How does the Human Brain Differentiate? —Normal and Abnormal Development—

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1. Three Primary Brain Vesicles Convert into Five Secondary Brain Vesicles

The central nervous system (CNS) appears during the 3rd week as a neural plate growing out from the ectoderm of the germ disc. The lateral edges elevate to form the neural folds, and finally fuse, forming the neural tube. Neurulation begins on day 22, and the cranial neuropore, which is an opening at anterior end of the embryonic neural canal, closes on day 24. The future eyes appear as outpouchings from the forebrain neural folds by day 22. Before neurulation begins, the primordia of the three primary brain vesicles are visible as broadenings in the neural plate as shown in Fig. 1, called the prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain). During the 5th week, the prosencephalon subdivides into a telencephalon (the future cerebrum) and a diencephalon, and the rhombencephalon subdivides into a metencephalon (the future pons and cerebellum) and a myelencephalon (the future medulla oblongata), thereby creating, along with the mesencephalon, five secondary brain vesicles (Fig. 2).

Between the 4th and 8th week, the elongation of the brain occurs at the same time as the appearance of three flexures; two are concave ventrally and one concave dorsally (Fig. 3). The first of these folds to develop is the cranial (mesencephalic) flexure in the midbrain region. The procencephalon rotates ventrally and then posteriorly around this hinge during the 4th and 5th weeks until it is folded back under the mesencephalon. A bend (cervical flexure) also appears at the junction of the rhombencephalon and spinal cord. This increases from the 5th to the 7th week. However, after the 7th week, extension of the head takes place, and the cervical flexure diminishes and eventually disappears. During the 5th week, reverse, dorsal flexion (pontine flexure) begins at the location of the developing pons. By the 8th week, the 3rd bend may form as a result of differential growth in the ventral part of the metencephalon.

2. Development of the Brain Ventricular System

The expanded primitive ventricles formed by the neural canal in the secondary brain vesicles give rise to the ventricular system of the brain (Fig. 2). The ventricles of the brain include the lateral, third, and fourth ventricles. The two lateral ventricles communicate through the interventricular foramina (of Monro) with the third ventricle. The third ventricle is connected to the fourth ventricle by the cerebral aqueduct (aqueduct of Sylvius). The fourth ventricle in turn is continuous with the narrow central canal of the spinal cord and, through the three foramina in its roof, with the subarachnoid space. From the fourth ventricle, the fluid passes through the median aperture (foramen of Magendie) and the lateral foramina (foramina of Luschka) of the lateral recesses of the fourth ventricle, and then enters the subarachnoid space. The central canal has a small dilatation at its inferior end. Cerebrospinal fluid (CSF) is produced in the choroid plexuses of the lateral, third, and fourth ventricles; some originates as tissue fluid in the brain. The choroid plexuses have a folded surface and consist of a core of vascular connective tissue covered with cuboidal epithelium of the ependymal cells. The blood of the capillaries is separated from the ventricular lumen by fenestrated endothelium, a basement membrane, and the surface epithelium. The ependymal cells of the choroid plexuses actively secrete the CSF. CSF is absorbed into the venous system through the arachnoid villi that project into the dural venous sinuses, principally the superior sagittal sinus. The arachnoid villi are grouped together to form arachnoid granulations. Each arachnoid villus is a diverticulum of the subarachnoid space that pierces the dura mater.

During development, the primitive ventricle of the mesencephalon becomes the narrow cerebral aqueduct. The CSF produced by the choroid plexuses of the forebrain normally flows through the cerebral aqueduct to reach the fourth ventricle. In the newborn, obstruction of the CSF flow through the aqueduct of Sylvius results in congenital **hydrocephalus**, in which the third and lateral ventricles are swollen with fluid, the cerebral cortex is abnormally thin, and the sutures of the skull are forced apart. Hydrocephalus is characterized by an abnormal accumulation of

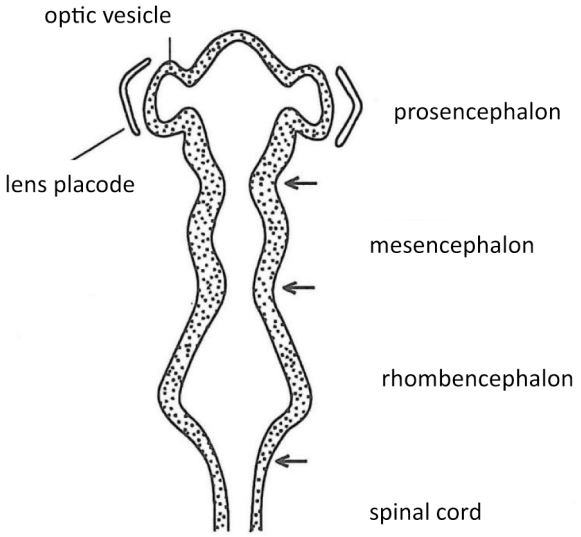

Fig. 1. The three primary brain vesicles.

