Case Series

Neural Tube Defect Spectrum - Study of Craniorachischisis

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Abstract:

Neural tube defect spectrum (NTD) includes anencephaly, spina bifida, craniorachischisis, inencephaly etc. Four cases of craniorachischisis were studied from a collection of 34 aborted fetuses. There was deficiency of scalp and cranial vault in all the four cases. In one case the defect was extending up to the cervical region, in rest of the three cases, vertebral column defect extended upto thoracic region exposing the spinal cord and spinal nerves. All the cases presented with bulging eyes, broad nose, folded ears, protruded tongue and absent neck. These defects result due to failure of closure of the neural tube during early embryonic life.

Key Words: Anencephaly, neural tube defect, rachischisis, craniorachischisis.

Introduction:

Neural tube defect spectrum includes the disorders related to the non-closure of the neural tube. Several types of NTDs are recognized. Major types of neural tube defects include anencephaly, spina bifida, craniorachischisis, encephalocele, inencephaly (Moore, 2006); anencephaly and spina bifida being the most common. Anencephaly is a developmental defect of the central nervous system in which the brain and cranial vault are grossly malformed. Craniorachischisis is congenital fissure of the skull and vertebral column. This defect results when the neural tube fails to close during the third to fourth weeks of gestation, leading to fetal loss & stillbirth. The present study was carried out to elucidate neural tube defects.

Material and method:

The study was carried out in a collection of 34 aborted fetuses in department of anatomy, People's college of Medical Sciences & Research Centre and Gandhi Medical College, Bhopal. The fetuses were observed for the defect in the cranium, vertebral column and face. Dissection of fetuses was not carried out to find out any other internal anomalies.

Observations:

All the four fetuses showed presence of anencephaly with extension of defect in the vertebral column i. e. craniorachischisis.

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Case 1: In a male fetus of 28 weeks the defect in the cranial vault was observed. The fetus showed absence of a major portion of scalp and cranial vault and the defect was extending to the cervical vertebrae. The brain tissue and spinal cord in the cervical region were exposed to exterior (Fig. I). Below the level of cervical region no defect was observed and vertebral column was covered by normal skin. In this case the nose was broad and ears were folded. The eyes were bulging outward. No abnormality of lips or palate was observed. The trunk was short and shoulders were broad. There was extreme extension of head. No other associated external deformities were observed.

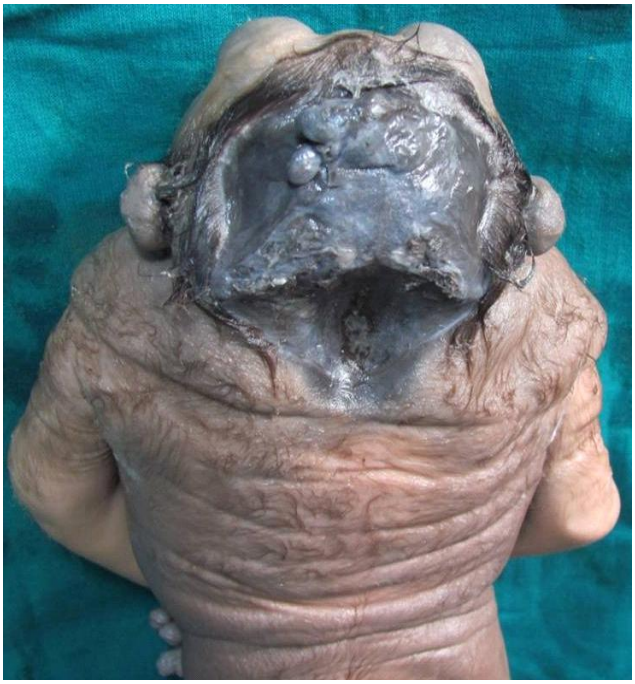

Fig. I: Illustration showing craniorachischisis with extension of defect into the cervical region.

Case 2: Craniorachischis was observed in a 29 week male fetus. There was a defect in the formation of the scalp and vault which was extending upto lower thoracic part of the **v**ertebral column (Fig. II). Brain tissue and spinal cord were covered only by a membranous tissue. Retroflexion of spine was observed. The neck was short, nose was broad and eyes were bulging. Omphalocele was observed (Fig. III). No other abnormalities were seen.

