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Developmental Anomalies of Central Nervous System in Human

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ABSTRACT *: The development of the central nervous system is a continuous process during the embryonic and fetal periods. For a better understanding of congenital anomalies of central nervous system, three major events of normal development, i.e., neurulation (3 to 4 weeks), brain vesicle formation (4 to 7 weeks) and mantle formation (over 8 weeks) should be kept in mind. The first category of anomalies is neural tube defect. Neural tube defects encompass all the anomalies arise in completion of neurulation. The second category of central nervous system anomalies is disorders of brain vesicle formation. This is anomaly that applies for "the face predicts the brain". Holoprosencephaly covers a spectrum of anomalies of intracranial and midfacial development which result from incomplete development and septation of midline structures within the forebrain or prosencephalon. The last category of central nervous system malformation is disorders involving the process of mantle formation. In the human, neurons are generated in two bursts, the first from 8 to 10 weeks and next from 12 to 14 weeks. By 16 weeks, most of the neurons have been generated and have started their migration into the cortex. Mechanism of migration disorders are multifactorial. Abnormal migration into the cortex, abnormal neurons, faulty neural growth within the cortex, unstable pial-glial border, degeneration of neurons, neural death by exogenous factors are some of the proposed mechanism. Agyria-pachygyria are characterized by a four-layerd cortex. Polymicrogyria is gyri that are too numerous and too small, and is morphologically heterogeneous. Cortical dysplasia is characterized by the presence of abnormal neurons and glia arranged abnormally in focal areas of the cerebral cortex. Neuroglial malformative lesions associated with medically intractable epilepsy are hamartia or hamartoma, focal cortical dysplasia and microdysgenesis.*

Key Words *: Developmental anomaly, Central Nervous System, Human*

I. NORMAL EVENTS OF CENTRAL NERVOUS SYSTEM DEVELOPMENT

The human nervous system makes its first appearance as a groove in the ectodermal component of the embryonic disk during the third week after fertilization. The groove becomes deeper and the upper edges gradually unite to produce a neural tube. The anterior part of the neural tube develops into the brain, the posterior part becomes the spinal cord, and motor nerves appear as local outgrowths from both regions. Development progresses sesrapidly and the brain of the average mature newborn infant weighs about 450 gm, almost one third as much as the adult brain. The hemispheres in early fetal life are smooth until the 5th months. The gyri of the cerebral hemispheres are produced as a result of unequal growth of the gray and white matter. The form and direction of the principal gyri and sulci are outlined during the 4th month, and by the time of birth all of the main ones are present. The neuroepithelial cells around the lumen of the neural tube, the germinal cells, generate the cells of the mature nervous system. Each distinct set of neuron originates according to a fairly rigid time table. Once young neurons have formed in the ventricular zone, they move away from it and take their final position in two pattern i.e., "outside-in" and "inside-out". Programmed cell death occurs as part of normal development.

The development of the central nervous system is a continuous process during the embryonic and fetal periods. There are three major events of normal development, i.e., neurulation (3 to 4 weeks), brain vesicle formation (4 to 7 weeks) and mantle forma-

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tion (over 8 weeks). (Sidman and Rakic, 1982).

1. Neurulation

At day 22, the first closure of the neural tube occurs at the upper level of the rhomhencephalon, upper cervical region, or both. The process by which the neural palte folds into a tube is known as neurulation. The neural plate lies over the notochordal proess and the medial edge of the paraxial mesoderm. Primary neurulation is a multifactorial process requiring intrinsic and extrinsic forces. It can be divided into four spatially and temporarily overlapping stages: neural plate formation, neural plate shaping, neural plate bending, and closure of the neural groove. (Schoenwolf and Smith, 1990) Secondary neurulation refers to the formation of the caudal portion of the spinal cord in avian and mammalian embryos. In the human fetus secondary neurulation begins at stage 13. (Mueller and O-Rahilly, 1987) Two processes, formation of the medullary plate and cavitation of the plate take place. The lumen formed in the medullary plate by cavitation is always continuous with the lumen of the neural tube formed by primary neurulation.

2. Cerebral Vesicle Formation

The neural tube cranial to the 4th pair of somitea develops into the brain. Fusion of the neural folds in the cranial region and closure of the rostral neuropore form three primary brain vesicles, i.e., forebrain (prosencephalon), midbrain (mesencephalon) and hindbrain(rhombencephalon). The anterior end of the neural tube, the prosencephalon, divides further into the telencephalon anteriorly, from which cerebral hemisphere will arise, and the diencephalon posteriorly, from which the eyes, thalamus, and hypothalamus will arise. This bilaterally symmetric process of diverticulum formation is thought to be induced by the prechordal mesodermal, so called midfacial mesoderm. By the fifth week there are five secondary brain vesicles, i.e., telencephalon, diencephalon, mesencephalon, metencephalon and myelencephalon.