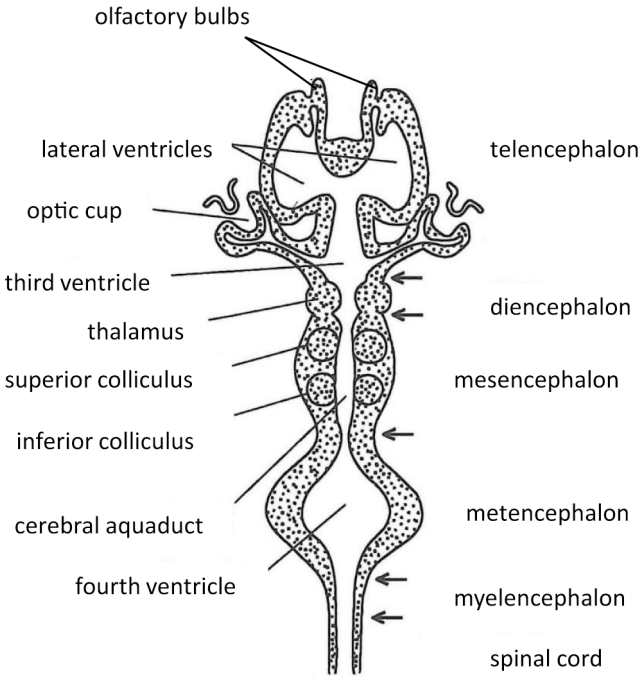

Fig. 2. Creating secondary brain vesicle.

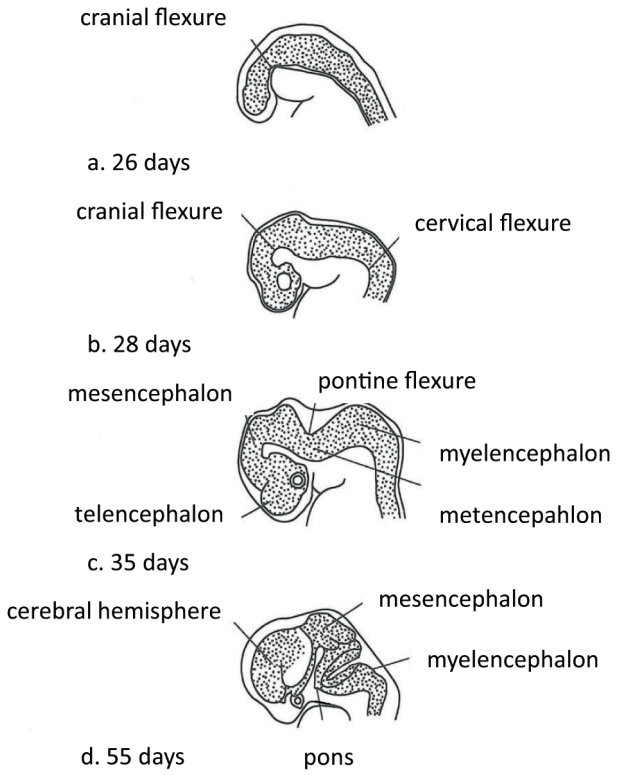

Fig. 3. Developmental change of the brain vesicles.

CSF within the ventricular system.

3. Cytodifferentiation of Neuroepithelium in the CNS

The neural tube neuroepithelium proliferates to produce successively the neuroblasts, glioblasts, and ependyma of the CNS. The neuroblasts migrate peripherally to establish a mantle zone, the precursor of gray matter. In the spinal cord and brain stem, the mantle zone immediately overlies the ventricular zone of proliferating neuroepithelium, and the growing neuronal fibers establish a marginal zone (the future white matter) peripheral to the mantle zone.

In the brain stem and spinal cord, all the cell types except for the microglia are produced by the neuroepithelium lining the neural canal. An intial wave of proliferation produces the neuroblasts, which also migrate peripherally. As neuroblast production ends, a second wave produces the glioblasts, which also migrate peripherally and differentiate to form astrocytes and oligodendrocytes. The layer of neuroepithelium lining the neural canal differentiates and then forms the ependyma. The neuroblasts migrate to form a mantle zone surrounding the proliferating neuroepithelium (ventricular zone). Neuronal fibers produced by the mantle neurons form a marginal zone external to the mantle layer. The mantle layer gives rise to the gray matter of the CNS, whereas the marginal layer gives rise to the white matter. The marginal layer contains the nerve fibers entering and leaving the CNS.