Case 3: A 26 week male fetus presented with a defect in skull vault which extended up to mid thoracic region. The brain tissue and spinal cord were exposed to exterior. Absence of some parts of brain, spinal cord, nerve roots and meninges was seen. Spinal cord and rootlets of spinal nerves were seen exposed to the exterior (Fig. IV). The neck was short, nose was broad, eyes were seen bulged out and ears were folded. The fetus also showed umbilical hernia.

Case 4: A 28 week male fetus showed craniorachischisis. The defect in this case was extending beyond the cranial vault (Fig. V). Brain tissue and spinal cord were exposed to the exterior. The neck was absent and head seem to arise directly from the trunk. The tongue was protruded and ears were folded (Fig. VI). No other external abnormality was observed.

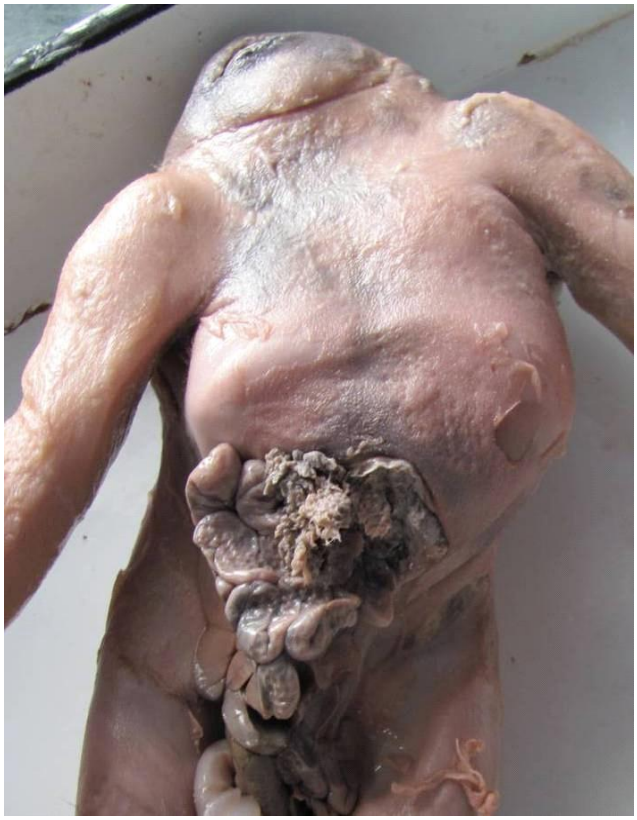

Fig. III: Illustration showing omphalocele.

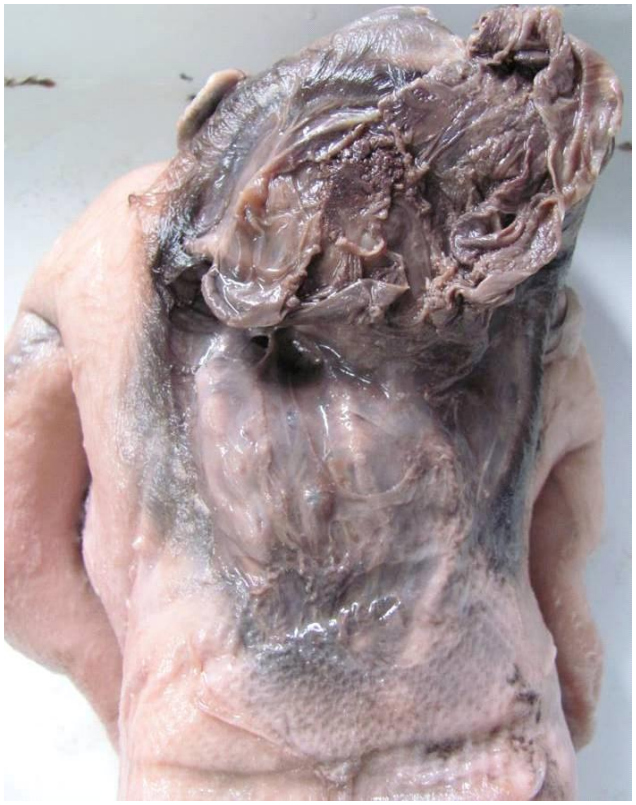

Fig. II: Illustration showing craniorachischisis with extension of defect into lower thoracic region.

