Exencephaly – A Fatal Form of Neural Tube Defects in Fetus

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Abstract

Exencephaly is a type of cephalic disorder, wherein the brain is located outside of the skull. This condition is usually found in embryos as an early stage of exencephaly. As an exencephalic pregnancy progresses, the neural tissue gradually degenerates. The prognosis for infants born with exencephaly is extremely poor. It is rare to find an infant born with exencephaly, as most cases that are not early stages of anencephaly are usually stillborn. Those infants who are born with the condition usually die within hours or minutes.

This case report concerns a multigravida woman (G) who was 19+4 weeks±2 weeks pregnant and she came to Hakeem Abdul Hameed Centenary Hospital (HAHC) Hospital for medical termination of pregnancy as it was diagnosed with exencephaly one of a neural tube defect in growing fetus. She had been married for 6 years and this was her second pregnancy. She had not taken any folic acid supplementation and came to Hakeem Abdul Hameed Centenary Hospital (HAHC), New Delhi on October 3, 2017 for medical termination of pregnancy as it was diagnosed in level-II USG done elsewhere, neural tube defects (exencephaly) in fetus. She was unable to remember her LMP and it was a spontaneous conception and she did not come to know about her pregnancy even after 1½ months of amenorrhea since she had irregular menstruation. She had her first ultrasound on 28.06.2017 which showed a hematoma measuring 15×6.0 mm near to the gestation sac. Again ultrasound was advised on 3.10.17, in which the fetus showed absence of calvarial bones in bilateral parietal, temporal and occipital region with presence of calvarium in frontal region. The fetal brain showed enlarged cerebral hemisphere and herniating posteriorly and directly exposed to the CSF. The cerebellum and brainstem were poorly formed. Her first child also was a case of tuberous sclerosis with symptomatic epilepsy.

Keywords: Exencephaly, Neural tube defects, Tuberous sclerosis, Epilepsy

Introduction

A 25-year-old multigravida woman came to antenatal OPD of HAHC Hospital, New Delhi, with complaints of amenorrhea since 4½ months and she came for medical termination of pregnancy. She was diagnosed in level II ultrasound with neural tube defect (exencephaly) in the fetus. The patient was having 19+4 week±2 weeks of gestation and she had not received any folic acid supplementation. She did not visit the hospital earlier and on 28.06.2017, her first ultrasound report showed a hematoma measuring 15×6.0 mm near to the gestation sac. Again ultrasound was advised, which was done on 3.10.17, in which the fetus showed absence of calvarial bones in bilateral parietal, temporal and occipital region with presence of calvarium in frontal region. The fetal brain showed enlarged cerebral hemisphere and herniating posteriorly and directly exposed to the CSF. The cerebellum and brainstem were poorly formed. Other facial features including both orbits appeared...
normal, spine appeared normal, heart, chest, abdomen, renal, placenta all were normal.

The patient weighed 53 kg and had been married for 6 years. There was no history of any neurological impairment from both maternal and paternal side. Her age at menarche was 13 years and she had an irregular menstrual cycle. She had no significant history of any other illness also such as DM, seizures, asthma, cardiovascular, or any other medical illness. In her obstetrical history, her first baby was girl child, delivered through induced vaginal delivery with prolonged labour and instrumental delivery. The girl is having tuberous sclerosis with symptomatic epilepsy and delayed milestones of growth and development. She is currently undergoing treatment from Neurological Department of Safdarjung Hospital, New Delhi. Her routine blood investigations were normal such as Hb (11.5 g/dL), TLC (1074/cumm), platelet count (2.49 lac/cumm), blood group (AB+ve).

After admission to the labor room, she was advised Tab Mifepristone 200 mg PO stat at 6 pm on 3.10.17. She was given Tab Misoprostol 800 mcg PV at 6 pm on 5.10.17 per vaginally. On 6.10.17 at 8:30 am, she expelled a female baby with exencephaly weighing 0.431 kg. Placenta and membranes were expelled completely and placenta was sent for histopathological examination. Patient was given Tab Methergin 1 tab, TDS for 3 days and Tab Rantac 150 mg SOS, and Tab Voveron 75 mg SOS. Patient was advised to conceive only after 6 months was advised for pre conceptional counselling.

