Recent advances in Neuroanatomy Extrapyramidal Disorders

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in Neuropsychiatry

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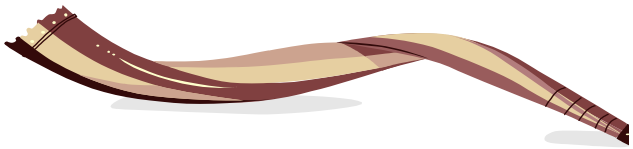

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Introduction

The brain is arguably the most complex organ of the human body, and our understanding of its structure and function is fragmentary. The past few decades have seen an enormous accumulation of neuroscientific data, making it impossible for any one individual to comprehend and assimilate more than a fraction of the available data ***(Talos et al, 2008)*.**

Historically, modern neuroscience started with neuroanatomy through the work of Golgi, Cajal, Lorente De No, and other pioneers. Neuroanatomy had become a coherently developed and deeply understood science well before the appearance of electrophysiology and molecular biology. Neuroanatomical data have been continuously collected for over a century and particularly in the last few decades, resulting in thousands of quantitative and qualitative publications, and in a large number of neuronal tracings accumulated in laboratories throughout the world ***(Ascoli, 1999).***

There are two spatial complementary views of neuroanatomy: (a) a structural view, concerned with shape, dimensions, spatial location and a relationships, and embryologic origin of neural structures, and (b) a functional view, dealing with functional (physiologic) relationships between entities assembled into neural functional systems (connections between these entities via neural pathways, physiologic actions – e.g. excitation or inhibition - of one entity on another exerted via neural pathways).These entities often do not share a common embryologic origin and may be spatially remote ***(Talos et al,2008)*.**

The extrapyramidal system or the motor initiation system consists of a family of parallel circuits linking subcortical structures with the motor cortex. Its principal

components are the basal ganglia (striatum, globus pallidus), the subthalamic nucleus, the ventral anterior nucleus of thalamus, the substantia nigra and the motor cortex ***(Talos et al, 2008)*.**

Basal ganglia are involved in many neuronal pathways having emotional, motivational, associative and cognitive functions as well. The striatum (caudate nucleus, putamen and nucleus accumbens) receive inputs from all cortical areas and, throughout the thalamus, project principally to frontal lobe areas (prefrontal, premotor and supplementary motor areas) which are concerned with motor planning ***(Herrero et al, 2002)***.

Neuroimaging techniques have evolved over the past several years giving us unprecedented information about the degenerative process in Parkinson's disease (PD) and other movement disorders. Functional imaging approaches such as positron emission tomography (PET) and single photon emission computerized tomography (SPECT) have been successfully employed to detect dopaminergic dysfunction in PD, even while at a preclinical stage, and to demonstrate the effects of therapies on function of intact dopaminergic neurons within the affected striatum. Structural imaging approaches include magnetic resonance imaging (MRI) and transcranial sonography (TCS) ***(Pavese and Brooks, 2009)*.**

Diffusion tensor imaging (DTI)-based fiber tractography holds great promise in delineating neuronal fiber tracts and, hence, providing connectivity maps of the neural networks in the human brain. An array of image-processing techniques has to be developed to turn DTI tractography into a practically useful tool ***(Mishra et al, 2007)*.**

The term, extra pyramidal disorders refer to group of diseases often associated with pathologic alteration in the basal ganglia. The main clinical entities are Parkinson disease,

chorea/ballismus, and dystonia. Attempts to understand their mechanisms and etiology were always a challenge to our intelligence ***(Stern, 1989).***

Parkinsonism is characterized by bradykinesia, muscle rigidity, postural instability and resting tremor that occur most often in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. In all three disorders the main regulators of the caudate nucleus and putamen (dopaminergic substantia nigra and glutaminergic caudal intralaminar nuclei), as well as the cortical projection from the presupplementary motor area, degenerate. Degeneration of the major basal ganglia circuit neurons also occurs in multiple system atrophy, while degeneration of the subthalamus and a widespread loss of inhibitory interneurons within the extrapyramidal system occur in progressive supranuclear palsy ***(Halliday, 2007).***

