

## Case Report

# Craniorachischisis Totalis: A Necropsy Analysis

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### ABSTRACT

Neural tube defects are common congenital anomalies seen most commonly among population of low socio-economic status. These anomalies range from spina bifida occulta to craniorachischisis totalis and iniencephaly, which are very rare conditions. In many cases neural tube defects are associated with other malformations. Neural Tube Defects are seen mostly affecting first pregnancy. Neural Tube Defects are seen in all corners of the world. India also has quite high incidence, and in many cases it is due to folic acid deficiency. Here we present a case of Craniorachischisis totalis (Anencephaly with spina bifida aperta) in a 32 week gestation male fetus, born as fourth child to a Muslim mother. Academic autopsy was performed to see the presence of other associated congenital malformations, if any.

**Keywords:** Craniorachischisis totalis, Neural tube defects, Anencephaly, Spina bifida aperta, Congenital anomalies, Folic acid deficiency

### INTRODUCTION

Open neural tube defects are common congenital anomalies seen in population of low-socio economic strata. The various defects are spina bifida, meningocele, myelocoele, encephalocoele, anencephaly, craniorachischisis and iniencephaly. In many cases neural tube defects are associated with other malformations<sup>1</sup>. NTDs are seen mostly affecting first pregnancy and isolated NTDs are more common in female fetuses<sup>2</sup>. NTDs are seen in all corners of the world with highest incidence in Northern China<sup>3</sup>. India also has quite high incidence, with northern states like Punjab, Haryana, Rajasthan and Bihar scoring highest among other states<sup>4</sup>. Neural tube defects are thought to be associated with folic acid deficiency in diet, though maternal diabetes and use of valproic acid especially during early pregnancy have also been implicated<sup>5,6</sup>.

Every year worldwide around 3-4 lakh infants are born

with anencephaly and spina bifida<sup>7</sup> with prevalence being 1-5/1000 live births and risk of recurrence is 2-3% in future pregnancies<sup>8</sup>. Out of these in more than 95% of cases first pregnancies are affected<sup>2</sup>. Northern China is the capital of NTDs, with overall prevalence being 5-6/1000 live births<sup>3</sup>. In India, the prevalence of NTDs is found to be 3.63/1000 live births with most affected states being Punjab, Haryana, Rajasthan and Bihar<sup>4</sup>, while in the United States the prevalence is 1/1000 live births<sup>9</sup>. Prevalence of craniorachischisis totalis *per se* is very low worldwide and that in India could not be found even after extensive search on Internet. Relative lack of data on associated malformations in India prompted us to perform detailed necropsy and present our findings. In this case report, we present a rare case of craniorachischisis totalis, which was delivered in the obstetrics and gynaecology department of our hospital, was preserved in the department of anatomy and later necropsy was performed in collaboration with the department of forensic medicine.

## OBJECTIVES

To perform necropsy examination, to find out other associated congenital malformations, to examine whether the development of internal organs is according to gestational age and to provide proper counseling to the couple for future pregnancy planning.

## MATERIALS AND METHODS

Clinical autopsy was performed on a small for date, still born, freshly preserved fetus with craniorachischisis, delivered at 32 weeks of gestation by Lower Segment Caesarian Section, in the Department of Obstetrics and Gynecology of Chirayu Medical College and Hospital, Bhopal. Free informed consent of parents for donation of the fetus for academic purposes was obtained.

## CASE REPORT

A 40 year old unregistered Muslim female, G4 P1 A2, with transverse lie, polyhydroamnios, malformed fetus (? anencephaly on USG done outside) and a history of previous caesarian section was referred to our hospital, Chirayu Medical College and Hospital, Bhopal, for a malformed fetus. She arrived at our hospital in labour with pain with mild pre-eclamptic toxemia.

The lady was married for 18 years and had two spontaneous abortions in her first two pregnancies, both in first trimester. The cause of pregnancy loss was not known to patient and no records were available. In her third pregnancy, she delivered a normal female child, by caesarian section about 21 months back. She had history of poor antenatal checkups during her previous pregnancies and was never evaluated for recurrent first trimester pregnancy losses. Nutritional history suggested that she did not receive adequate nutrition and supplements during her present pregnancy.

On admission, she was hypertensive; all her abdominal findings confirmed the diagnosis of polyhydroamnios with transverse lie, mild Pre-eclamptic Toxemia and labour pains with previous caesarian section. Menstrual history suggested that the gestational period was 32 weeks. On USG abdomen, findings were confirmed in our hospital. She was taken for emergency caesarian section in view of above findings.

