Anencephaly

A Case Report with Brain and Ocular Pathologic Studies
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Anencephaly is the most common lethal congenital malformation of the central nervous system.1 Anencephaly is a grotesque anomaly. The "frog-face" features, with short neck, bulging eyes, absence of the cranial vault and "pancake" cerebrum, make the diagnosis simple. The defect is so overwhelming, it is incompatible with prolonged life.

Although the brain defects have been studied in great detail, there is still considerable doubt as to the most likely pathogenesis of anencephaly. Since the eyes are grossly well developed, in contrast to the massive brain disorganization, it would seem of interest to attempt to correlate the ocular and the cerebral pathology.

The following report represents our findings of central nervous system defects in a case of anencephaly:


Clinical History:

A 16 year old colored primiparous woman delivered twin girls spontaneously on April 21, 1966. The prenatal history was not remarkable. The first-born infant "A" was normal. The second infant "B" required forceps for delivery and was found to be anencephalic; the birth weight was 1150 grams, and the baby died three hours after birth.

The post-mortem examination on April 22, 1966 revealed a congested hemorrhagic mass lying on top of the head covered by a thin transparent membrane continuous with the hair-bearing skin at its border.

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No gross evidence of cerebral hemispheres, brain stem or cerebellum was seen (Figs. 1, 2.) Only the caudal end of the medulla and the spinal cord were identified. The cranial vault was almost completely non-existent; the frontal bones above the orbital ridges, along with the parietal bones, and the squamous portions of the temporal and occipital bones were absent. The basal bones were also abnor-

Fig. 1: Anencephalic Head. The roof of the skull is absent, exposing the "area cerebro-vasculosa". The orbits are shallow and the eyes are proptosed. (top view).

Fig. 2: Anencephalic brain represented by a pancake of glial remnants with highly vascular meninges (basal view). Note the small pituitary gland in the mid-line.
nal with contracted orbits, small anterior and posterior cranial fossae and absent pituitary fossa. A small nubbin of pituitary gland was found in the midline.

Microscopic Examination of the Brain:

The “brain” consisted of a mass of connective tissue, greatly dilated and engorged blood vessels and clumps of poorly developed nervous tissue. Replacing the cerebral hemispheres there were two flattened saccular areas of disorganized nervous elements, mostly glial cells without identifiable ganglion cells or nuclear masses; the saccules were lined by greatly altered ependymal cells, featuring abundant choroid plexus near the midline junction (Figs. 3, 4). No evidence of myelination was present by specific staining. The cranial nerve tissue was invested by a thin membrane of low cuboidal epithelium which laterally merged with the stratified squamous epithelium of the normal skin and adnexae.

Structures representative of the optic chiasm and optic tracts could not be identified.

The lower medulla and the continuing spinal cord showed a failure of normal organization and differentiation into grey and white matter, and corresponding nuclear structures. No long fibre tracts were noted and myelin was absent (Fig. 5).

The ependymal canal was moderately dilated and lined by columnar-shaped cells. The surrounding meninges were well developed. The pia-arachnoid contained a large number of thin-walled, engorged blood vessels.

The pituitary gland was very small, represented only the anterior lobe (Fig. 6). The adrenal glands were small and hypoplastic.

Gross Examination of the Eyes:

The eyes were equally small. The right eyeball measured 16 mms. antero-posteriorly, 14.5 mms. horizontally and 15 mms. vertically. The cornea measured 8.5 mms. horizontally and 7 mms. vertically (Fig. 7). Grossly the optic nerve was small in diameter, thin and friable.
Fig. 6: Anencephalic Pituitary. Only the anterior lobe is present. Note the hypoplastic optic nerve fibres superiorly. Mallory trichrome stain (x52).

Fig. 7: Right Eye. The cloudy lens is apparent in the pupillary zone. (x8).

Fig. 8: Anencephalic Eye. Antero-posterior section of the right eye. Retina detached due to cutting and fixing procedures. The optic nerve is hypoplastic. (x7.5).

Fig. 9: Prominent pectinate ligaments in the anterior chamber angle. (x105).

Fig. 10: Pupillary vascular membrane remnants extend from the anterior iris. Pigment epithelium of iris adherent to cataractous lens. (x430).

Fig. 11: The retina is well developed except for the sparse ganglion cells and the poorly defined nerve fibre layer. (x510).

Microscopic Examination of the Right Eye: (Fig. 8).

The corneal epithelium is thin. Imperfect cleavage of the anterior chamber angle meshwork with heavy prominent pectinate ligaments (Fig. 9). Pupillary vascular membrane remnants (Fig. 10). Early cataract changes. The ciliary processes encroach upon the posterior surface of the iris.

The retina is detached due to cutting and fixing procedures. The rods and
cones with their nuclei, and the bipolar cells are well developed. The ganglion cells are somewhat sparse and the nerve fibre layer is poorly defined in areas (Figs. 11, 12). The optic papilla is cupped due to the absence of nerve fibres (Fig. 13). The optic nerve is small, and hypoplastic with fibrous septae but few axis cylinders. Special stains show absence of myelin within the optic nerve (Fig. 14).

**Final Diagnosis:**

1. Hypoplasia of the optic nerve associated with anencephaly.
2. Secondary atrophy of the nerve fibre layer and the ganglion cells of the retina.
3. Cataract.
4. Persistent pupillary vascular membrane remnants.