Parkinson disease (PD) is a chronic and progressive adult-onset neurodegenerative disorder that results from the progressive loss of dopaminergic neurons in the substantia nigra pars compacta. The characteristic symptoms of PD are a tremor at rest, bradykinesia, rigidity, and postural instability ***(Tobin et al, 2008).***

Chorea is defined as a syndrome characterized by brief, abrupt involuntary movements resulting from a continuous flow of random muscle contractions. There are genetic and non-genetic causes of chorea. The most common genetic cause of chorea is Huntington's disease (HD). Non-genetic forms of chorea include vascular choreas, auto-immune choreas, metabolic and toxic choreas, and drug-induced choreas ***(Cardoso, 2009).***

Huntington's disease is a chronic progressive neurodegenerative disorder affecting movement, cognition and personality. It is genetically transmitted as an autosomal dominant trait with complete penetrance and thus has an equal

likelihood of affecting males and females ***(Purdon et al, 1994).***

Hemiballismus is a relatively rare movement disorder that is characterized by uncontrolled, random, large-amplitude movements of the limbs. It is usually caused by a vascular lesion that involves the contralateral subthalamic nucleus STN) (also known as the nucleus hypothalamicus or corpus luysi) and its afferent and efferent pathways ***(Slavin et al, 2004).***

Dystonia is a common movement disorder which is thought to represent a disease of the basal ganglia. However, the pathogenesis of the idiopathic dystonias, i.e. the neuroanatomic and neurochemical basis is still a mystery. Research in dystonia is complicated by the existence of various phenotypic and genotypic subtypes of idiopathic dystonia, probably related to heterogeneous dysfunctions. In neurological diseases in which no obvious neuronal degeneration can be found, such as in idiopathic dystonia, the identification of a primary defect is difficult, because of the large number of chemically distinct, but functionally interrelated, neurotransmitter systems in the brain ***(Richter and Löscher, 1998).***

Aim of the work:

Aim of this work is to

- Review the recent neuroanatomical studies of the commonest extrapyramidal disorders
- Discuss the role of recent neuroimaging techniques in diagnosis and management of these extrapyramidal disorders.

Overview of Neuroembryology in Extrapyramidal Disorders

1-Historical overview

Modern developmental neurobiology emerged from the convergence of two traditions that had their roots in quite different and separate fields of inquiry, and with different conceptual and methodological frames of reference. The one, the histogenetic tradition, was descriptive and became sophisticated through refined technology. The other, experimental neuroembryology, was causal-analytical and experimental, and was originally a modest side branch of general experimental embryology.One cannot, of course, ascribe the beginning of a branch of science to a single year, but the years between 1885 and 1890 saw major publications by the German anatomist Wilhelm His (183l - l904) and the Spanish histologist S. Ramon y Cajal (l852-1934) both of whom laid the foundation to our present understanding of the structure and embryonic origin of the nervous system ***(Hamburger, 1988)***.

His realized the need for magnified three dimensional (3D) imaging and the need for a model of the dissected object. He made 3D reconstructions from freehand drawings of histological slices. Born, who in 1876 was the first to describe the technique of making solid reconstructions by stacking wax plates of histological slices, made use of the camera lucida, a device that aided the accurate sketching of small objects. Wax was later substituted by more durable materials such as wood, plaster, glass, or plastic. Imaging by graphic reconstructions with the aid of special devices has commonly been used in modern human embryology. The development of computer technology has opened new possibilities for 3D reconstructions. The first attempt at constructing 3D images of

the fetus from ultrasound recordings was made in the early 1980s ***(Blaas et al., 1998)***.

2-Development of the nervous system

The development of the nervous system occurs through the interaction of several synchronized processes, some of which are complete before birth, while others continue into adulthood (Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging ***(Lenroot and Giedd, 2006)***.

