Development of brain and spinal cord in anencephalic human fetuses*

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Abstract

Objectives: Anencephaly is the severest form of neural tube defects. The present study was undertaken to evaluate the development of brain and spinal cord in anencephalic human fetuses (specimens).

Methods: 43 specimens with anencephaly were collected after obtaining written consent from parents and clearance from ethics committee of the institute as per declaration of Helsinki guidelines. All the specimens were fixed in buffered formalin. Gross examination and histological studies of the brain and spinal cord were performed in each specimen.

Results: Gestational age of fetuses varied from 18 to 40 weeks, the majority being female fetuses. 31 (72%) fetuses had only anencephaly while 9 (21%) fetuses had additional spina bifida and 3 (7%) had meningomyelocele. The brain was observed as a dark brown undifferentiated mass with complete absence of the cerebellum, pons, medulla and midbrain. In 31 fetuses (72%), the spinal cord continued rostrally into an open neural tube that connected to the undifferentiated brown mass while in 12 fetuses (28%), it merged directly into the undifferentiated brown mass. Spinal cord was normal in appearance in all fetuses with anencephaly. Spinal cord was deformed in 3 fetuses (7%) having meningomyelocele. Histological examination of brain showed venous vessels of varying caliber interspersed with connective tissue, similar to an angioma along with islets of nervous tissue which mainly comprised of scattered nerve cells, astroglial cells and cavities lined by ependyma.

Conclusion: Our findings indicate that there is no functional organization of brain in anencephalic fetuses, and the survival of such fetuses is not possible. The spinal cord is normal in fetuses with anencephaly only while it is deformed in anencephalic fetuses with meningomyelocele.

Keywords: anencephaly; brain development; spina bifida; spinal cord development; meningomyelocele


Introduction

Congenital malformations have emerged as the 3rd commonest cause of perinatal mortality in India. Among all congenital anomalies, central nervous system anomalies are the commonest. Anencephaly is the most common CNS malformation. Kalra et al. presented the incidence of anencephaly as 2.57/1000 followed by spina bifida 2.2/1000, hydrocephalus 1.8/1000 and meningomyelocele 1.47/1000. Verma et al. observed anencephaly 3.6 in 1000 births, followed by hydrocephalus 2.2, meningomyelocele and meningocle 1 and microcephaly 0.2 in 1000 births. Goravalingappa and Nashi however found hydrocephalus and meningocele as the most common CNS malformations (2.0/1000 births) followed by anencephaly (0.83/1000 births). Chaturvedi and Banerjee showed that among CNS malformations, anencephaly and hydrocephalus were the commonest (1.32/1000 births each). Coffey and Jessop observed incidence of anencephaly as 5.9 in 1000 births in Dublin.

Vare and Bansal conducted an anatomical study on 41 anencephaly fetuses and observed that the cerebral hemispheres were either absent or rudimentary while the cerebellum was absent in majority.

Andersen et al. studied the skull and brain tissue of 21 anencephaly fetuses. Authors observed free undiffer-
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A total of 43 fetuses were studied. The observations of the study are shown in Tables 1–3.

Materials and Methods

This study was conducted in 6 hospitals of 3 districts in Gujarat state over the period of 3 years from 2002 to 2004 and 2014 to 2015. 43 specimens with anencephaly were collected after obtaining written consent from parents and clearance from Ethic committee of the Institute as per declaration of Helsinki guidelines. Gross anatomy and histological studies were done on their brain and spinal cord. Age estimation was done with the help of menstrual history, crown-rump (CR) length and external appearance of fetus. All the specimens were fixed in buffered formalin. After 4 to 6 weeks of fixation with buffered formalin, each specimen was dissected for central nervous system and other system malformations. Two paramedian incisions extending from occipital bone to sacrum were given to expose central nervous system. Skin fascia and paravertebral muscles were reflected. Laminae of all the vertebrae were cut to expose spinal cord and upper part of brain. In the region of skull, brain was separated from its coverings and taken for histological examination. Spinal cord was also taken for histological study. Sections were stained with H&E (Haematoxylin and Eosin) staining, silver stain and cresyl fast violet staining.

Results

Gestational age of fetuses varied from 18 to 40 weeks (Table 1). There was a predominance of female fetuses (Table 2, Figure 1). 31 (72%) fetuses had only anencephaly (Figure 2), while 9 (21%) fetuses had additional spina bifida (Figure 3) and 3 (7%) had meningomyelocele (Figure 4).