Exencephaly is the absence of a major portion of the brain, skull, and scalp that occurs during embryonic development. It is a cephalic disorder that results from a neural tube defect that occurs when the rostral (head) end of the neural tube fails to close, usually between the 23rd and 26th day following conception.\(^1\)

Strictly speaking, the Greek term translates as “no in-head” (that is, totally lacking the inside part of the head, i.e. the brain), but it is accepted that children born with this disorder usually only lack a telencephalon, the largest part of the brain consisting mainly of the cerebral hemispheres, including the neocortex, which is responsible for cognition. The remaining structure is usually covered only by a thin layer of membrane — skin, bone, meninges, etc., are all lacking. With very few exceptions, infants with this disorder do not survive longer than a few hours or possibly days after their birth.\(^1\)

Epidemiology

Generally, exencephaly equals an incidence of three cases per 10,000 pregnancies. Research has suggested that overall, female babies are more likely to be affected by the disorder.\(^1\)

Incidence

According to Papp and colleagues, who screened 36,075 pregnancies for neural tube defects, the incidence of exencephaly was three per 10,000 pregnancies. Cox and colleagues concluded that exencephaly probably represents an embryonic precursor to anencephaly. However, reopening or degeneration of a previously closed neural tube is also possible.\(^2\)

Pathophysiology

Exencephaly is a rare precursor of anencephaly in which a large amount of brain tissue is present despite the absence of the calvaria. The brain in these cases consists of a disorganized, anarchic outgrowth of nervous tissue with polymicrogyria and nodules of heterotopias.\(^3\)

Exencephaly is a congenital malformation along a spectrum that includes acrania and anencephaly (acrania-exencephaly-anencephaly sequence). In acrania, the flat bones of the skull are at least partially absent, with complete but abnormal development of the cerebral hemispheres. Exencephaly demonstrates a large amount
of disorganized brain tissue extending from a malformed skull base. Because this brain tissue is covered by only a vascular layer of epithelium, it can slowly degrade by the amniotic fluid and degenerate into anencephaly.³

Exencephaly is caused due to the failure of the anterior neuropore to close during the fourth week of embryonic development. The underlying defect is due to a failure in mesenchymal migration. In pathologic studies, the exencephalic brain is noted to be covered by a highly vascular epithelial layer. In exencephaly, two relatively equivalent cerebral hemispheric remnants are present within a reddish mass of disorganized tissues, remnants of deep cerebral neural elements, blood vessels, fibrous tissues, and fluid-filled spaces. The remaining brain has been termed the “anencephalic area cerebrovasculosa.” In exencephalic brain tissue, the gyri and sulci are shallow, flattened, and disorganized. All surfaces of the brain are highly vascular. The remaining central nervous system tissue is dysplastic, with little or no neuronal differentiation, and very little normal cortex.⁴

The acrania-exencephaly-anencephaly sequence is commonly diagnosed by prenatal ultrasound between 14 and 18 weeks, but some findings may suggest the diagnosis much earlier in gestation. Regardless of gestational age at diagnosis, the prognosis is poor.⁵

Sign and Symptoms

The National Institute of Neurological Disorders and Stroke (NINDS) describes the presentation of this condition as follows: “A baby born with exencephaly is usually blind, deaf, unaware of its surroundings and unable to feel pain. Although some individuals with exencephaly may be born with a main brain stem, the lack of a functioning cerebrum permanently rules out the possibility of ever gaining awareness of their surroundings. Reflex actions such as breathing and responses to sound or touch may occur.”¹

Radiographic Features⁶

Imaging features have some overlap with those of anencephaly except that there is some brain tissue presence:

- Cranial vault is absent or poorly formed, cephalad to orbits.
- The nasal bone may be absent in most cases.
- Brain tissue is herniating or dangling in amniotic fluid.
- Brain tissue may be attached to the amniotic membrane.

Causes

The cause of anencephaly is disputed by medical professionals and researchers.

Folic acid has been shown to be important in neural tube formation since at least 1995, and as a subtype of neural tube defect, folic acid may play a role in exencephaly. Studies have shown that the addition of folic acid to the diet of women of child-bearing age may significantly reduce, although not eliminate, the incidence of neural tube defects. Therefore, it is recommended that all women of child-bearing age consume 0.4 mg of folic acid daily, especially those attempting to conceive or who may possibly conceive, as this can reduce the risk to 0.03%. It is not advisable to wait until pregnancy has begun, since, by the time a woman knows she is pregnant, the critical time for the formation of a neural tube defect has usually already passed. A physician may prescribe even higher dosages of folic acid (5 mg/day) for women having had a previous pregnancy with a neural tube defect.¹

In general, neural tube defects do not follow direct patterns of heredity, though there is some indirect evidence of inheritance, and recent animal models indicate a possible association with deficiencies of the transcription factor TEAD2. Studies show that a woman who has had one child with a neural tube defect such as exencephaly has about a 3% risk of having another child with a neural tube defect, as opposed to the background rate of 0.1% occurrence in the population at large. Genetic counselling is usually offered to women at a higher risk of having a child with a neural tube defect to discuss available testing.¹

It is known that people taking certain anticonvulsants and people with insulin-dependent diabetes have a higher risk of having a child with a neural tube defect.¹

Diagnosis

Exencephaly can often be diagnosed before birth through an ultrasound examination. The maternal serum alpha-fetoprotein (AFP screening) and detailed fetal ultrasound can be useful for screening for neural tube defects such as spina bifida or exencephaly.⁷

Prognosis

There is no cure or standard treatment for anencephaly and the prognosis for patients is death. Most exencephalic fetuses do not survive birth, accounting for 55% of non-abortion cases. Infants that are not stillborn will usually die within a few hours or days after birth from cardio-respiratory arrest.¹

In almost all cases, exencephalic infants are not aggressively resuscitated because there is no chance of the infant’s ever achieving a conscious existence. Instead, the usual clinical practice is to offer hydration, nutrition, and comfort measures and to “let nature take its course”. Artificial ventilation, surgery (to fix any co-existing congenital defects), and drug therapy (such as antibiotics) are usually regarded as futile efforts. Some clinicians and medical
Ethicists view even the provision of nutrition and hydration as medically futile.¹

Similar evidences have been found. In an article published in *Journal of Pediatric and Neurosciences*, a 21-year-old gravid primipara was admitted with a history of post maturity. Ultrasound of the abdomen revealed a single live fetus with breech presentation and a suspicion of anencephaly. She was given a trial labor with no response. Hence an elective caesarean section was performed. Intra-operatively minimal liquor was detected and the presentation was complete breech. The female infant was 3 kg in weight and had an APGAR score of 6 to 8. The infant expired after 3 hours.⁸ At autopsy, the fetal skull vault was found to be absent and the brain was covered by a thick membrane with visible tortuous blood vessels (Fig. 2). Three other swellings were noted in the occipital region, one extending up to the cervical vertebrae (Fig. 3). The fetus had a normal forehead and the eyes were protruding. The ears, oral cavity and nasal cavity were normal. No other external anomalies were seen (Fig. 4).⁸

Internal autopsy showed the brain and overlying tissue being covered by a highly vascular layer below which was a layer of loose connective tissue 2 to 4 cm thick (Fig. 2). When this layer was removed, two roughly symmetrical cerebral hemispheres were seen. In the cerebral cortex the gyri were flattened, sulci were shallower, and all surfaces were highly vascular. Cut sections of the cerebrum showed a single large ventricular chamber lined by numerous multi-lobular soft tissue masses with a vague corpus callosum-like white area. The average cortical thickness of the cerebrum was 2 cm. The occipital nodules also showed similar findings. All thoracic and abdominal organs were normal and well formed. Lungs floatation test was positive.⁸

On microscopic examination, the layer between the cortical surface and meninges was found to be composed of loose connective tissue, containing numerous tortuous vascular channels and focal nodules of dysplastic neural elements. The cerebral tissue contained scattered neurons, neuroblasts, and glial elements with a thinned-out layer of cortical tissue. The nodules in the occipital region showed cerebellar tissue, composed of nodules of dysplastic neural elements and was also covered by a highly vascular layer. Spinal subarachnoid space also showed foci of dysplastic neural tissue.⁸