**Discussion:**

The incidence of anencephaly is fairly well documented. In the caucasian population, anencephaly is encountered approximately in 18 per 10,000 births; in orientals the frequency is only 9 per 10,000 births; and in the colored only 3 per 10,000 births. In Ireland, an unusually high incidence of 59 per 10,000 births has been reported, while in Japan the frequency is only 6 per 10,000 births.

The sex ratio in anencephalics is quite remarkable; females predominate in the ratio of 3:1.

There appears to be a genetic basis to the anomaly since it occurs more frequently in families with history of abortion, and spina bifida. Maternal factors such as "O" blood group, cardiac anomalies (Tetralogy of Fallot), malnutrition, and drug ingestion (e.g. Aminopterin) have been associated with the defect.

Experimental work with laboratory mice has produced strains of anencephalics by the use of X-rays, hypothermia, ultrasonic radiation, chemicals (lithium, salicylates, actinomycin, insulin, quinine,) nutritional deficiencies (lack of vitamin B complex, and vitamin A), and maternal anoxia. The defect in mice is apparently more related to the time of injury to the developing foetus (stage of gastrulation, i.e. the 10th day of gestation) than to the mode of induction of the injury.
Pathogenesis of Anencephaly

Morgagni suggested that anencephaly developed following a rupture of a hydrocephalic cerebrum; though this theory was previously accepted as logical, it no longer satisfies the current thinking of many pathologists.

Von Recklinghausen postulated that anencephaly resulted from a primary arrest in the closure of the neural tube. This thesis was supported by Sternberg who studied 4 to 8 week old human embryos which displayed non-closure of the anterior neuropore, related parts of the roof of the brain and the attached spinal cord. The exposed neural tissue subsequently degenerated leaving an "area cerebro-vasculosa" or a totally disorganized neural plate. The failure of the roof of the skull to develop (acrania) in anencephaly is due to a total failure of development of the bone primordia in the vault of the skull; when the brain fails to develop, the bony roof elements fail to appear.

Experimentally induced anencephaly in mice illustrates that the teratogenic effect of drugs, X-rays, etc., is exerted just after the stage of gastrulation. In man, this would correspond to the period between the 16th and 26th day after conception.

The remarkable feature of anencephaly is the fact that commonly the eyes are relatively well developed. Reviewing normal human ocular embryology, it is noteworthy that by the 16th day of life, the embryo shows optic pit depressions at the anterior and of the open neural plate. By the 18th day, the optic vesicles form by closure of the anterior end of the neural tube, and the vesicles soon move out to contact the surface ectoderm lens placode. By the 22nd day, the hyaloid artery forms from the vascular mesoderm and by the 24th day the optic vesicle invaginates to form the optic cup. By the 27th day the optic vesicle has fully invaginated and the foetal fissure is recognizable. Simultaneously, the cerebral hemispheres develop, while in the spinal cord, the anterior horns of grey matter, and the anterior and posterior columns are apparent. By the 30th day the lens vesicle has detached from the surface ectoderm and develops in contact with the optic cup. This would suggest that the early separation of the optic vesicle from the neural plate and the independent blood supply via the hyaloid artery may be significant factors accounting for well developed eyes, despite the presence of anencephaly.

Since the eyes have a relatively good start on independent development by the 22nd day, the critical time for damage to the developing anterior tip of the neural plate is the 4th week of intra-uterine development. Probably the time of injury is more important than the mode of injury in inducing anencephaly. Thus, toxic drugs, X-rays, etc., which injure the rapidly differentiating anterior tip of the embryo in the 4th week of development, should, theoretically at least, be capable of inducing anencephaly, if the proposed thesis is correct.

Thiersch reported that in a series of 12 women who ingested aminopterin to induce abortion, one delivered an anencephalic monster. A 25 year old primiparous woman took 20 mgm. of aminopterin over a 3 day period starting on the estimated 17th day of pregnancy. The fetus, born 6 weeks prematurely, had the classic features of the monstrosity and lived only 12 days. This would add clinical support to the thesis that, certain drugs, given at the crucial time of development can induce anencephaly in man as well as the laboratory animal. Toxicity, dosage, time of administration and the foetal hereditary make-up, are probably key factors when drugs are termed "teratogenic" in humans.

In 1958, Vogel and McClenahan proposed that anencephaly was due to anomalous development of the cerebrovascular tree. Conceivably, the injury induced by drugs, X-rays, etc., may act on the vascular buds rather than on the
neural epithelium directly.

The most common ocular pathology in anencephaly is the combination of hypoplasia of the optic nerve and sparsity of the ganglion cells in the retina. With the failure of the brain to develop, the axones of the ganglion cells within the optic nerve have no lateral geniculate body to synapse within. This accounts for the thin optic nerves and the absence of the optic chiasm and the optic tracts.

Summary:

A case of anencephaly with pathologic findings in both the brain and the eye is described. The basic eye pathology is a hypoplasia of the optic nerve and a sparsity of the ganglion cells within the retina. In view of the relatively complete development of the eye in contrast to the massive brain disorganization, it is suggested that damage to the developing human foetus occurs about the 4th week of gestation. Injury to the anterior tip of the neural plate at the critical stage in brain development, acting on a particular foetal hereditary constitution, is probably significant in the pathogenesis of anencephaly.

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References: