CASE REPORT

Craniorachischisis Totalis: A Detailed Case Report

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ABSTRACT

Neural tube defects (NTDs) are severe congenital anomalies resulting from improper neural tube closure. Craniorachischisis totalis, the most extreme form, involves failure of neural tube formation along the entire cranio-spinal axis. This rare condition is fatal, with limited reported cases globally.

We report a case of a 35-year-old G3P1L1A1 woman admitted at 20 weeks and 4 days gestation for medical termination of pregnancy following second-trimester ultrasound findings of anencephaly and spinal dysraphism. The patient began folic acid supplementation only after pregnancy confirmation. The fetus exhibited acrania, bifid vertebrae, exposed neural tissue, frog-eye deformity, and limb contractures. Butterfly vertebrae was observed in infantogram. Retrospective ultrasound review revealed an absent cranial vault, disorganized brain matter, and a large open spinal defect extending to the upper lumbar region. Genetic and infectious panels were largely unremarkable, except for reactive rubella IgG.

Craniorachischisis totalis arises from failure of neural tube closure, potentially linked to genetic mutations, folate deficiency, and multiple maternal risk factors. Here, we also revisit the various theories of neural tube closure. Early prenatal diagnosis and counseling are critical for managing craniorachischisis. Periconceptional folic acid supplementation remains the most effective preventive measure.

Introduction

Neural tube defects (NTDs), one of the most frequent causes of congenital malformations, are a collection of abnormalities caused by disruption of neural tube closure. These affect around 0.5-2 per 1000 live births globally (1). In India, four to eight infants per 1,000 live births are born with NTDs, which are serious and life-threatening (2). Craniorachischisis, in which the central nervous system fails to transition from a neural plate to a neural tube, is the most severe type of NTD (3). Its prevalence varies widely from 0.1 to 10.7 per 10,000 live births (4,5). The term itself originates from three Greek words – kranion

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(skull), rhakhis (spine), and schisis (separation). Its defining characteristics are anencephaly (the lack of a brain, cranial vault, and skin covering) and a bone deformity of the cervical spine (the absence of meninges covering the neural tissue). Rarely, in a condition called craniorachischisis totalis, the open defect spreads to the thoracic or even lumbosacral spine (4). Knowingly, a neural plate forms at the beginning of the third week, and its lateral edges, called neural folds, approach each other and fuse at the midline to form a neural tube. Fusion is initiated at the cervical region, proceeds both craniocaudally ("zipper" model), and is completed by the 28th day (6). Though NTDs are multifactorial, folic acid deficiency is a well-established factor, and preconception folic acid supplementation has been shown to reduce the occurrence of NTDs by 62 to 70% (7). The present study presents a case of craniorachischisis totalis.

Case

A 35-year-old G3P1L1A1 was admitted at 20 weeks and four days of gestational age for Medical Termination of Pregnancy (MTP) as her second-trimester ultrasound showed anencephaly. She had a normal menstrual cycle. No history of diabetes mellitus, hypertension, epilepsy, tuberculosis, or thyroid disorders was reported. She is a known case of Asthma on inhaler salmeterol and fluticasone. She started taking 400 µg folic acid only after pregnancy diagnosis at around the fifth week. After the second-trimester ultrasound detected NTD, she was advised to take 5 mg of folic acid. Her first child, a 15-year-old girl, is normal. She went for an induced abortion 14 years back. A history of hydrocephalus was observed in a child born to her sister-in-law, who was treated using a ventriculoperitoneal shunt. The family history was recorded as a pedigree chart (Figure 1).

After informed consent of the patient, the pregnancy was terminated. The fetus was male, weighing 215 g. A gross external examination revealed the absence of a cranial vault (acrania) and an underdeveloped brain. Bifid vertebrae up to the upper lumbar level led to exposed neural tissue (Figure 2A). The eyes were bulging out (frog-eye deformity) (Figure 2B). Upper and lower limbs were normally developed but had contractions at the elbow and knee (Figure 2C).