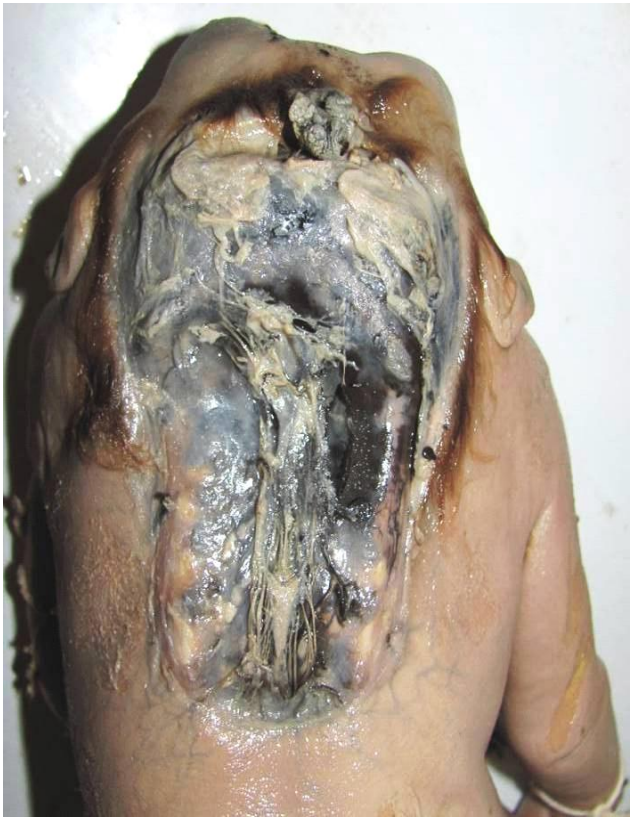

Fig. IV: Illustration showing craniorachischisis with exposed spinal cord and rootlets of spinal nerves.

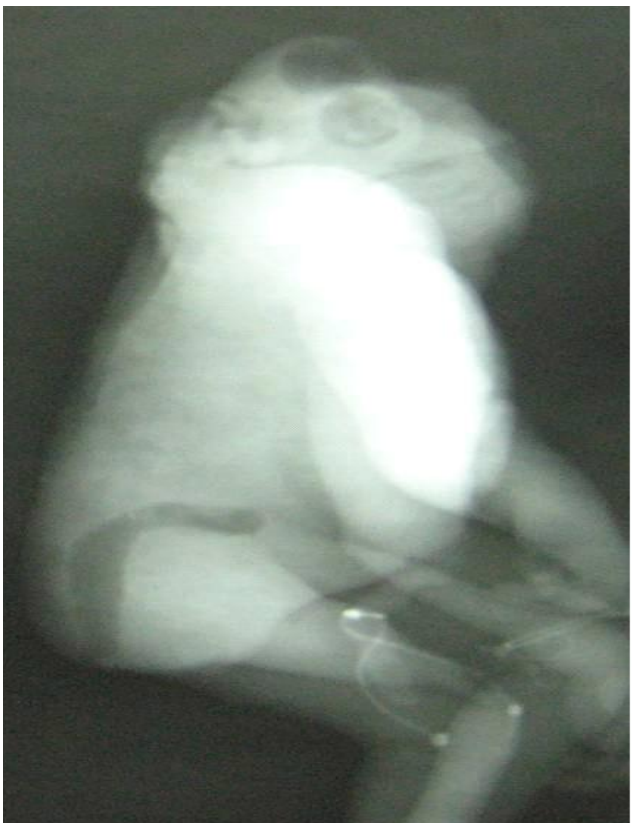

Fig. V: X ray lateral view of spine showing extension of defect beyond cranial vault in case no. 4.