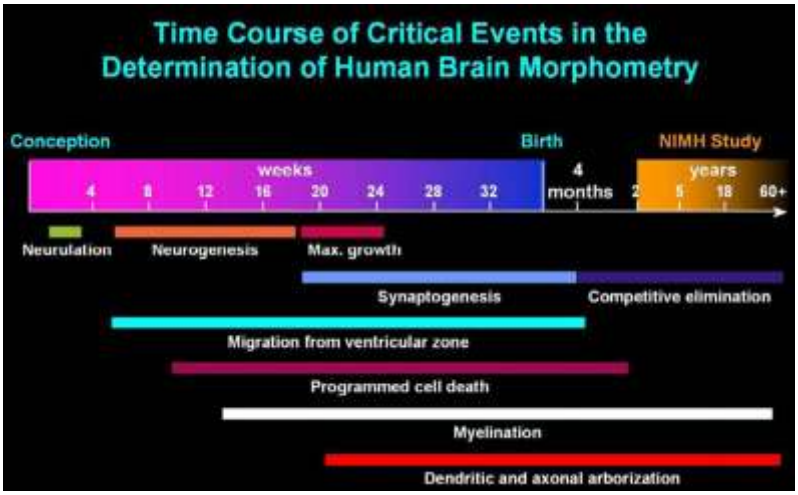

Fig. (1): Sequence of events in brain maturation Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging ***(Lenroot and Giedd, 2006)***.

The development of the human brain and spinal cord may be divided into several phases. After implantation, formation and separation of the germ layers occur (gastrulation), followed by dorsal and ventral induction phases, and phases of neurogenesis, migration, organization and myelination (Fig.1) ***(Hans and Ton, 2006)***.

Originally, the term gastrulation referred to the invagination of amonolayered blastula to form a bilayered gastrula, containing an endoderm-lined archenteron as found

in amphibians Nowadays, the term is more generally used to delimit the phase of development from the end of cleavage until the formation of an embryo possessing a defined axial structure. ***(Hans and Ton, 2006)***.

Gastrulation begins at the posterior side with the formation of the primitive streak and the node, a structure equivalent to the amphibian organizer. Axial mesendoderm derived from the node (pharyngeal endoderm, prechordal mesendoderm, chordamesoderm) migrates anteriorly and displaces the visceral endoderm (Fig.2). The AVE, which contacts the future anterior CNS during early gastrulation, induces the forebrain and midbrain ***(Beddington and Robertson, 1998)***.

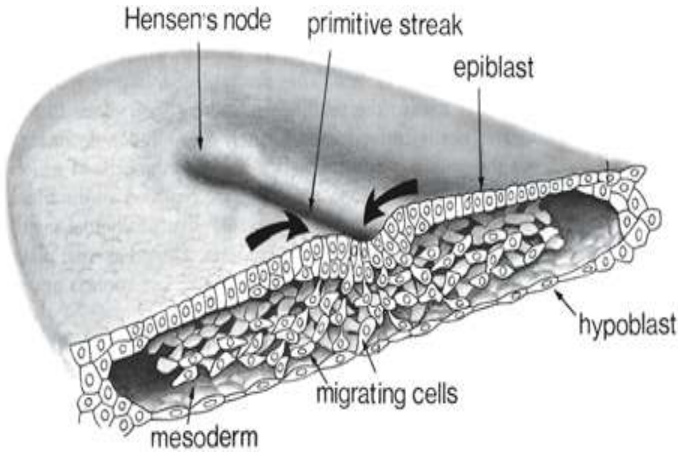

Fig. (2): Ingression of mesoderm and entoderm (*arrows*) during gastrulation in the chick embryo. ***(Hans, 2006).***

The embryonic period in man, i.e. the first 8 weeks of development, can be divided into 23 stages, the Carnegie stages, the first four embryonic weeks are also described as the period of blastogenesis, and the fifth to eighth weeks as the period of organogenesis ***(Opitz et al., 1997).***

The embryonic period includes three in time overlapping phases: formation and separation of the germ

layers, dorsal and ventral induction phases during the first phase, the neural plate is formed. In the dorsal induction phase, the neural tube is formed and closed, and the three primary divisions or neuromeres of the brain (the prosencephalon, mesencephalon and rhombencephalon) appear. In the ventral induction phase (telencephalization), the cerebral hemispheres, the eye vesicles, the olfactory bulbs and tracts, the pituitary gland and part of the face are formed. In the sixth week of development strong proliferation of the ventral walls of the telencephalic vesicles gives rise to the ganglionic or ventricular eminences. These elevations do not only form the basal ganglia but, in addition, give rise to many neurons that migrate tangentially to the cerebral cortex. Neurogenesis starts in the spinal cord and the brain stem. Neurogenesis in the cerebellum and the cerebral cortex occurs largely in the fetal period ***(Hans and Ton, 2006)***.