Table 1

<table>
<thead>
<tr>
<th>Gestation in weeks</th>
<th>Number</th>
<th>Percentage (%)</th>
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<tbody>
<tr>
<td>Less than or equal to 20 weeks</td>
<td>5</td>
<td>11.63</td>
</tr>
<tr>
<td>20-27 weeks</td>
<td>7</td>
<td>16.27</td>
</tr>
<tr>
<td>28-36 weeks</td>
<td>21</td>
<td>48.84</td>
</tr>
<tr>
<td>37-40 weeks</td>
<td>10</td>
<td>23.25</td>
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Table 2

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<thead>
<tr>
<th>Sex</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>36</td>
<td>83.72</td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>16.27</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly</td>
<td>31</td>
<td>72.09</td>
</tr>
<tr>
<td>Anencephaly with spina bifida</td>
<td>9</td>
<td>20.93</td>
</tr>
<tr>
<td>Anencephaly with meningomyelocele</td>
<td>3</td>
<td>6.97</td>
</tr>
</tbody>
</table>

Figure 1. Anencephalic female fetus - 36 weeks of gestation showing absence of skull vault; brain rudiments are covered by skin and hairs.
On internal examination of 43 fetuses with anencephaly, the brain was seen as a dark brown undifferentiated mass with complete absence of the cerebellum, pons, medulla and midbrain (Figure 5). Spinal cord was normal in appearance in all fetuses with anencephaly only (Figure 6). It was deformed in 3 anencephalic fetuses (7%) having additional meningomyelocele. In 31 fetuses (72%), the spinal cord continued rostrally into an open neural tube that connected to the undifferentiated brown mass (Figure 7) while in 12 fetuses (28%), spinal cord merged directly into the undifferentiated brown mass (Figure 6).

Microscopic appearance of brain in the 43 fetuses with anencephaly was reminiscent of an angioma, consisting of venous vessels of varying caliber interspersed with connective tissue and islets of nervous tissue which mainly comprised of scattered nerve cells, astroglial cells and cavities lined by ependymal cells (surface epithelium) (Figures 8–11). Microscopic appearance of spinal cord was normal and showed well-formed central canal lined by ependymal cells and differentiated gray and white matter.
Discussion

Anencephaly is the severest form of neural tube defect with 100% fatality and is associated with stillbirth or very early neonatal demise and occasionally abortions. This developmental defect is believed to have a multifactorial cause, namely genetics, environmental and nutritional, besides illness and drugs, and occurs primarily due to the failure of closure of the rostral pore of the neural tube. In the present study, the rate of occurrence of anencephaly in the studied population was 2.6/1000 births, while in most studies it has varied from 0.5 to 12/1000 births.\[3,4,6,9,10,23–25\]

Present study had 43 fetuses with anencephaly out of which 72.1% (31) were of the gestational age 28 to 40 weeks. This is similar to the observations made by Laurence et al.\[26\] and Larsen\[27\] who observed that anencephaly fetuses mostly survive till late gestations in uterus. 36 of the 43 fetuses (83.7%) were female, and the female to male ratio was 5.1:1. The findings of predominance of female fetuses with anencephaly in this study are similar to the findings of Panduranga et al.,\[1\] Menasinki,\[25\] Laurence et al.,\[26\] and Coffey and Jessop.\[12\]

In all 43 fetuses, the gross examination of central nervous system revealed complete absence of cerebral hemispheres, midbrain, pons and cerebellum. Brain was seen as a dark brown, undifferentiated mass. This is similar to the findings of Panduranga et al.\[28\] However, Vare and Bansal\[11\] demonstrated presence of rudimentary
cerebrum in 53.7% fetuses and rudimentary cerebellum in 14.6% fetuses with anencephaly in their study. The spinal cord in all fetuses studied appeared normal in present study. A well-formed open neural tube above the level of spinal cord was seen in 72% fetuses. This part of neural tube seemed to correspond to medulla, pons and mid brain. In the other 12 (28%) fetuses the spinal cord was seen to merge directly into the undifferentiated brown mass in present study.

Andersen et al.[14] observed that the brain of anencephaly fetuses mainly consisted of a humpy, dark red mass and its microscopic appearance was reminiscent of an angioma with venous vessels of varying caliber interspersed with connective tissue and islets of neurogenic tissue comprising mainly of astroglia and cavities lined with ependyma. Rarely, degenerated nerve cells and fragments of myelin were also seen. Spinal cord was often well preserved with normal looking anterior horn cells and some degree of myelination. In the present study, the dark brown mass representing the brain of all 43 anencephaly fetuses showed the same appearance as described by Andersen except that there were more nerve cells present in the islets of neurogenic tissue. Undifferentiated neural tube was seen in 67.3% fetuses showing clusters of nerve cells cavities, large blood vessels and white matter. Surface of the brain was lined by columnar epithelium.

Ashwal et al. [2] in their neuropathological study on anencephaly fetuses, observed unrecognized cerebral structures which was also seen in the present study. They also noted that sections of brainstem contained only small groups of scattered, dysplastic neurons with absence of fiber tracts. In the present study, on histology, scattered neurons were seen with bundles of fibers going in different directions without any organization. Hence, this confirms the findings of Ashwal et al. [15] that shows no functional organization of brain in anencephaly fetuses.

**Conclusion**

In fetuses with anencephaly, brain was replaced by dark brown undifferentiated mass. On histological examination it consisted of blood vessels of varying caliber interspersed with connective tissue and islets of nervous tissue. Spinal cord was normal in fetuses with only anencephaly while it was deformed in anencephalic fetuses with meningomyelocele. The above findings indicate that there is no functional organization of brain and the survival of such fetuses is not possible. This may help facilitate harvesting tissues/organ from anencephalic human fetuses for donation for doing research on brain death on these.

**References**


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