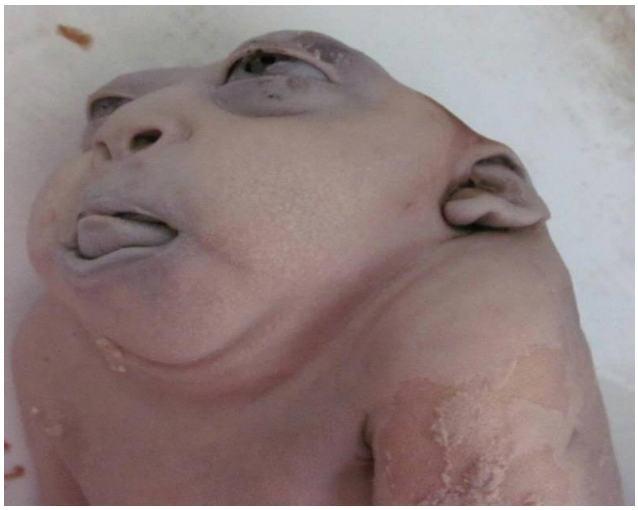

Fig. VI: Illustration showing folded ears, bulging eyes and protruded tongue.

Discussion:

Neural tube defects (NTDs) are very frequently and encountered congenital abnormalities (Moore & Persaud, 2003). There are several morphological forms of anencephaly. Chourasia (1984) has given simpler classification of anencephaly based on occipito-vertebral and parieto-occipito-vertebral defects. Currently, if the defect is limited to the vault then it is classified as anencephaly and if it extend beyond the cranium then it is known as craniorachischisis.

The neural tube develops and closes during the 3rd & 4th weeks after conception and is normally completed by 28 days post conception (Botto et al, 1999). Craniorachischisis presents with vertebral and cranial vault defect, bulging eyes, broad nose, and folded ears, as seen in the present study. Craniorachischisis can be detected on ultrasound scan at gestational age of 13 weeks (Coskun et al 2009). Anencephaly is often associated with rachischisis and other congenital defects (Kulkarni et al, 1989). Chaurasia in 1984 reported 21 anencephalic fetuses, in all of which defect extended into the vertebral column.

Neural tube defects may also presents with large thymus, small adrenal glands, hypo -plastic lungs, cyclopia, syndactyly, absent radius and thumbs, club foot, imperforate anus, cleft palate, renal and cardiac anomalies. It can also be associated with meningomyelocele, hydrocephalus and Chiari II malformation (Jones, 2006). In the present study, umbilical hernia was seen in one case and an another case it was associated with omphalocele**.** Neural tube defects may be associated with the unbalanced form of a structural chromosomal abnormality in some families (Cunningham et al, 2005). Johnson et al (2004) reported 16 cases of craniorachischisis in a Texas-Mexico border population. Kajaer et al (1994) investigated the axial skeleton related to the notochord in human anencephalic fetuses. Abnormal ossification of cranial base was observed with or without cervical rachischisis.

Fetus with neural tube defects lack functioning cerebrum which rules out the possibility of ever gaining consciousness. They are blind, deaf and unable to feel pain. Some individuals with anencephaly may be born with a rudimentary brainstem, which controls autonomic and regulatory function. Hence, reflex actions such as respiration and responses to sound or touch may occur. Depending on the extent of the skull deficit, descending tracts associated with disrupted structure are absent (Frosch et al, 2004). During pregnancy, polyhydramnios may occur due to lack of the swallowing mechanism.

The cause of NTDs is multifactorial. Exposure to valproic acid and other antimetabolites of folic acid and other toxins like lead etc during critical period i.e. up to 6 weeks after last menstrual period, interfere with normal folate metabolism and increases the likelihood of anencephaly (Cunningham et al, 2005).

Maternal type 1 or pregestational insulin-dependent diabetes mellitus (IDDM), maternal fever in early gestation and amniotic band disruption during pregnancy also increases the risk for anencephaly.

NTDs result from the combined effects of genetic and environmental influences. But the cellular and molecular mechanisms underlying NTDs are very complex, poorly understood and difficult to study in humans. Mouse models are being used in an attempt to identify genes that could be involved in these malformations. . Recent genetic studies of NTDs have identified a number of genes and proteins that play critical roles in neural tube closure. Only two mouse mutations are known to lead to craniorachischisis. The gene for one of these, Loop-tail, has now been identified and sequenced. It has been given the designation Ltap/ Lpp1 and appears to function in floor plate formation (Kapron, 2002). Identifying the genetic factors is critical for these will provide the basis for designing novel preventive strategies and for offering accurate reproductive risks to couples

In the normal human embryo, the neural plate is formed approximately 18th days after fertilization. During the fourth week of development, the neural plate invaginates to form the neural groove. The neural tube is formed due to closure of the neural groove by fusion of neural folds as a process initiated at a single site, and extending bi-directionally, rostrally and caudally, to the rostral and caudal neuropores. Closure completes by day 24 for the cranial end and day 26 for the caudal end. Anencephaly results from failure of neural tube closure at the cranial end of the developing embryo leading to incomplete development of calvaria and brain (Moore & Persaud, 2003; Jones, 2006).