Postnatal radiography of the fetus in the anteroposterior and lateral views showed abnormal cranial vault and vertebrae (Figures 3A and 3B). The skull vault was underdeveloped, and vertebral arches were open until the lumbar vertebrae. We also found butterfly vertebrae in the upper thoracic region (Figure 3C), resulting from a lack of fusion of both halves of the vertebral bodies.

On retrospectively examining the mother's second-trimester ultrasound, we observed the absence of a cranial vault, and residual disorganized brain matter was seen floating in the amniotic fluid (Figure 4A). A large open spinal defect was found in the cervical, thoracic, and upper lumbar levels (Figure 4B). Bilateral enlarged protruding orbits were seen (Figure 4C). The rest of the organ systems were within normal limits.

Noninvasive prenatal testing (NIPT) of the mother using time-resolution fluorescence immunoassay for trisomy 21, trisomy 18, and trisomy 13 showed negative results. Enzyme-linked immunosorbent assay testing for toxoplasmosis, rubella, cytomegalovirus, and herpes simplex infections showed that rubella immunoglobulin-G (IgG) serology was reactive.

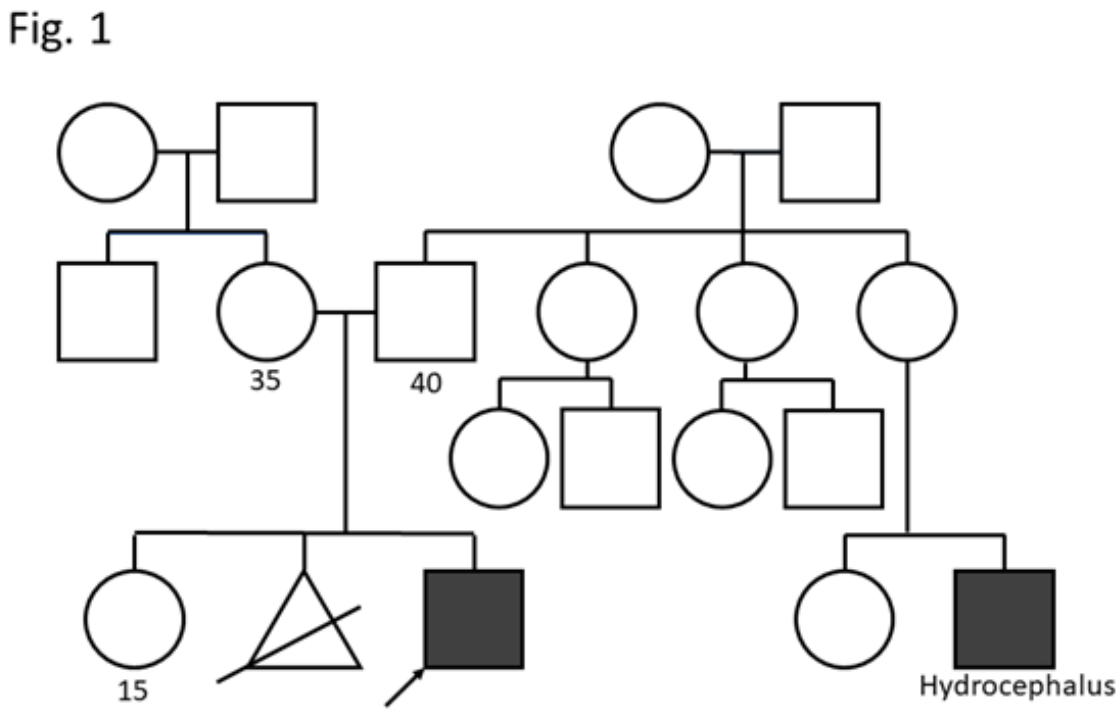

Figure 1. Pedigree chart showing the family history of the patient. Arrow denotes the Craniorachischisis totalis case. Sister-in-law of the mother having a child born with hydrocephalus

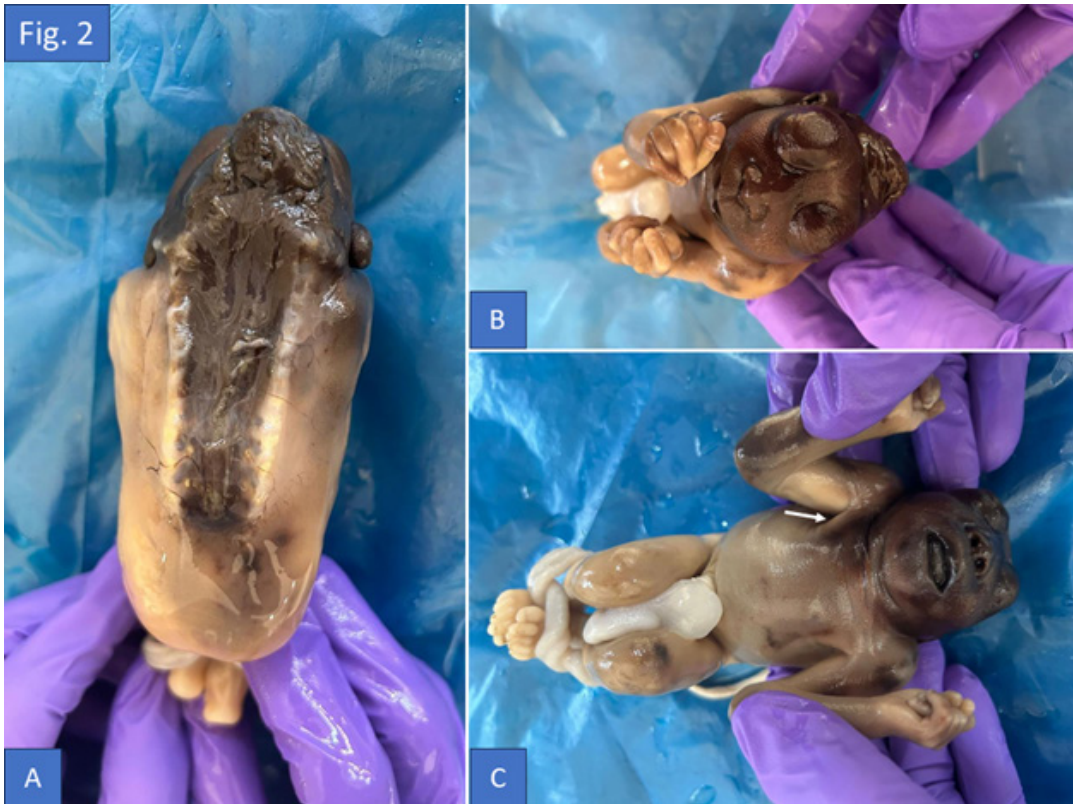

Figure 2. Gross anatomy of the fetus. 2A: posterior view showing exposed brain tissue with open spinal defect; 2B: view from cranial end showing frog-eye deformity and broad nose; 2C: anterior view showing contractures at the shoulders (arrow) and knees

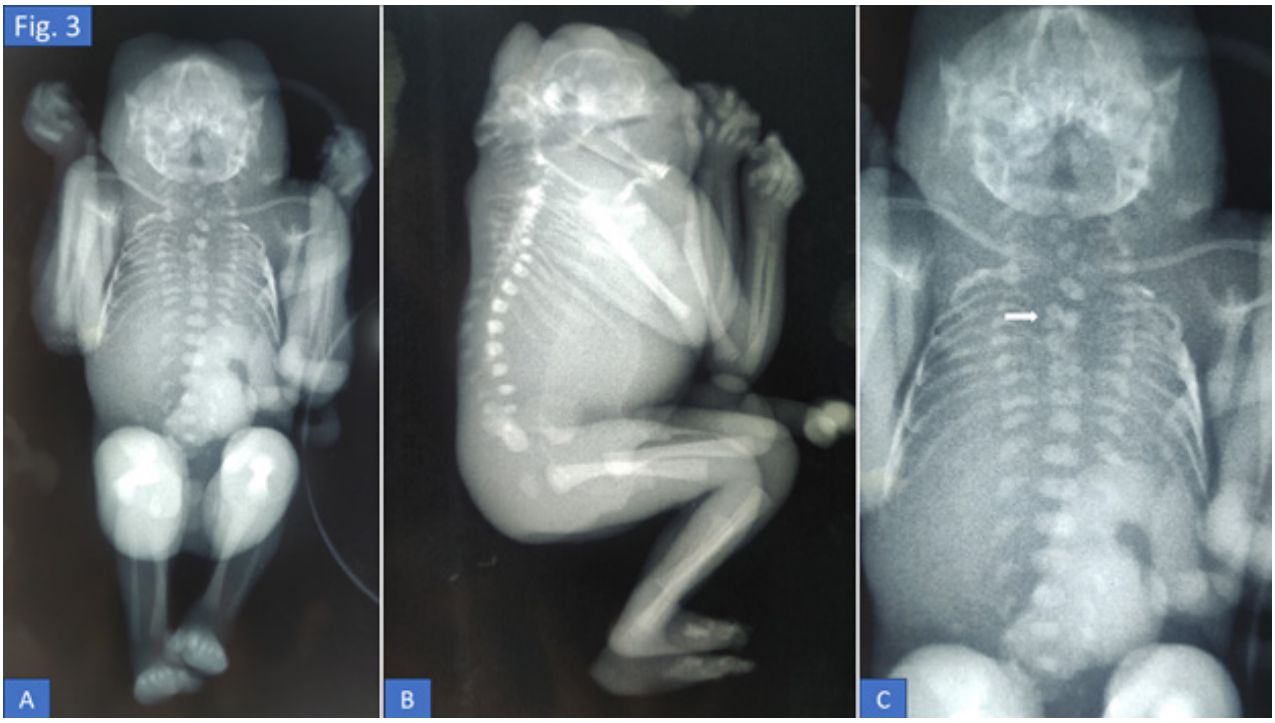

Figure 3. Infantogram of the fetus. 3A. Antero-posterior (AP) view; 3B. Lateral view showing acrania; 3C. AP view showing Butterfly vertebrae (arrow)

Discussion

The brain and spinal cord are derived from the neural tube, formed from a central flat layer of specialized ectodermal cells (neural plate) cranial to the primitive node. During the fourth week, the neural plate progressively folds to form the neural groove, and neural folds fuse to form the neural tube. The fifth somite marks the beginning of the fusion of the neural folds and the creation of the neural tube, developing cranially and caudally (Figure 5A) until only small portions of the tube are still open at both ends-rostral neuropores that close on the 25th day, followed by caudal neuropore at 27th day (8). Some other literature proposes initiating neural tube closure starting at three locations along the body axis in the mammalian embryo (Figure 5B). The first de novo closure site (also known as closure 1) is located in the future cervical area, whereas the second and third sites (also known as closures 2 and 3) are located, respectively, at the forebrain-midbrain border and the forebrain's most rostral extension (9). Craniorachischisis, the most severe form of NTD, results from a failure to commence neurulation at closure 1, the beginning of neural tube creation (10). Currently, the rostrocaudal axis has been divided into four to five (and occasionally six) potential sites for closure (8,11). In the four sites model, closure 1 occurs between the second and fourth somite pairs, closure 2 at the prosencephalic-mesencephalic border, closure 3 starts next to the stomodeum at the most anterior portion of the neural folds, and closure 4 is initiated at the caudal end of the rhombencephalon (Figure 5C). In the five closure sites model, three sites are in the head, two in the spinal region, and the fifth site is at the region of the second lumbar (L2) to the second sacral (S2) vertebral level (Figure 5D). Beyond S2, closure occurs by secondary neurulation. To explain the