Caesarian section was performed after obtaining informed and free high-risk consent for procedure and anaesthesia. On caesarian section, a preterm, small for date, male stillborn fetus was delivered.

## EMBRYOLOGICAL ANALYSIS OF CRANIORACHISCHISIS

In developmental process in embryonic life, on 15th day, primitive streak is formed by active migration and invagination of pluripotent ectodermal cells into space between epiblast and hypoblast. This process is known as gastrulation. This primitive streak acts as primary organiser and induces differentiation of notochord, which in turn induces the differentiation of neural tube from medullary plate<sup>10</sup>. Neural tube formation starts on day 22 at the level of somite 3, and fusion proceeds, both rostrally and caudally. The neural tube closes by day 26 to day 28<sup>11,12</sup>.

For the formation of neural tube, embryonic neural folds undergo major morphological changes. They elevate from semi-horizontal position to the vertical position and change from convex pattern to concave. Thus, their tips which were formerly pointed away from midline, tilt towards midline, touch and fuse. Failure in the process of elevation to become vertical and concave prevents making of contact to fuse and form a tube<sup>12</sup>.

When neural groove fails to close completely, open neural tube defects result ranging from anencephaly, spina bifida occulta with meningocele or meningomyelocele to spina bifida totalis<sup>10</sup>. Sometimes, even a closed neural tube may re-open. Open spinal defects of the thoracic and cervical spinal cord are least common. A primary disturbance in the axial mesodermal may impair the formation, elevation, rotation, approximation and fusion of neural folds, leading to craniospinal rachischisis<sup>11-14</sup>.

Craniorachischisis is a type of neural malformation in which open cranial defect is in continuation with complete spinal dysraphism and thus, represents a complete failure of neurulation. It is postulated that it results from dysmorphogenesis, occurring at 20–22 days after conception. It has been suggested that embryonic midline is a weak and developmentally vulnerable developmental area, susceptible to the actions of a variety of

dysmorphogenetic forces. Various dysmorphogenetic forces, which may cause embryogenetic insults, could be as varied as mechanical disruption via amniotic bands, single-gene mutations, chromosomal aberrations (trisomy 18) and/or disruptive vascular events<sup>15,16</sup>.

In mouse studies, genetic factor has been studied in detail and a gene located has been labelled as *Loop tail*, which is found to be responsible for functioning in the floor plate formation. The gene is designated as *Ltap/Lpp 1*. The mutations in these genes have been associated with the occurrence of craniorachischisis<sup>17</sup>. Recently, 'multisite neural tube fusion' hypothesis has been used against traditional single-site model of Neural Tube closure for best explanation of neural tube defect in human beings and to explain most of the NTD variants, e.g., anencephaly results from failure of closure at site 2, whereas Craniorachischisis at sites 2, 4 and 1<sup>18, 19</sup>.

**OBSERVATIONS**

**External Examination**

During autopsy, examination of skin and other findings confirmed that fetus was fresh still born. Finding of Craniorachischisis totalis was confirmed (Figure 1). Forebrain was completely absent; some brain tissue was identified attached by pedicle. Specific structures could not be differentiated. Total spina bifida was seen with defect in continuation of anencephaly and extending from cervical region to sacral region and covered by meninges. Skull vault was absent.

External ears were curled, low set; eyeballs were bulging and nose wide and flat (Figure 2). Lips were not cleft. Neck was short and fused. Chest and upper limbs were normal. Umbilical cord was normal containing three vessels. Anal opening was present. External genitalia (penis and scrotum) were developed according to the gestational age (Figure 3). Lower limbs were normal.



Figure 2:



Figure 3:

**Internal Examination**

Oral cavity: Lips and alveolar arches were normal. Lower lip and mandible were split to see the palate, which was non-cleft, high arched and tongue was normal (Figure 4).

Thoracic cavity: Rib cage was normal. Heart and lungs were of normal size as per gestational age. No gross abnormalities were seen in heart and lungs. Heart was



Figure 1:

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Figure 4:

dissected, no septal or other structural malformations were present. Thymus gland was identified in superior and anterior mediastinum, 4x3x1 cm in size and bi-lobed (Figure 5). Right and left domes of diaphragm were normal.

