Indian Journal of Forensic Medicine and Pathology
Volume 14 Number 4, October - December 2021
DOI: http://dx.doi.org/10.21088/ijfmp.0974.3383.14421.5

ORIGINAL ARTICLE

Spectrum of Neural Tube Defects Among the Fetal Autopsies in a Tertiary Care Hospital in Southern India

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ABSTRACT

Background: Neural tube defects (NTDs) are congenital disorders with multifactorial etiology that increase the risk of death as well as disability in early neonatal period and infancy.

Objective: The study was conducted in a tertiary care referral hospital to analyse the disease burden of neural tube defects and to study the associated anomalies in the affected fetuses.

Materials and Methods: This study was conducted retrospectively from January 2011 to December 2020 on a total number of 402 fetal autopsies received after abnormal ultrasonographic findings and intrauterine deaths diagnosed prenatally.

Results: Out of the total 402 cases of fetal autopsies, 42 neural tube defects were detected, 33 (79%) were open type and 9 (21%) were closed type neural tube defects. Out of the open type, majority were meningomyeloceles with 18 (43% of NTDs) cases, 11 (26% of NTDs) cases were of anencephaly. Arnold chiari malformation was associated in 4 cases and a rare case of craniorachischisis was encountered. Among the closed type, 6 (14%) were meningoceles and 3 (7%) were encephaloceles. A case of Meckel Gruber syndrome with an associated encephalocele was diagnosed.

Conclusion: The present study would contribute to the prevalent disease burden of neural tube defects in Southern India, proving to be useful in the design and implementation of appropriate comprehensive preventive strategies including nutritional fortification, swift antenatal diagnosis and prompt intervention to reduce the morbidity.

Keywords: Neural tube defect; Rachischisis; Meningocele, Meningomyelocele; Meckel gruber.

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Received on: 29.04.2021
Accepted on: 31.07.2021

How to cite this article
Rajalakshmi BR, Sapna Patel/Spectrum of Neural Tube Defects Among the Fetal Autopsies in a Tertiary Care Hospital in Southern India/Indian Journal of Forensic Medicine and Pathology/2021;14(4):811-818

INTRODUCTION

Neural tube defects (NTDs) are birth defects associated with consequential mortality, morbidity, disability with associated economic and psychological costs. NTDs are known to be preventable with folic acid,[1-4] while the long-term survival and quality of life of the affected children can be improved through access to appropriate clinical care and rehabilitative services.[5,6] However, the formulation of preventive and rehabilitative strategies have been hampered by the lack of studies on the transparent prevalence of these NTDs and hospital based surveys can provide an insight in the respective geographic regions.

Neural tube defects (NTDs) are a heterogeneous and complex group of congenital central nervous system (CNS) anomalies. Anencephaly, spina bifida, encephalocele, meningocoele and meningomyelocoele are included in this group. Neural malformations and anomalies of the other organ systems are frequently associated with NTDs.[7-9] This study was performed retrospectively to study the neural tube defects in a tertiary care centre in South India. The study is of substantial help in understanding the disease burden and help in implementation of the preventive strategies.

MATERIALS AND METHODS

- The present study was conducted retrospectively from January 2011 to December 2020 on 402 fetal autopsies received in the department of pathology, out of which 42 fetuses were found to have neural tube defects (NTDs).
- Each fetus was examined according to predetermined protocol which included ultrasound diagnosis, external and internal examination. The autopsy protocol included en bloc evisceration with subsequent dissection into organ blocks. The placenta and fetal membranes were studied wherever possible and umbilical cord was studied in all the cases. Histological sections were taken from all the internal organs, placenta, umbilical cord and stained with Hematoxylin and Eosin. In cases where the antenatal ultrasonography diagnosis were available, findings were compared with the postnatal autopsy.

RESULTS

Among 402 fetal autopsies studied, 42(10.4%) fetuses showed evidence of neural tube defects. Table 1 and Table 2 describe the different neural tube defects and the clinical characteristics respectively. Antenatal ultrasound findings were available only in 28 cases where the findings were correlated with fetal autopsy findings and were found to be consistent.

Table 1: Neural tube defects and associated abnormalities.