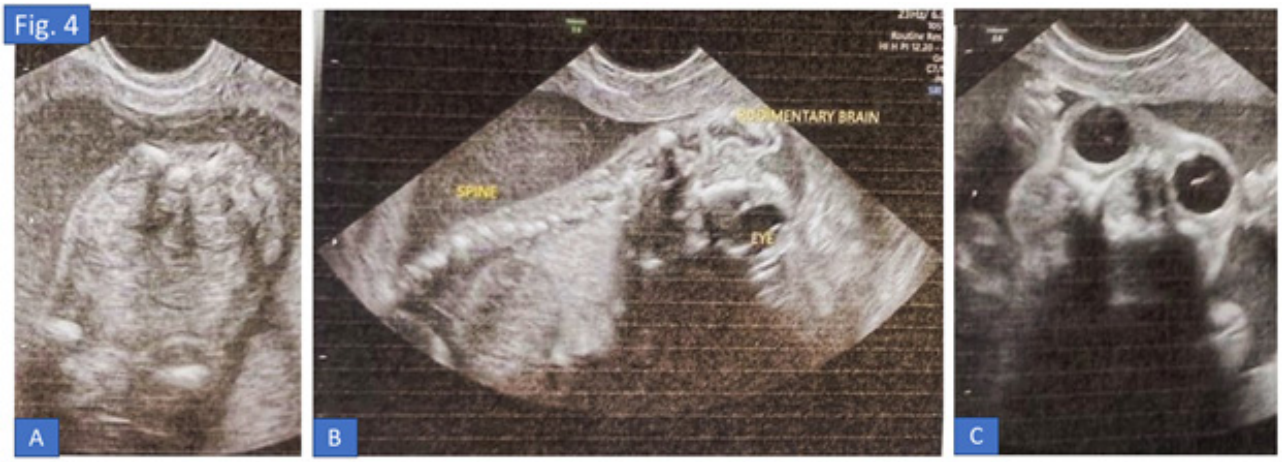

Figure 4. Second-trimester ultrasound. 4A. cranial vault absent; 4B. sagittal view showing a rudimentary brain with open spinal defects; 4C. coronal section through fetal face showing frog-eye deformity and absence of calvaria

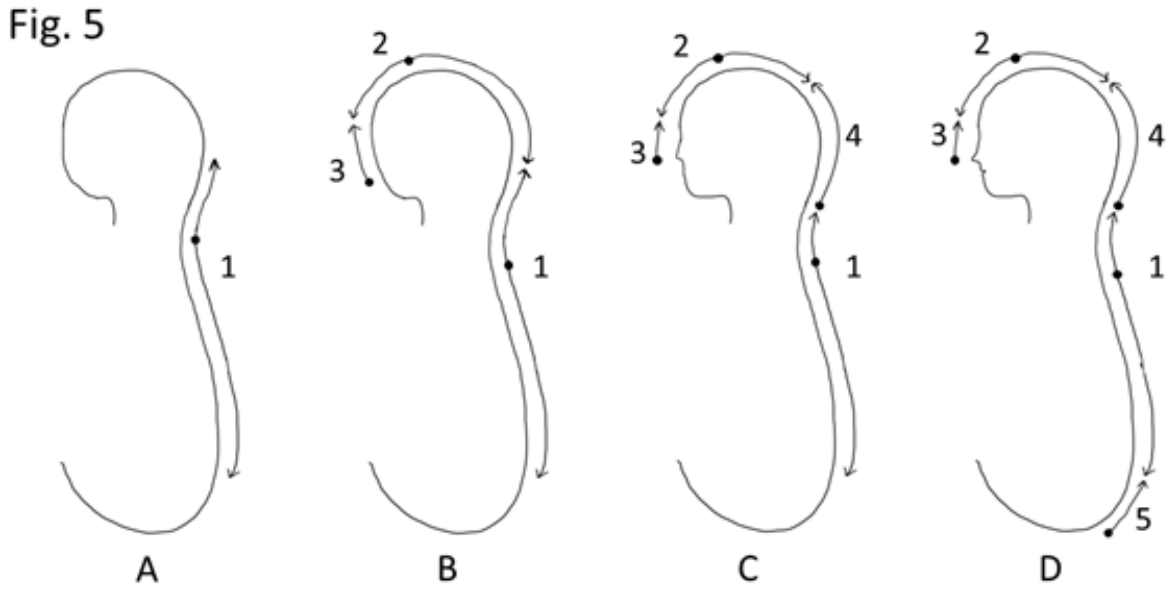

Figure 5. Models of neural tube closure. Dots represent the location of closure initiation sites, and arrows represent the directions of further fusion. 5A. 1 site closure theory; 5B. 3 sites closure model. 5C. 4 sites closures model; 5D. 5 sites closure model

