. The congenital malformations of human structure and are of great interest to anatomists, obstetricians, pediatricians and radiologists. NTDs are among the commonest and most severe disorders, affecting 0.5-2 per 1000 established pregnancies, and are second commonest group of birth defects, after congenital heart defects. A valuable contribution of this study, the neural tube defects aimed at clinical methods and refined for the prenatal diagnosis in utero.

Materials and Methods: This comprehensive study was undertaken to know the incidence of detail knowledge of neural tube defects in KIMS Narketpally and KAMS & RC Hyderabad, among 1000 births during the period of two years. We found seven fetuses with neural tube defects involving brain and spinal cord. A detailed study was done emphasizing on embryology and genetic and non-genetic concepts.

Results & Conclusion: The seven fetuses were stillbirths and aborted babies between 20 to 40 weeks, presented with neural tube defects (0.7%). Five fetuses were females and two fetuses were males. The spinal defects were 0.4%, cranial defects 0.2% and complete neural tube defects is 0.1%. This review article discusses the classification, clinical research and epidemiological understanding of NTDs and correlated with the available literatures.

KEY WORDS: Neural tube defects (NTDs), Alpha Feto Protein (AFP), Ultra Sonography (USG), Spina Bifida, Hydrocephalus, Anencephaly, Craniorachisis.

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Access this Article online

Quick Response code

DOI: 10.16965/ijar.2015.255

Web site: International Journal of Anatomy and Research
ISSN 2321-4287
www.ijmhr.org/ijar.htm

Received: 01 Sep 2015 Accepted: 14 Sep 2015
Peer Review: 01 Sep 2015 Published (O): 31 Oct 2015
Revised: None Published (P): 31 Dec 2015

INTRODUCTION

Congenital malformations are important causes of infant morbidity and mortality in developing nations. Neuralization is the process where the neural tube is formed and completed within 28 days after fertilization before many women are aware that they are pregnant [1]. Neural tube defects are caused by the failure of the neural tube closure although it has been suggested that closed tube may re-open in some cases. It has been proposed that, in humans closure of neural tube occur at several sites and clinical types of NTDs differ depending on the site at which closure fails [2,3].

NTDs constitute a major health problem worldwide and they cause stillbirth, neonatal and infant death or significant lifelong handicap [4-6]. In these cases neural tissue is exposed to

the extra- embryonic environment and it leads to neuro-degeneration in utero, with loss of neurological function at and below the level of the lesion.

Those who live beyond one year of age are destined for a lifetime of ill health. The challenging surgical procedure, practiced in few specialized centers has been shown to offer palliation of the defects.

MATERIALS AND METHODS

This comprehensive study was undertaken to know the incidence of neural tube defects in KIMS Narketpally and KAMS & RC Hyderabad, among 1000 births during the period of two years. The unclaimed fetuses were sent from the gynecology and obstetrics department. A proper family history and obstetrics history were not collected. The fetuses were embalmed and later studied for NTDs in detail.

OBSERVATIONS

The seven fetuses were stillbirths and aborted babies between 20 to 40 weeks, presented with neural tube defects (0.7%). Five fetuses were females and two fetuses were males. Dissection of fetuses was not carried out to find out any other internal anomalies. Fetuses were photographed and their findings were appropriately documented.

Fig. 1: Female fetus around 34 weeks presented with spina bifida occulta at thoraco lumbar region. The region was covered with skin and thin hair. The neck was short and ears were folded. No other abnormalities were seen.

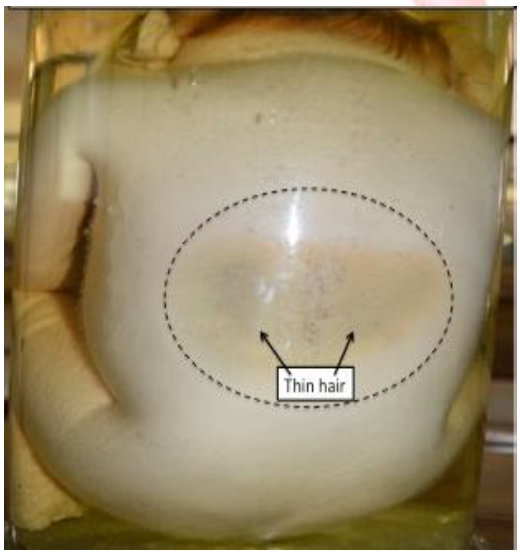


Fig. 2: Female Fetus around 20 to 24 weeks presented with spina bifida with meningocele at thoraco lumbar region. The region had thin meninges. And showed unfused vertebral arches in the thoraco lumbar region. No other abnormalities were seen.

Fig. 3: Male full term Fetus with spina bifida with meningomylocele at thoraco lumbar region. Fetus also presents large hydrocephalus (due to ventricular obstruction). No other external abnormalities were observed.

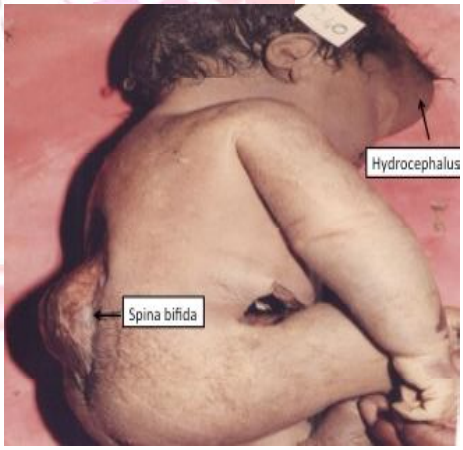


Fig. 4: Female Fetus around 20 to 24 weeks with spina bifida aperta at sacral region. The nervous tissue was dark and necrotic in appearance highly edematous. No other external abnormalities were observed.

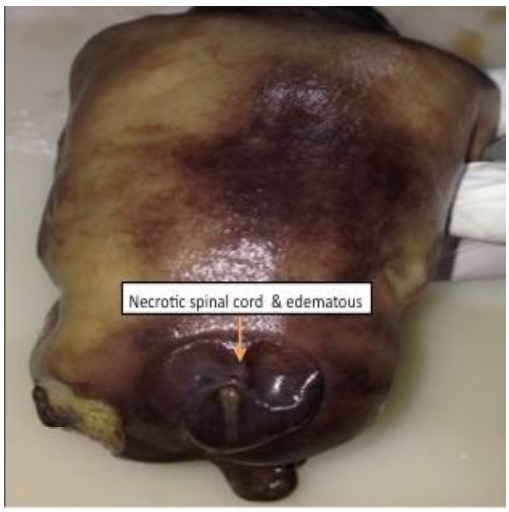


Fig. 5: Female Fetus around 24 weeks with anencephaly due to lack of closer of neural folds and bones of cranial vault. The skull vault was defective and the brain tissue is highly disorganized and necrotic, extending from the frontal to the occipital region. The neck was short, nose was broad and eyes were seen bulged out. No other abnormalities were seen.

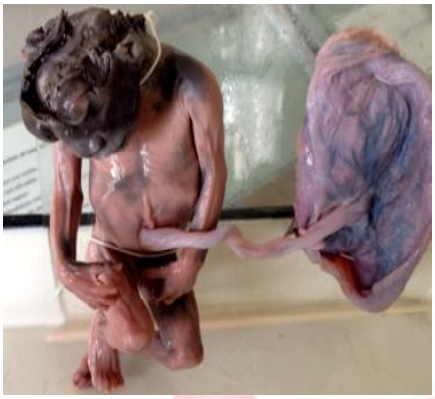


Fig. 6: Male Fetus around 24 to 26 weeks with occipital meningoencephalocele. Fetus also presented with bilateral bulging of the eyes, nose was broad and flat. The neck was absent and head seems to arise directly from the trunk.

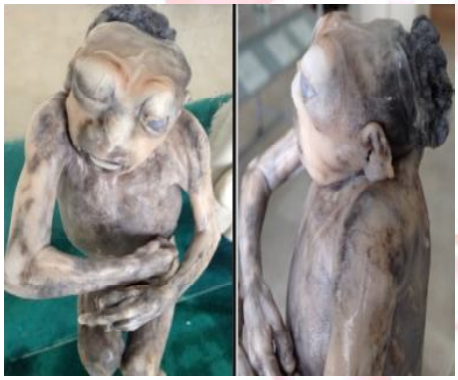
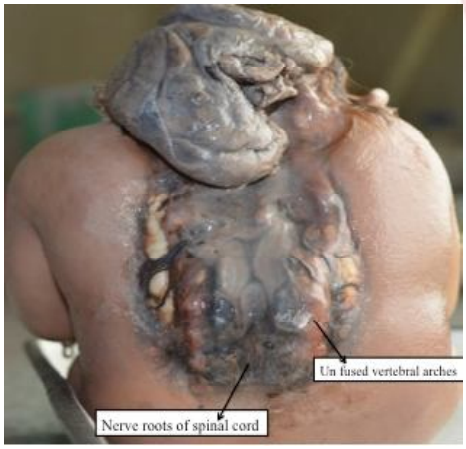


Fig. 7: Full term female fetus with craniorachisis totalis extending from the cranium to the lumbosacral region. The defect was in the skull vault, which extended up to the lumbosacral region, presenting with un-fused vertebral arches. The brain tissue and spinal cord were exposed to exterior and were covered with thin membranous tissue. The caudal most part of spinal nerve rootlets were exposed to exterior. Retro flexion of the spine was observed with absence of neck. The fetus showed no other abnormalities.