Type	Neural tube defects and associated ablnormalities	No. of Cases	%
Open NTDs	Craniorachischisis	1	2.4 %
	Anencephaly	8	26.2 %
	Anencephaly with cystic renal dysplasia	1	
		1	
	Anencephaly with bladder exstrophy	1	
	Acrania with anencephay		
	Myelomeningocele	16	43 %
	Myelomeningocele with renal ectopia	1	
		1	
	Myelomeningocele with b/l club feet		
	Arnold chiari malformation II with Meningomyleocoele, and holoprosencephaly (failure of forebrain to divide into lobes).	1	7 %
		1	
	Arnold chiari malformation II with kyphosis and Meningomyleocoele,	1	
	Arnold chiari malformation II with Meningomyleocoele,		
Closed NTDs	Meningocoele	5	14.3 %
	Meningocoele with Arnold chiari malformation II	1	
	Encephalocoele	2	7 %
	Meckel gruber syndrome (Encephalocoele)	1	

Table 2: Clinical Characteristics.

Characteristics	Distribution
Maternal age in years	Median age -25 Range -19yr-40 yr
Period of Gestation in weeks	
	< 20 weeks - 11 cases
	20–25 weeks - 29 cases
	> 25 weeks - 02 cases
Order of gestation	Primiparous-11
	Multiparous-21
	Not known-9
	History of previous pregnancy loss-11 cases
Prenatal Ultrasound findings/ diagnosis	Available in 28 cases (67%)

- The case of craniorachischisis (Fig. 1) had bilateral adrenal hypoplasia with associated right cystic renal dysplasia.

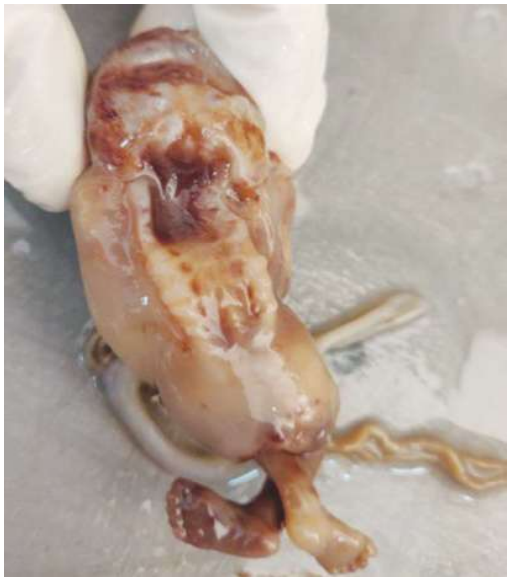

Fig. 1: Craniorachischisis showing a dorsal defect in skull extending through the length of spinal canal.

Fig. 2: Anencephaly with urinary bladder exstrophy (protrusion of bladder through the abdominal defect).

- Arareanomalyofbladderexstrophywasseenin a case of anencephaly (Fig. 2).
- Among the meningomyelocoeles described, associated anomalies such as hydrocephalus, bilateralclubfootandectopickidneywerealso noted.
- Arnold chiari malformation II with kyphosis and Meningomyleocoele in a 13 weeks of gestation fetus weighing 85gms (Fig. 3). Internal examination of skull showed ventriculomegaly with herniated cerebellum and brain stem into foramen magnum suggestive of chiari II malformation associated with lumbosacral meningomyelocoele and kyphosis.

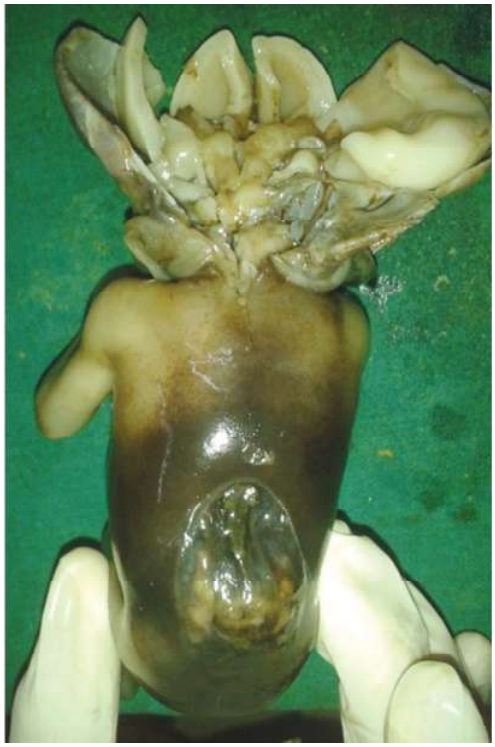

Fig. 3a: Arnold chiari malformation II with kyphosis and meningomyleocoele, displaying cerebral ventriculomegaly.