3. Maturation of Neurons

The neuron undergoes changes in its appearance as it matures, reflecting the synthesis of new material and change in its function. Each class of neurons matures at its own rate. Maturation involves the establishment of neuronal shape and polarity, which is done chiefly through the presence of microtubules. (Tucker, 1990).

Axons grow out from neurons before any other sign of maturation occurs. The axon grows in length by adding new material to the surface membrane near the advancing axonal tip; advance of the growth cone requires microtubule assembly in the growth cone. Dendrites grow from neurons after axons have developed. In contrast to axons, which are straight with few branches, the dendrites can form elaborate, multiple branching "trees". The dendritic tree allows the axons and dendrites of other neurones to synapse on any one neuron. Neurons communicate at synapses, which are composed of specialized portions of two cell membranes, the pre and post-synaptic portion.

4. Neuronal Death

Cell death occurs as part of normal development. Neuronal death is a normal phenomenon that is ubiquitious in the nervous system. Three types of cell death are phylogenetic cell death seen during the regression of vestigial organs; morphogenetic cell death, which seems to be due to the obsolescence of cells whose function has been completed during such processes as cavitation, folding, or fusion of organ anlage; and histogenetic cell death, which seems to be a process of adjustment of the final number of cells after a period of excessive cell production. (Jacobson, 1991).

5. Development and Maturation of the Cerebral Cortex

Once young neurons have formed in the ventricular zone, they move away from it and take their final position in two pattern. Central nuclei close to the ventricle have an "outside-in" pattern; that is, the neurons furthest from the ventricle migrate first, and those closest to the ventricle migrate last. Most of the cerebral cortex is formed by an "inside-out" migration; the cells that migrate last migrate through the earlier arriving lower layers of cortex.

The formation of the cortex has been divided into five stages. (Sidman and Rakic, 1982).

1. Initial formation of cortical plate - 7-10 weeks
II. Primary condensation - through 10-11 weeks
III. Bilaminate cortical plate - 11-13 weeks
IV. Secondary condensation - 13-15 weeks
V. Maturation - 16 weeks on

The cerebral cortex does not mature uniformly. The first parts of the cortex to mature are the projection areas that receive precisely patterned afferents from the thalamus or send long axons to subcortical areas. Despite the division of cerebral cortex into these functionally distinct areas with apparently different times of maturation, Rakic *et al.* (1986) reported that in the monkey synapses develop concurrently and at identical rates in different layers of visual, somatosensory, motor, and prefrontal areas.

II. ABNORMAL EVENTS OF CENTRAL NERVOUS SYSTEM DEVELOPMENT

1. Defects of Neural Tube Closure

Neural tube defects encompass all the anomalies arise in completion of neurulation.

1) Anencephaly

Anencephaly is characterized by replacement of most of the intracranial contents by a ragged, cavitated, vascular mass, the area cerebrovasculosa. Remaining neural tissue usually includes the gasserian ganglia, distal parts of the cranial nerves, a variable amount of the medulla, and rarely a few cerebellar folia. The skull shows various abnormalities including: an absent or hypoplastic skull vault, a thickened and flat skull base, shallow orbits so that the eyes protrude and a shallow sella (Chi and Park, 1982). Spinal involvement varies from failure of fusion of the upper cervical vertebrae to craniorachischisis. Histologically, the area cerebrovasculosa consists of an angiomatous mass of small blood vessels mixed with disorganized neuroepithelial tissue, particularly glia, some neuroblasts or neurons, ependyma, and choroid plexus. Rarely, ependymal-lined cavities suggest forebrain ventricle.

2) Chiari malformations

Chiari defined three anatomic types of cerebellar deformity associated with hydrocephalus.

Chiari type I malformation is the herniation of a peg of cerebellar tonsil through the foramen magnum in the absence of an intracranial space occupying lesion or preceding hydrocephalus.

Chiari type II malformation combines herniation of the cerebellar vermis with malformation and downward displacement of the brain stem. The degree of cerebellar herniation varies from slight (in fetuses) to extensive, at which point the choroid plexus and tonsils may be included. The cerebellar tail is bound by fibrous adhesions to the dorsal surface of the medulla or occasionally is situated within the fourth ventricle. Folia in the herniated cerebellar tissue show neuronal loss, absence of myelinated fibers, and gliosis.