However, recently a hypothesis of "multiple site of neural tube fusion" has been investigated in animal models and in humans. Four sites of neural tube fusion have been identified. Site 1 initiates in the future cervical region between the third and fourth somites at the caudal part of the hindbrain, and progresses both caudally and rostrally. Caudally, it proceeds all the way down to the end of the neural groove until the caudal neuropore. The next two sites of initiation of fusion are located rostral to site 1. A second fusion initiates at the prosencephalon-mesencephalon boundary (Site 2) and extends both rostrally and caudally. This second fusion completely closes the roof of the telencephalon and the metencephalon. A third fusion site (site 3) progresses caudally, and closes the rostral end of the neural plate. Finally, the fourth fusion site (site 4) appears at the caudal end of the neural plate and extends rostrally to meet the fusion extending back from site 1(Detrait et al, 2005). Phenotype of NTD will vary depending on the involvement of the site of fusion.

Van Allen et al (1993) compared the multisite model vs. the traditional single-site model of neural tube closure for the best explanation for NTDs in humans. With the multi-site neural tube closure model majority of NTDs can be explained by failure of fusion of one of the closures or their contiguous neuropores. They hypothesize that anencephaly results from failure of closure at site 2 and craniorachischisis results from failure of closures at sites 2, 4, and 1.

In NTDs the first defect is in the notochord development resulting in failure of the neural folds to fuse in the midline and to make a normal neural tube. The next defect is failure of the mesoderm to develop; mutual induction of all three germ layers in temporally related sequence fails to occur.

Therefore, the calvaria and vertebrae fail to form correctly exposing the neural tissue to further insult. Finally the skull and dural defect permits the neural tissue to be exposed to amniotic fluid thus destroying the neural tissue. Well-preserved brain tissue is usually found until 10 weeks gestation (Becker et al, 2000). Closer contact of the fetus with the uterine wall usually starts from about 10 weeks, when substantial portions of the amnion are fused with the chorion. The fetal brain is then exposed to increasing mechanical trauma, resulting in progressive "rubbing off" of the brain tissue. The exposed neural tissue undergoes secondary degenerative changes that convert it into a mass of vascular connective tissue, the area cerebrovasculosa, which is a flattened remnant of degenerated brain tissue admixed with choroid plexuses, ependyma and mesothelial cells. The exposed base of the skull is covered only by a vascular membrane (Wilkins-Haug & Freedman, 1991; Bronshtein & Ornoy, 1991; Timor-Tritsch et al, 1996; Powers & Horoupian, 1996; Frosch et al, 2004; Crowley, 1999).

This defect can be diagnosed during Alpha-fetoprotein (AFP) screening. Fetal ultrasound can also be useful for screening of neural tube defects (Baker, 2006). The recurrence risk is 1.9% for parents who had one affected child. Folic acid supplementation has been shown to be an effective means of lowering recurrence risks for future pregnancies (Jones, 2006).

The prognosis in severe form of neural tube

defects is exceptionally poor; death of the neonate is unavoidable. There is no cure or standard treatment for craniorachischisis. Therefore, pregnancy should be terminated if diagnosed early.

Conclusion:

NTDs can be prevented by taking folic acid supplementation during reproductive age. Screening tests like AFP and USG can diagnose the condition early and termination can be decided earliest possible. Parents of babies with NTDs should be educated about preventive measures for future pregnancies. Genetic counseling may be helpful in this respect.