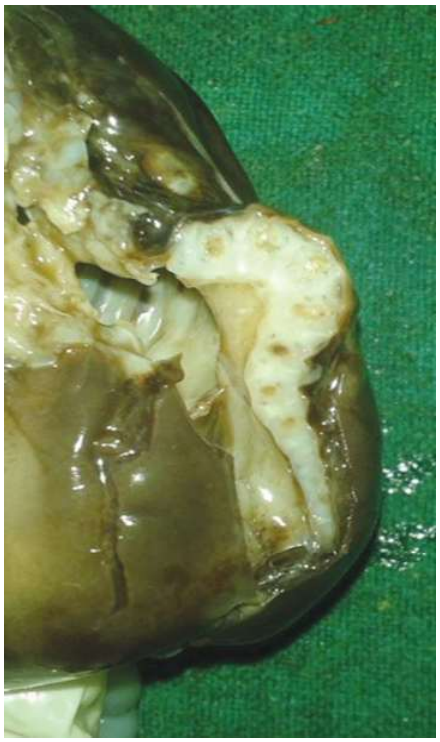

Fig. 3b: Cut opened spinal canal showing kyphosis.

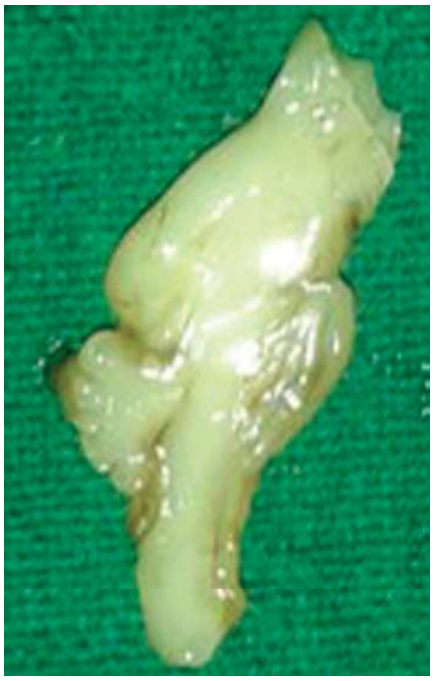

Fig. 3c: Dissected foramen magnum with herniated cerebellum.

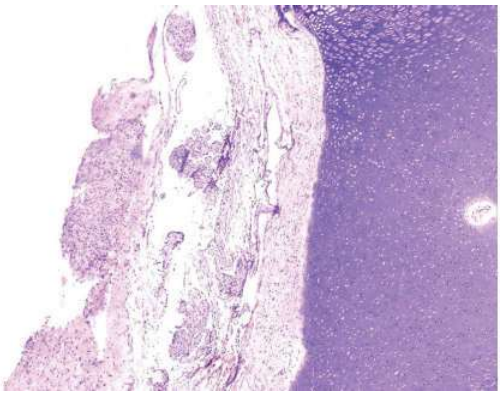

Fig. 4: Microscopy showing thin meningeal lining and neural tissue adjacent to the intervertebral cartilage consistent with meningocoele (Haematolxylin and Eosin, x200).

- All the cases of meningoceles were subjected to histopathology to demonstrate the meningeal lining (Fig. 4).
- Three of the encephalocoele cases displayed occipital swelling with microscopy confirming the thin fibrocollagenous lining and brain parenchyma in the lumen.
- A rare Case of Meckel Gruber syndrome in a male fetus with 16 weeks period of gestation weighing 141gms. Occipital region showed defect m/s 2.5 x 2cms, suggestive of encephalocoele (Fig. 5), abdomen appeared distended with bilateral cystic dysplastic kidneys (Fig. 6).

Fig. 5: Fetus with posterior encephalocele–Meckel Gruber Syndrome.

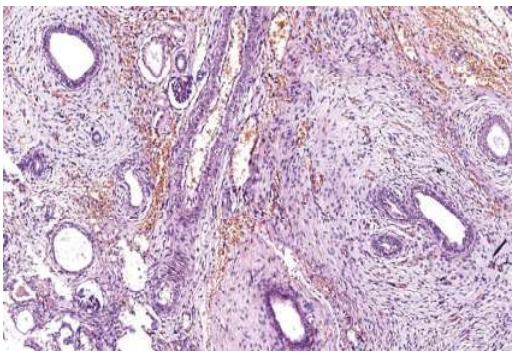

Fig. 6: Microscopy of kidney displaying variable sized cysts lined by cuboidal epithelium with intervening mesenchyme suggestive of renal cystic dysplasia (Haematolxylin and Eosin, x200).

- Sections from umbilical cord were examined in all cases, however all of them showed three vessels (two arteries and a vein).

DISCUSSION

Neural tube defects (NTDs) are congenital structural abnormalities of the central nervous system and vertebral column affecting 4.5 per 1000 total births. Neural tube defects constitute the most common birth defects in India.[1] As there is no national registry to record the birth defects, hospital based studies provide valuable information to record the disease burden.[1,2]

Etiology of NTDs is multifactorial, attributed to genetic and environmental factors such as maternal malnutrition and exposure to alcohol and tobacco.[1,10] Other associated risk factors include micronutrient insufficiency, maternal diabetes, obesity, and the use of certain teratogenic drugs in early gestation. Consangunity has also been implicated as a risk factor with an incidence of NTDs in 11.5/1000 total births born out of consanuinous marriges, in contrast to 4.3/1000 in non consangunous marriages.[1] Consanguinity is suggested to contribute to higher incidence of NTDs in several countries, including Saudi Arabia.[5] The risk of recurrence of NTD for a second affected child is increased by 3-5 folds for couples with one affected infant, requiring early implementation of preventive strategies.[5] In our study, out of 42 cases, 11 mothers had history of previous pregnancy loss, warranting the fetal autopsy study to evaluate the cause and plan the prevention. One study from China reported an estimate of recurrence risk of 6.9% for NTDs, based on a retrospective survey in the early 1990s.

Studies have suggested that genes of folate and methionine metabolism can be involved in the etiology of NTDs. The genotype MTHFR 677C>T was significantly associated with NTDs with synergistic effects in the absence of folate supplementation and also in the presence of gestational diabetes mellitus (GDM), while 5-Methyltetrahydrofolate-homocysteine methyltransferase (MTHM) 501A>G genotype was significantly associated with NTDs in case of gestational diabetes.[5]

The prevalence of neural tube defects has been reported to be 7.7, 1.1, 2.5 and 4.2 per 1000 total births in Northern, Eastern, Western and Southern India respectively.[1] The higher prevalence in Southern India has been attributed to consanguinity, delayed age of marriage and childbirth and dietary factors.[1] The risk of NTDs can be reduced by the use of folic acid supplements in peri-conceptional period and some behavioural modifications such as avoiding tobacco and alcohol in early pregnancy.[1-4,11]

These malformations result from failure of the neural folds to fuse and form the neural tube in the third and the fourth week of development of embryo. This leads to secondary abnormal development of skeletal and muscular structures from mesoderm that cover the underlying neural structures. Cranial dysraphism refers to failure of cranial neural tube closure, comprising anencephaly and encephaloceles, while spinal dysraphism is due to failure of caudal neuropore closure resulting in spina bifida.

They are also known as open when exposed through a skin defect in the skin, or closed if covered by skin. A rare form of NTD is craniorachischisis, resulting from failure of the neural tube closure over the entire body axis.[5] The present case series encountered a case of craniorachischisis with associated bilateral adrenal hypoplasia and right cystic renal dysplasia in a 12 week fetus born to a 23 year old primigravida.

Anencephaly results from failure of the cephalic folds to fuse into a neural tube with absence of a major portion of diencephalon. Failure of bony skull development results from secondary mesodermal defect dorsal to the neural elements. The brainstem, cerebellum, and spinal cord are normally present. Anencephaly is lethal resulting in still birth within a few hours to weeks, and is easily diagnosed antenatally.[5] Among the eleven cases of anencephaly in our study, one case each of associated renal cystic dysplasia and bladder exstrophy have been noted.

Anencephay has been reported to co-exist with feta acrania among one of the cases of our study. The coexistence has been described as a sequence of acrania exencephaly anencephaly.[12] Fetal acrania (exencephaly) is characterized by

the complete or partial absence of skull bones surrounding the fetal brain with abnormal brain tissue development.[13] The lack of cranial bones cause protrusion of the cerebral parenchyma (exencephaly). With the sudden fetal movements and the chemical irritation of the exposed brain parenchyma by the amniotic fluid causes degeneration and destruction of the brain leading to its absence (anencephaly).[12]

Encephalocele is a type of cranial dysraphism resulting from failure of closure of anterior neuropore. Encephaloceles are uncommonly associated with defined syndromes, such as Meckel Gruber syndrome, an autosomal recessive ciliary dysfunction disorder characterized by an occipital encephalocele.[9] Other associated features include holoprosencephaly, polydactyly, polycystic kidneys, hydrocephalus, micrognathia, Chiari malformation and cardiac anomalies. Our case had a triad of posterior encephalocele, polydactyly and cystic renal dysplasia .

Spinal dysraphisms result from aberrant formation of the midline mesenchymal and neural elements.[5] Subtypes of NTDs relate to the stages of closure. Primary neurulation takes place at weeks 3-4 during which the neural ectoderm bends, and folds along the midline to form the neural tube. Defective primary neurulation leads to craniorachischisis, anencephaly and spina bifida. Secondary neurulation occurs during weeks 5-6, when an additional part of the neural tube is produced caudal to the posterior neuropore resulting in the formation of the tip of the conus medullaris and the filum terminale. Malformations resulting from disturbance of secondary neurulation are closed (skin covered) and usually involve tethering of the spinal cord.[5,10]

Myelomeningocele and myelocele constitute the most prevalent NTDs (95%), that appear as sac-like structures with nerve roots covered by a thin membrane, when ruptured, cause a cerebrospinal fluid (CSF) leak.[5] In our study, myelomeningocele and myeloceles together constituted 57% of total cases (24/42). Meningocele and myelomeningoceles represent the two different types of spina bifida, a closed and open defect respectively with different prognosis, although both are macroscopically similar. In open spinal dysraphisms, the neural structures are exposed without a skin covering, including myelomeningocele, myelocele, hemi myelocele, and hemi myelomeningocele.[5,14] The CNS anomalies associated with myelomeningocele include Chiari II malformation and hydrocephalus in upto 90% of cases.[5] Chiari II malformation is a hindbrain anomaly characterized by herniation of the cerebellar vermis, fourth ventricle, and brain stem through the foramen magnum. In our study, four cases of Arnold Chiari malformation type II were found in association with three cases of meningomyeloceles and one case of meningocele.

Closed spinal dysraphisms comprise lipomas with a dural defect (lipomyelomeningocele, lipomyelocele), meningoceles and spina bifida occulta.[5,14] Meningocele is a type of spina bifida resulting from herniation of the meningeal covering through the bony defect without nerve roots into the dural sac.[5] Clinical severity of NTDs varies depending on the extent of defect. Open lesions that affect brain (anencephaly, craniorachischisis) are invariably lethal before or at birth. Encephalocele may also be lethal depending on the extent of brain damage during herniation.

Open spina bifida though compatible with postnatal survival, causes neurological impairment below the level of the lesion leading to features of sensory loss, motor weakness and urinary incontinence. Closed spinal lesions are less severe and may be asymptomatic, as with spina bifida occulta.[6]

Among the studies aimed at prevention of NTDs in 1970s, Smithells and colleagues implicated deficiency of several vitamins such as folate, riboflavin and vitamin C, in the serum of pregnant mothers with fetuses affected by NTD. A meta-analysis of the randomized trials indicated a 69%-87% reduction with use of folic acid for the prevention of NTDs and 85-100% reduction in observational studies. In accordance with the recommendation of the US Center for Disease Control and Prevention (CDC), all women of childbearing potential must receive 0.4mg folic acid per day.[11] The present study in a tertiary care hospital in Southern India has shown a disease burden of 10.4% of neural tube defects among the 402 cases of fetal autopsies.

CONCLUSION

There is a need to systematically record the epidemiological data including the incident cases of NTDs and associated risk factors in different geographic regions. This would help in the design of pertinent preventive strategies to reduce the recurrence, decrease the incidence and to provide supportive health care to already affected neonates with mild disabilities.

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