Abdominal cavity: Liver and gallbladder were normal. Spleen was lobed and normal for gestational age. Stomach, small and large intestine were normal in size and position and no rotational defect was seen (Figure 6). Large intestine contained meconium. Cecum and appendix were sub-hepatic. Kidneys were lobed and normal in size. Suprarenal glands were normal for gestational age. Ureters were identified on both sides and were normally placed (Figure 7). Urinary bladder was normal. Right testis was descended up to superficial

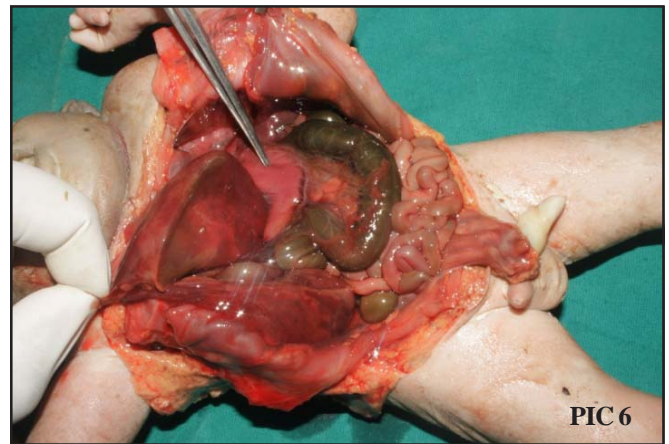


Figure 6:

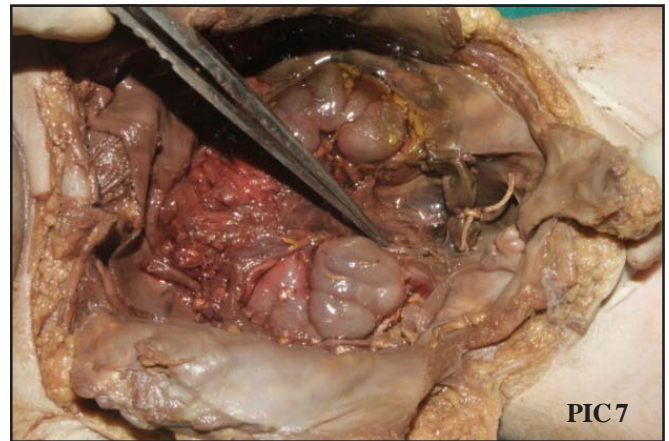


Figure 7:

inguinal ring and left testis was descended into the scrotum (Figure 3).

## DISCUSSION

Neural tube defects are one of the three most common serious congenital anomalies, viz., heart defects, neural tube defects and Down syndrome<sup>20</sup> and include a spectrum of conditions like spina bifida, menigomyelocele, encephalocele, anencephaly, craniorachischisis, iniencephaly singly or in combination with other congenital malformations and organ dysfunctions<sup>21</sup>. Association of other congenital anomalies has been found to vary from 24 to 33.3%. Females are approximately three times more commonly affected than males<sup>1</sup>.

Craniorachischisis can be detected by USG as early as

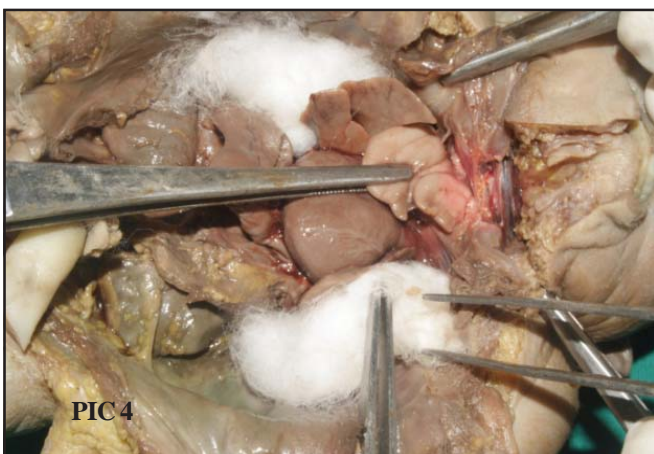


Figure 5:

13–14 weeks and by alpha-feto protein screening during ante-natal care. There is no treatment or cure available for this malady. Fetal death is certain. If fetus remains viable at birth, neonatal death is certain shortly after birth. These fetuses are deaf, blind, mute and unable to feel any pain. They would never gain consciousness as they lack cerebrum. Along with craniorachischisis, there can exist other anomalies like large thymus, small adrenal glands, hypoplastic lungs, cyclopia, syndactyly, absent radius and thumbs, imperforate anus, club foot, sirenomelia, single umbilical artery, pentalogy of Cantrell, cleft palate, cleft lip, horse shoe kidney, absent or hypoplastic kidney, exomphalos, umbilical hernia, diaphragmatic hernia, skeletal defects, hydronephrotic or polycystic kidney and other NTD variants<sup>1,11,15,22</sup>.