Brain stem malformation include : fusion of the inferior colliculi, which gives a beak-like appearance to the quadrigeminal plate, an indistinct pontomedullary junction and rod-shaped pons, abnormal elongation of the lower medulla over the cervical cord, and less frequently, dysplasia of cranial nerve nuclei, olivary nuclei, and pontine nuclei. Disproportion between the growth of the posterior fossa and its contents is a more likely mechanism; the cerebellar weights and posterior fossa volumes are both reduced, and experimental vitamin A administration to pregnant hamsters induces a shortened basichondrocranium and reduced posterior fossa volume, suggesting that the neurologic anomalies are secondary to skeletal defects.

Chiari type III malformation is the rare cerebelloencephalocele through an occipitocervical or high cervical bony defect. Associated brain stem deformities and lumbar spina bifida resemble those of Chiari type II malformation.

2. Disorders of Forebrain Induction : Brain Vesicle Formation

1) Holoprosencephaly

Holoprosencephaly is a defect of diverticulum formation of the neural tube. This is anomaly that applies for "the face predicts the brain". Holoprosencephaly covers a spectrum of abnormalities of intracranial and mid-facial development which result from incomplete development and septation of mid struc-

tures within the forebrain or prosencephalon.(Yakovlev, 1959; Chi and Kim, 1984).

Alobar holoprosencephaly is the severest form and is characterized by a very small brain, monoventricular and undivided into hemispheres and a globular holosphere with abnormal convolutional pattern and no interhemispheric fissure, gyri recti, or olfactory structures. The horseshoe-shaped dorsal surface of the holosphere continues posteriorly as a delicate membranous roof to the single ventricle, which attaches distally to the tentorium. A cavity is thus formed, which may be small or balloon into a dorsal cyst. In the floor of the ventricle are fused basal ganglia and thalami, from the lateral edges of which the hippocampus makes a continuous arch around the ventricle and attaches to the roof membrane. Corpus callosum and septum are absent. Holospheric white matter is much reduced in volume.

Craniofacial malformations are associated with alobar holoprosencephaly. The face tends to predict the brain, particularly midfacial hypoplasia. The severest is cyclopia with fused orbits and eyes. Other anomalies include a proboscis (ethmocephaly), absent jaw (agnathia), fused ears (synotia, otocephaly), flat nose with a single nostril (cebocephaly), microphthalmia, hypotelorism, and occasionally hypertelorism. Microscopically there is histologic evidence of 1) neocortical hypoplasia with a relative lack of prefrontal association cortex and excessive allocortex, and 2) cortical disorganization or disturbed neuronal migration such as polymicrogyria, and more deeply placed aneuronal neuropilic glomerular structures. The anterior part of the circle of Willis is anomalous. The anterior and middle cerebral arteries are replaced by forward directed branches of one or both internal carotids.

Semilobar holoprosencephaly is intermediate between the alobar and lobar forms.

There are mild microcephaly, a partly formed shallow interhemispheric fissure, and some lobar structure with rudimentary temporal and occipital horn, but continuity of the cortex across the midline. Olfactory structures are usually absent. Lobar holoprosencephaly is the mildest form. Despite near normal brain size, normal lobe formation, and separated hemispheres, the cerebral cortex is continuous across the midline, at the frontal pole, or in the orbital region, or above the callosum. (Yakovlev, 1959).

3. Disorders of Mantle Formation : Defect of Migration and Differentiation

The last category of central nervous system malformation is disorders involving the process of mantle formation. The cerebral mantle is formed through the cellular processes characterized by proliferation, migration and differentiation.

1) Agyria and pachygyria

Agyria and pachygiria refer to an absence of gyri and sulci, or reduced numbers of broadened convolutions, respectively, associated both macroscopically and microscopically with a thickened cortical ribbon. The skull vault is small, misshapen, and thickened. Brain weight is usually low, and very occasionally heavy. A markedly thickened cortical ribbon is associated with reduced white matter. Pachygyria is occasionally combined with polymicrogyria. The claustrum and extreme capsule are absent. Lateral ventricles are dilated and often associated with periventricular nodular heterotopia. The characteristic histological appearance is a four-layer cortex; i.e., molecular layer, thin, external neuronal layer, sparsely cellular layer with a tangential myelin fiber plexus, a thick, inner neuronal layer which splits in its deeper zone into columns of cells. (Norman *et al.*, 1995).

Associated findings include olivary heterotopia, and hypoplastic pyramidal tracts.

Less common associations are dentate dysplasia, cerebellar heterotopia and granule cell ectopia.

Various histologic pattern may be encountered in macroscopically smooth or poorly convoluted cortex:

a) a gyria or pachygyria with or without four layers (lissencephaly type I).

b) cerebro-ocular dysplasia (lissencephaly type II).

c) polymicrogyria (unlayered or four-layered).

d) cortical dysplasia with cytomegaly-localized, multifocal or hemimegalencephalic.

2) Cerebro-ocular dysplasias

Cerebro-ocular dysplasias show a distinct histologic form of cerebral cortical thickening and dysplasia (lissencephaly type II).

They occur in several rare overlapping autosomal

recessive familial syndromes that combine complex cerebral and ocular malformations and muscular dystrophy.

An occipital meningocele or encephalocele is common. The cerebral hemispheres are usually enlarged, but occasionally small, and have a smooth surface that lacks convolutions and is covered by adherent thick white leptomeninges. Fusion of the medial surfaces of the frontal lobes, olfactory aplasia or hypoplasia, thin optic nerves and optic chiasm, small flattened cerebellar hemispheres with a coarsely nodular surface, and a small or absent vermis are sometimes found. A massive hydrocephalus throughout the ventricular system and a thin corpus callosum are evident. A thickened and disorganized cortical ribbon is divided by centripetal fibrovascular septa into irregular neuronal clusters, which sometimes have a wave-like arrangement. The cortical ribbon is separated by a narrow hypocellular zone with thin-walled blood vessels from an inner layer of heterotopic gray matter islands. Cortex on the medial aspects of the hemispheres is often thin and undulating, like polymicrogyria.

3) Polymicrogyria

Polymicrogyria is characterized by a hyperconvoluted cortical ribbon of miniature thin gyri, which are often fused together. Polymicrogyria manifests with varying degrees of neurologic disability depending upon the extent of the lesion, and causes profound psychomotor retardation if it is extensive. The macrogyric cerebral surface is irregular like cobblestones. Sections of the cerebrum reveal heaped up or submerged gyri that widen the cortical ribbon.

The cortical gray matter is abnormally thin and excessively folded, and there is fusion of adjacent gyri and abnormal cortical lamination. The commonest subtype is unlayered polymicrogyria. A thin unlayered undulating band of gray matter is interrupted by pegs of poorly cellular tissue that has central blood vessels and radiates out from the overlying molecular layer.

Polymicrogyria may be : 1) widespread in one or both hemispheres, 2) bilateral and symmetric in a particular arterial territory (usually the middle cerebral artery), 3) confined to the opercular region or depths of the insula, 4) around porencephalic or hydranencephalic defects, or 5) focal in almost any neocortical area except the cingulate or striate cortex.

A rarer subtype is four-layer polymicrogyria, which consists of a molecular layer and two layers of neurons sandwiching a paucicellular zone of myelinated fibers.

The cortical ribbon is thin and undulating.

Concerning the pathogenesis, the topography, bilateral symmetry, frequency of middle cerebral artery distribution, juxtaposition to porencephaly, and clinical data suggest a hypoxic-ischemic pathogenesis or transient intrauterine perfusion failure. Clinical reports of antecedent catastrophic intrauterine events have led to an estimation that polymicrogyria develops in the fourth to fifth gestational months.

4) Neuronal heterotopia

Diffuse neuronal heterotopia occurs in some epileptic patients and is occasionally a principal finding in early myoclonic epilepsy. It is characterized by the presence of many haphazardly scattered neurons in gyral and central white matter and may be associated with other cerebral malformations. Occasional neurons are a normal finding in the cerebral white matter, particularly in the anterior temporal region. Nodules of heterotopic neurons are most often situated in the wall of the lateral ventricle and bulge into its cavity, but are also found in gyral cores and the centrum ovale. Heterotopias may be single or multiple. Laminar heterotopias are located just beneath and parallel to the cortex, but separated from it by a located layer of white matter. The deep gray nuclei are normal except for the incorporation of the claustrum into the heterotopia. In its outermost part, the heterotopic gray matter shows a haphazard arrangement of neurons and neuropil. It is thought that laminar heterotopia, pachygyria, and gyria and different manifestations of the same disorder. (Friede, 1989).

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