In the higher centers of the brain such as the cerebral cortex, the process of proliferation, migration, and cytodifferentiation is more complex and unique. The proliferating cells of the ventricular layer undergo a series of regulated divisions to produce waves of neuroblasts, which migrate peripherally and establish the layers of the cortex. Namely, the cortical layer neurons are settled in a sequence from deep to superficial (inside-out): that is, the neurons of each wave migrate through the preceding layers to establish a more superficial layer.

4. Malformations of the CNS

Development of the CNS is complex, and the proliferation, migration, and interconnection of each of the neural cells unfold regularly even after the formation of brain vesicles has ceased. Therefore, the period of sensitivity to teratogenic insults is longer in the brain than in the other organs. The neuroepithelium, which forms the brain tissue, is sensitive to various extrinsic factors, such as radiation, heavy metals, viral and bacterial infections, and alcohol.

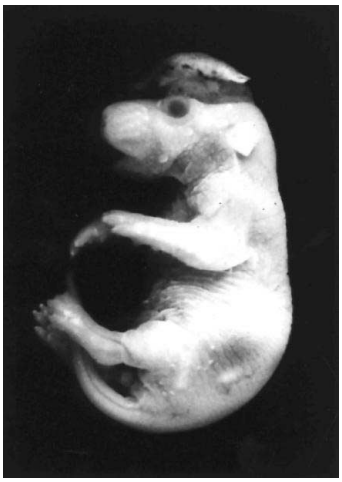

Fig. 4. A mouse with exencephaly (embryonic day 18).

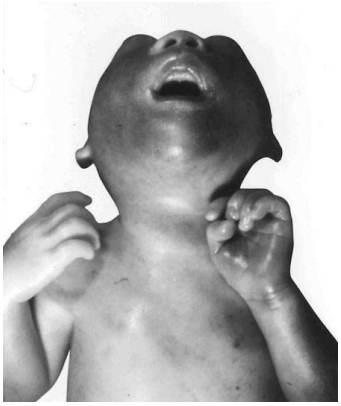

Fig. 5. Anencephaly.

Some typical brain malformations will be explained.

Excencephaly (Fig. 4) is characterized by failure of the cephalic part of the neural tube to close. As a result the top of the skull does not form, leaving part of the brain outside of the skull. Then, the tissue degenerates, leaving a mass of necrotic tissue. This defect is called **anencephaly** (Fig. 5), although the brain stem remains intact. Usually, a child with anencepholy survives only a few days after birth. Anencephaly affects girls 4 more times than it does boys.

Cyclopia (Fig. 6) is a type of holoprosencephaly in which there is only one eye. A loss of the midline in the brain causes the lateral ventricles to merge into a single chamber and the eye to fail to separate. Mutation in the gene *sonic hedgehog* (*SHH*), which fixes the midline of the CNS in the early embryonic stages, is a cause for this spectrum of anomalies.

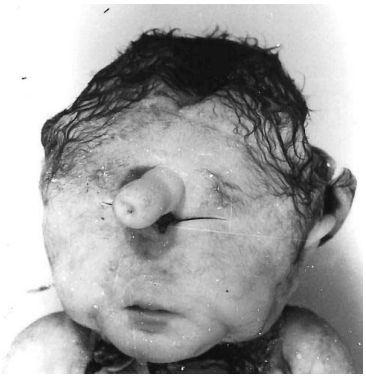

Fig. 6. Cyclopia.

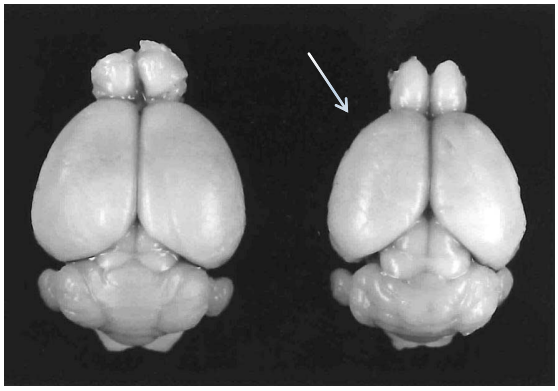

Fig. 7. Normal (left) and microcephalic (right) mouse brains. Hypoplasia of the cerebral cortex (arrow) is prominent compared to other brain parts in microcephaly.

Microcephaly describes an abnormally small head. Since the size of the cranium depends on growth of the brain, especially the cerebral cortex, this underlying defect in brain development causes microcephaly. The causes of the abnormality vary; they may be genetic or due to prenatal insults such as viral infections, X-irradiation, alcohol, or other teratogens. Figure 7 shows normal and microcephalic brains of mice. In the abnormalities, hypoplasia of the cerebral cortex is more severe than in the other brain regions.

Two references are given below for further studies.

References

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