DISCUSSION

Neural tube defects (NTDs) are congenital anomalies of the central nervous system and rank amongst the most common birth defects alongside congenital heart anomalies and genitourinary defects [7].

The embryonic development of NTDs is complex, with diverse cellular and molecular mechanisms operating at different levels of the body axis involving multifactorial etiology, genetic and environmental factors interacting with one another.

The NTDs are generally sporadic both genetic and non genetic, involving the etiological factors. The recurrence risk for the second affected child increases 3 -5 folds for couples [8,9].

The syndromes are often associated with chromosomal anomalies account for <10% of all NTD cases, which include trisomy 13, trisomy 18, etc. [10,11].

Many genes are required for neuralization expression and specific pathways. The genes, which encode and disrupt NTDs, include Hectd1, Mib2 and Smurf1/2. There is a strong implication that these proteins function as signaling the foliate metabolism pathways for neural tube closure [12-14].

The reduction of 60-70% of NTDs following periconceptional folic acid administration initiated series of clinical studies by number of authors. This suggested that genes correlated with folate and methionine metabolism could be involved in the etiology of NTDs. [15,16].

Present study includes seven unclaimed fetuses, which were sent to the Anatomy department. The family history and obstetric history were not collected. Probably these stillborn and aborted fetuses belong to poor and economically backward families with no prenatal follow up. Neural tube defect (NTDs) is an embryonic induction disorder, which results from failure of formation of both mesoderm and neuroectoderm [17].

Neurulation is broadly divided into two phases. The primary phase occurs in 3rd and 4th week, which involves the formation of brain and spinal cord in the cervical region up to the lumbar

region. The secondary phase completes the sacral and coccygeal regions [18]. 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 [19,20].

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. Caudally it proceeds to the end of the neural groove until the caudal neuropore.

2. Second closure is at forebrain / midbrain boundary extends both rostrally and caudally and completes the roof of telencephalon and metencephalon.

3. Third closure site is at the end of forebrain and closes the rostral end of the neural groove closing the cranial neuropore.

4. The fourth site appears at the caudal end of the neural groove and extends rostrally to meet the fusion extending back from site one [21][22]. Phenotype of NTD will vary depending on the involvement of site of fusion [22].

In the present study the spina bifida results from the failure of closure at site 4, Anencephaly results from the failure of closure at site 2 and Craniorachischisis is the most severe disorder of primary neurulation, clinically characterized by the complete absence of skull, defects in vertebrae and skin, results from failure of closure at sites 2, 4 and 1[23].

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) [2].

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.

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

Present study has a female fetus with spina bifida occulta (fig1) covered by skin and hair in the lumbosacral region, (1 in 1000) which accounts for 0.1%.

Spina bifida open types are of two types.

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 meningomylocele [1].

Spina bifida Aperta where the nervous tissue is completely exposed to the exterior forming a necrotic tissue without the meningeal sac, seen mainly in the lumbosacral region.

In the present study there were three spinal cord defects of open type. The female fetus with spina bifida Aperta (fig4), a female fetus with spina bifida meningocele (fig. 2) and a male fetus with spina bifida meningomylocele associated with hydrocephalus (fig. 3).

The Spinal cord NTDs accounts for 0.4% of defects in the present study.

Neural defects involving the failure of cephalic part of the neural tube (brain) to close, is known as exencephaly. It results in the non-formation of skull vault leaving malformed brain exposed. The brain tissue degenerates and becomes necrotic, this defect is known as anencephaly. In such cases the brainstem remains intact.

In some cases neural tube closure defect extends caudally to the spinal cord and the abnormality is called craniorachischisis.

Types of exencephaly are meningocele, meningoencephalocele and, meningohydroence phalocele. All resulting in ossification defects of skull bones. Most frequently affecting the squamous part of the occipital bone [1].

In the present study there were two NTDs involving the cephalic part of the neural tube. One of which is female fetus with anencephaly (fig5) showing severe necrotic nervous tissue and the other male fetus presented with occipital meningoencephalocele, bilateral bulging of the eyes and absence of neck (fig6). The NTDs involving the brain accounts for 0.2% in the current study.