Bibliography:

1. Baker PN: Prenatal Diagnosis. In: Obstetrics by 10 teachers, 18th Edn.; Book Power publishers. Hodder Arnold. London. 2006; pp 107-108.
2. Becker R, Mende B, Stiemer B, Entezami M: Sonographic markers of exencephaly at 9 + 3 weeks' gestation. *Ultrasound in Obstetrics and Gynecology*. 2000; 16(6): 582–584.
3. Botto LD, Moore CA, Khoury MJ, Erickson JD: Neural-tube defects. *New England Journal of Medicine*. 1999; 341: 1509–1519.
4. Bronshtein M, Ornoy A: Acrania- Anencephaly resulting from secondary degeneration of a closed neural tube: Two cases in the same family. *Journal of Clinical Ultrasound*, 1991; 19(4): 230–234.
5. Chaurasia BD: Calvrial defect in human anencephaly. *Teratology*. 1984; 29(2):165-172.
6. Coskun A, Kiran G. Ozdemir O: Craniorachischisis totalis: A case report and review of literature. *Fetal diagnosis and therapy*, 2009; 25 (1):21-25.
7. Crowley LV: The Nervous system. In: Pathological Basis of the disease (Introduction to Humans Disease). 4th Edn.; Jones and Bartlett publishers Inc. USA. Boston, 1999; pp 753-800.
8. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap L, Wenstrom KD: Genetics. In: Williams's obstetrics. 22nd Edn.; Mc Graw-Hill, New York, 2005; pp 285-312.
9. DetraitER, George TM, Etchevers HC, Gilbert JR, Vekemans M, Speer MC: Human Neural Tube Defects: Developmental biology, epidemiology and genetics. *Neurotoxicology & Teratology*, 2005; 27(3): 515–524.
10. Frosch MP, Anthony DC, Girolami UD: The Central Nervous System. In: Robbins and Cotran, Pathological basis of disease. Eds. V Kumar, A k Abbas, N Fausto. 7th Edn.; W.B. Saunders Elsevier, Philadelphia. 2004; pp 1353-1354.
11. Johnson KM, Suarez L, Felkner MM, Hendricks K: Prevalence of craniorachischisis in a Texas-Mexico border population. *Birth defects Research, Part A: Clinical and Molecular Teratology*, 2004; 70(2): 92-94.
12. Jones KL: Smith's recognizable patterns of human malformation. 6th Edn.; Saunders Elsevier, Philadelphia. 2006; pp 704
13. Kapron C: Identification of the mouse *Loop-tail* gene: a model for human craniorachischisis. *BioEssays*, 2002; 24(7): 580–583
14. Kjaer I, Keeling JW, Graem N: Cranial base and vertebral column in human anencephalic fetuses. *Journal of Craniofacial Genetics & Developmental Biology*, 1994;14(4): 235-244.
15. Kulkarni ML, Mathew MA, Reddy V: The range of neural tube defects in Southern India. *Archives of disease in childhood*, 1989; 64(2): 201-204.
16. Moore CA. Classification of Neural tube defects. In: Neural tube defects from origin to treatment. Diego F. Wyszynski (Eds.), Oxford University Press, New York, 2006; pp 66.
17. Moore KL, Persaud TVN: The developing human. Clinically Oriented Embryology, 7th Edn.; Saunders Elsevier Philadelphia, 2003; pp 428.
18. Powers JM, Horoupian DS: Central nervous system. In: Anderson's Pathology. Damjanov & J Linder. Vol. 2, (Eds.), 10th Edn.; Mosby-Year Book.Inc. St. Louis, Missouri. 1996; pp 2693-2798.
19. Timor-Tritsch HE, Greenebaum E, Monteagudo A, Baxi L: Exencephaly-anencephaly sequence: proof by ultrasound imaging and amniotic fluid cytology. *Journal of Maternal-Fetal and Neonatal Medicine*, 1996; 5(4):182–185.
20. Van Allen MI, Kalousek DK, Chernoff GF, Juriloff D, Harris M, McGillivray BC, Yong SL, Langlois S, MacLeod PM, Chitayat D, Friedman JM, Wilson RD, McFadden D, Pantzar J, Ritchie S, Hall JG: Evidence for multi-site closure of the neural tube in humans: *American Journal of Medical Genetics*, 1993; 47(5):723-743.
21. Wilkins-Haug L, Freedman W: Progression of exencephaly to anencephaly in the human fetus: an ultrasound perspective. *Prenatal Diagnosis*. 1991; 11(4): 227–233.