presence of three meningomyeloceles, a study proposed closure of site 6 at the midthoracic cord, then proceeding cranio-caudally to meet site 1 and site 5, respectively (11). Site 3 is the least susceptible to non-fusion. Failure to seal sites 2, 4, and 1 result in craniorachischisis. (8). It typically develops in the third to fourth week of pregnancy and affects the central nervous system and nearby tissues. Defects in neural tube closure can lead to ectodermal and mesodermal abnormalities. Fetuses lack the cranial vault, with varying degrees of abnormality spreading to the vertebrae. The neck may be short or non-existent, and there may be facial dysmorphisms such as a large nose, exophthalmos, low-set ears, and folded ears. The hindbrain, spinal cord, and posterior telencephalon are frequently externally accessible (12).

In Atlanta, the reported prevalence for cases with 20 weeks or more of gestation is about 0.1 per 10,000 live births; this prevalence has been adjusted upward by 30% to account for prenatal terminations. In a population on the Texas-Mexico border, the reported prevalence was 0.51 per 10,000 births; this population's prevalence ascertainment included prenatal terminations. In Northern China, the reported prevalence is 10.7 per 10,000 births; in Southern China, it is 0.9 per 10,000 births (12). The rarity of craniorachischisis totalis makes a study on non-genetic risk factors important. The planar cell polarity (PCP) route, a single molecular signaling cascade, has been identified as the primary cause of the bulk of mice craniorachischisis cases currently known. More than 100 genes are required for the mouse's neural tube to close, and most mutant genes that stop PCP signaling resulting in craniorachischisis have also been investigated in human abnormalities (3). According to new genetic research, craniorachischisis totalis can be caused by missense mutations in the *SCRIB* and *CELSR1* genes (13).

Risk factors for NTDs include maternal diabetes, obesity, hyperthermia, drugs like valproic acid, carbamazepine, and others (12). An established positive correlation was observed between folate deficiency in mothers and NTDs. Folate, an essential water-soluble B-complex vitamin, is involved in synthesizing nucleotides, which are required in large numbers by the rapidly dividing neuroectodermal cells. A deficiency in folate results in an insufficient supply of nucleotides to the cells in the neural plate, slowing down the development of neural folds. Folates are also part of the methylation pathway, and studies in mouse models have shown that disruption of this pathway may lead to an increased prevalence of NTDs (14). Certain congenital infections can also hamper brain development, and rubella infection may be associated with fetal anencephaly (15).

Due to the amniotic fluid's intrinsic toxicity, the brain and spinal cord are exposed to the intra-amniotic environment in these situations, leading to the destruction of nerve tissues. The remaining cerebral tissue is seen as an amorphous mass covered in meninges, vascular tissue, glia, and a few neuroblasts or neurons and is connected to an abnormal spinal cord (12).

Prenatal diagnosis of craniorachischisis is possible with ultrasound showing acrania and spinal dysraphism (16). It is a lethal condition and has no cure or surgical intervention. The fetuses are stillborn and, if diagnosed prenatally, are advised to undergo MTP.

In Conclusion

Craniorachischisis is a rare abnormality resulting from a defect in neural tube closure. Being a lethal condition, it must be identified prenatally. Prenatal counseling and periconceptional folic acid supplementation should be implemented as preventive measures for mothers.

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Authors' Contribution

Dr. Gaikwad was responsible for the study concept. Dr. Praisy Joy coordinated the study and interviewed the parents. Dr. Sayan and Dr. Suranjana helped with data collection under the supervision of Dr. Jasmina and Dr. Deep and carried out the literature search. Dr. Sayan led the drafting of the manuscript with input from

Dr. Suranjana and Dr. Praisy Joy. All authors contributed to revising and final approval of the manuscript.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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