The NTDs involving cranial and spinal neural tube comprises of 10% and it is termed as craniorachischisis, in which the entire neural tube remains open from midbrain to lower spine associated with the bony fissure of the skull and the vertebral column. Such fetuses show a characteristically short rostro caudal body axis. AFP and fetal USG can diagnose this defect as early as 6th week of gestation. The prognosis of this severe type is very poor; death of the fetus is unavoidable. There is no cure or standard treatment for craniorachischisis. Medical termination of pregnancy is done, if diagnosed early.

In the present study the full term female fetus with craniorachischisis totalis extending up to the lumbosacral region with exposure of caudal spinal nerve rootlets, which accounts for 0.1%(fig. 7).

There are three types of anencephaly described:

1. Meroanencephaly, where there is rudimentary brain tissue and partial formation of the cranium.

2. Holoanencephaly, the most common type, in which the brain is completely absent.

3. Craniorachischisis, the most severe, where the defect extends beyond the cranium [24].

As shown in this presentation, the two female fetuses one with Holoanencephaly (fig 5) and other with craniorachischisis totalis (fig 7).

NTDs overall have a female sex bias. Females more often than males tend to have Craniorachischisis, spina bifida involving the cervico-thoracic region, while males have spina bifida affecting the lumbosacral region [24].

In Our study, five fetuses were females and 2 fetuses were males. Female fetuses with NTDs were more, which obeys the trend (F: M- 0.5 : 0.2).

Non-genetic factors also involve in the etiology of NTDs and they are multifactorial in origin.

Exposure to valproic acid (antiepileptic drug), metabolites and toxins like lead during the critical period of gestation interferes with normal foliate metabolism and increases the likelihood of NTDs. Therefore women taking anti-epileptic drugs during pregnancy are advised to undergo routine antenatal check-up with AFP [25].

Cyclophosphamide is a strong inhibitor of DNA synthesis resulting in anti-proliferative activity of axial mesoderm leading to axial skeletal malformations, which may result in skull vault and vertebral defects. [26].

A study was conducted and published regarding maternal pre-conceptional smoking and alcohol consumption on the risk of NTDs. Maternal alcohol increases the risk of NTDs whereas smoking was associated with low risk of NTDs. These observations are elusive [17].

Maternal hyperthermia in early pregnancy, during critical periods of gestation is associated with increased risk for neural tube defects, particularly the brain is very sensitive and hyperthermia may be a human teratogen [27].

Sharada B. Menasinkai [2010] studied 3000 births and reported 32 cases of neural tube defects. [28]

Dhapate S.S. et al [2007] reported a USG study of 8640 pregnant women attending antenatal care observed NTDs in 35 cases [0.40%] [29].

Balakumar K. [2007] studied 30,030 singleton under USG analysis reported 250 NTDs [0.83%] [30].

Sania Tanveer et al [2008] reported study of 3310 deliveries and 46 cases with NTDs giving incidence of 1.39% [31].

Johnson et al (2004) reported 16 cases of craniorachischisis in Texas-Mexico border population [32].

In the present study we reviewed the incidence of congenital malformations of NTDs is 0.7%, five female fetuses (0.5%) and two male fetuses (0.2%) in 1000 births for a period of 2 years. To

summarize, the spinal defects were 0.4%, cranial defects 0.2% and complete neural tube defects is 0.1%. That is comparable with standard textbooks and review of literature. The detailed obstetric history of the mothers was not available for all the seven cases. Probably the mothers were from low socio-economical status with no antenatal checkups.

CONCLUSION

In conclusion, refined prenatal diagnosis by the available screening protocols such as estimation of alpha feto-protein (AFP) in amniotic fluid, maternal serum and diagnostic USG and MRI. Prenatal surgical repair (in utero) is tried for spinal defect babies.

One of the concerns regarding NTDs is to strengthen the evidence of future studies with more detail and precision, along with counseling and incorporating folate intake as an effective modifier.

ACKNOWLEDGEMENTS

All authors are thankful to the Department of Obstetrics and Gynecology for providing us the fetuses with rare anomalies. Authors of this study also acknowledged to authors, editors and publishers of all those articles, journals and books from where literature for this article has been reviewed and discussed.

Conflicts of Interests: None

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How to cite this article:

Himabindu. N, Asra Anjum, S.Saritha, Ramani, D. Nagajyothi, P. Gayathri. COMPREHENSIVE STUDY OF NEURAL TUBE DEFECTS IN 1000 FOETUSES WITH CLINICAL SPECTRUM. Int J Anat Res 2015;3(4):1456-1462. **DOI:** 10.16965/ijar.2015.255