Various aetiological factors have been linked to these anomalies. In largest ever comparative study, it has been observed that there is too much aetiological heterogeneity in the occurrence of NTDs, and plays a significant role, as in other congenital malformations<sup>1,23</sup>. It is postulated that aetiologies of occurrence are different in cases of neural tube defects with and without other non-neural malformations<sup>24</sup>. Aetiopathological factors responsible for causing of NTDs are mostly genetic and environmental influences combined together. The risk factors are: (1) pregnancy, (2) consanguineous marriage, (3) white race, (4) low socio-economic status, (5) low folate intake, (6) febrile illness in early pregnancy, (7) viral infection, (8) amniotic band disruption during pregnancy, (9) exposure to teratogenic drugs and elements, e.g., lead, (10) maternal diabetes, (11) maternal intake of antiepileptic drugs like valproic acid, (12) single-gene mutation, (13) chromosomal aberrations (translocation/trisomy 18) and (14) congenital malformation/genetic abnormality or early childhood deaths in the family of couple<sup>6,16,25,26</sup>.

In our case, both the parents were in their 40s. The couple was Muslim and there was no history of consanguinity. History of previous two first trimester spontaneous abortions was present. Nutritional history was suggestive of poor and inadequate dietary and supplement intake during pregnancy. Thus, risk factors in our case were low socio-economic status of the couple and poor maternal nutrition. This conception was spontaneous conception

and except for poor ante-natal care; there was no other significant history in ante-natal follow-up. Her ultrasonography, done outside at 28 weeks gestation, revealed hydroamnios, absence of flat bones of calvaria and non-visualisation of brain tissue. Spinal dysraphism was not quoted.

Standard cytogenetic studies on fetal cord blood, necrogram and histological examination of testicular tissue were not done as fetus was fixed in formalin before necropsy.

This case is presented to highlight variations and deviations in many established facts about craniorachischisis. These are:

1. The case has occurred in 4th gravida, as against the most of literature showing contribution of more than 95% case by the first pregnancy. Although there was history of first trimester pregnancy loss, the cause of such loss could not be established as abortions were spontaneous, and dilatation and curettage was done by some rural quack. It is postulated that chances of recurrence of NTDs increase by 2–3% after first affected fetus with neural tube defects and further increase in subsequent affected pregnancies. As this female had a normal baby from her third pregnancy, chances of first two pregnancy losses due to neural tube defects seem less. Because there was no history of consanguinity, chances of genetic factors playing role for such anomaly in fetuses of this couple are also less.
2. Except for the presence of low set curled external ear and short fused neck, which are features of anencephaly, there were no other associated external or internal anomalies in our case. Other associated anomalies are seen in approximately one-third of cases with NTDs<sup>1</sup>. Some of the commonly found associated anomalies like cleft lip, cleft palate, hypoplastic lungs, small adrenal glands, absent/hypoplastic or horse-shoe kidneys, umbilical and diaphragmatic hernia were not present in our case.
3. Though it is said that isolated NTDs are more common in female fetuses,<sup>5</sup> in our case the fetus was a male fetus.

4. Presence of meconium was noted in large intestine. It is thought that swallowing reflex is absent in cases of anencephaly and craniorachischisis, but the presence of meconium in intestine in our case, prompts the need for further evaluation and research.

## CONCLUSION

1. Awareness of defects and different causative factors can help in reducing or preventing NTDs in future generations.
2. Genetic mapping of parents of affected fetuses and infants should be done in cases, where history of consanguinity or NTDs in any of the parents' family is present.
3. Genetic counseling should be given more importance, encouraged in every case and should be made easily available and affordable to population. This will help in reducing prevalence of NTD in the community.
4. Though a number of programmes are implemented by the government to ensure regular ante-natal check up and registration of pregnant women in villages and urban areas; further strengthening, awareness of population at large and monitoring is required to give expected and desired outcome.
5. Knowledge about adequate ante-natal screening and role of folic acid supplementation through various public health agencies and programmes on large scale should be executed more thoroughly. General population should be made well aware of beneficial effects of folic acid supplements, folate-rich food and importance of adequate maternal nutrition during pregnancy.
6. In spite of knowing much about NTDs, there are still grey areas to explore.
7. Because of relative lack of well-studied data in Indian literature, we suggest maximum reporting of cases of NTDs, especially craniorachischisis totalis, and publication of findings after thorough necropsy examination.
8. We also agree, suggest and share the view of Pleydell *et al.* that all infections in pregnancy should be

notifiable and also maintenance of registers of congenital abnormalities is to be made compulsory so that we get exact records for comparisons throughout the country.

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