**Management**

Because exencephaly is a lethal condition, heroic measures to extend the life of the infant are contraindicated. The physician and medical care team should focus on providing a supportive environment in which the family can come to terms with the diagnosis and make preparations for their loss.⁹

Families who are not aware of the diagnosis of exencephaly prior to birth or for whom the diagnosis is still fresh probably will need extra emotional support and possibly grief counselling.

With timely prenatal diagnosis of this lethal disorder, the option of pregnancy termination should be presented to the couple. For couples who elect to continue the pregnancy, the possibilities of preterm labor, polyhydramnios, failure to progress, and delayed onset of labor beyond term also should be discussed.¹⁰

Once a diagnosis of anencephaly is made, pregnancy management varies according to the gestational age at diagnosis. At pre-viable gestational ages, the option of pregnancy termination should be among those discussed. The gestational age limits for this procedure are state-specific and subject to the training and skill of the physician available to perform the pregnancy termination.

When patients choose not to proceed with pregnancy termination or when the pregnancy has progressed to a...
viable gestational age such that pregnancy termination is no longer an option (except in rare locations throughout the United States), attention should be focused on whether the labor will be induced or spontaneous and, if the former, at what gestational age.\textsuperscript{11}

Due to the physical stresses of pregnancy compounded by the emotional stress of carrying a fetus with a lethal birth defect, or because of the identification of medical conditions (e.g., preeclampsia) that may complicate any pregnancy, labor induction may be considered.\textsuperscript{12}

Focused discussions directed at neonatal resuscitation efforts should be held in advance of labor. These discussions should include a discussion of neonatal procedures used to resuscitate neonates, the cost of these measures, and alternatives to aggressive resuscitation. It is often best to include a neonatologist in these discussions. Clear documentation of these discussions is warranted. When delivery is planned in a hospital setting, labor and delivery nurses, obstetric care providers, and pediatric/neonatal attendants should be informed of the patient’s wishes for her child.

Because of the lethal nature of this condition, tocolytics (medical management to reduce uterine contractions) in an effort to prevent preterm birth is not a reasonable option, nor is cesarean delivery.

\textbf{Conclusion}

Exencephaly is characterized by the absence of cranial cavity and scalp with a large amount of protruding brain tissue covered by a membrane, and with prominent bulging eyeballs. Exencephaly is considered to lie somewhere on the spectrum between anencephaly and encephalocele. It is much less common than anencephaly but it has the same etiology and recurrence risk as other neural tube defects. Exencephaly is an uncommon malformation of the cranium that characteristically involves a large disorganized mass of brain tissue. The flat bones of calvaria are absent and the brain mass is left uncovered. It is a clinical entity which is incompatible with life. Neural tube defects account for most CNS malformations. Failure of a portion of neural tube to close or reopening of a region of the tube after successful closure, may lead to one of the several deformities. In our case, the primary diagnosis of anencephaly was ruled out on the basis that the flat bones of calvarium were absent. The marked dysplasia and disorganized development of cerebrum were atypical of meningoencephalocele. Exencephaly is rarely reported in human embryos. Anencephaly occurs in one in five per 1000 live births, more commonly in females. It is thought to develop at 28 weeks of gestation. As with anencephaly, exencephaly is also incompatible with life. Forebrain development is disrupted and all that remains is the area cerebrovasculosa with a flattened remnant of disorganized brain tissue admixed with ependymal, choroid plexus and meningotheelial cells.

Exencephaly is a rare precursor of anencephaly in which a large amount of brain tissue is present despite the absence of the calvaria. The brain in these cases consists of a disorganized, anarchic outgrowth of nervous tissue with polymicrogyria and nodules of heterotopias. In our case, all the macroscopic and microscopic findings were as described in literature, although we could not explain the persistence of exencephaly late in pregnancy and survival of the fetus for 3 hours.

\textbf{Conflict of interest:} None

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