The fetal period cannot be divided into a series of morphologically defined stages. It is the period of phenogenesis the fetal period extends from the ninth week of development to the time of birth. ***(Opitz et al. 1997)***.With regard to the prenatal ontogenesis of the cerebral cortex, Marin-Padilla (1990) suggested dividing this long developmental period into two separate ones: (1) the fetal period proper (9-24 gestational weeks), characterized by the formation of the cortical plate; and (2)the perinatal period, extending from the 24th week of gestation to the time of birth. This period is characterized by neuronal maturation ***(Hans and Ton, 2006)***.

Neurulation is usually described as the developmental process that results in the rolling up of a flat sheet of epithelial cells into an elongated tube ***(Colas and Schoenwolf, 2001).***

In human embryos, the neural tube forms by means of two distinct developmental events, i.e., primary and secondary neurulation. During primary neurulation, the lateral ends of the

neural plate elevate and bilateral neural folds fuse with each other to form the primary neural tube. Primary neurulation is completed by the closure of the anterior and posterior neuropores, at 24 and 28 days, respectively, after fertilization Subsequently to the closure of the posterior neuropore (the last part of the primary neural tube to be fused), the secondary neural tube begins to develop by elongation and cavitation of the tail bud, an aggregate of undifferentiated mesodermal cells at the caudal end of embryos. This process is called secondary neurulation. Closure of the posterior neuropore occurs at the upper sacral level during Carnegie stage 12 (CS 12). Although the closure of the posterior neuropore occurs at the level of the thirty-first somite (corresponding to the future S2 level), the junction of the primary and secondary neural tubes is apposed at the lumbosacral level of the vertebral column in neonates (Fig.3). Therefore, development of the posterior neural tube (PNT), which develops into the future lumbar, sacral, coccygeal, and equinal cord, involves both the primary and secondary neurulation and is a rather complicated process ***(Saitsu et al., 2007)***.

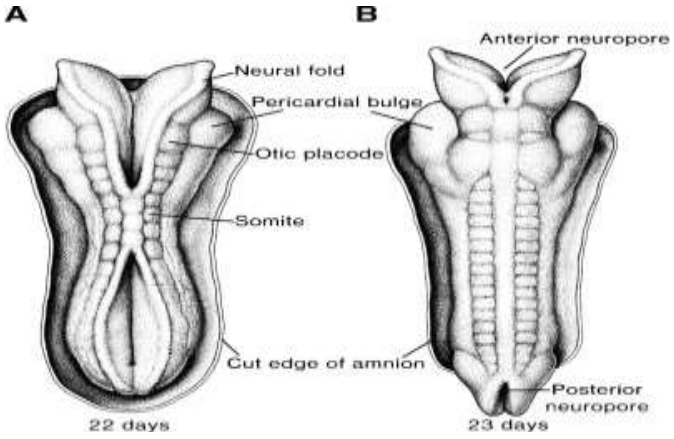

Fig. (3): Dorsal views of neurulating embryos at different stages of neural tube closure (postfertilization). A: Closure begins at the caudal end of the hindbrain near its junction with the spinal cord. The neural folds then zipper in both directions.B: Continued zippering closes the neural tube ***(Sadler, 2005)***.

Neurulation is a multifactorial process that requires both extrinsic and intrinsic forces acting in concert. The intrinsic forces arise within the neural plate responsible for neural plate shaping and furrowing are generated by fundamental changes in cell shape, position and number of neuroepithelial cells. Tissue transplantation experiments in chick embryos suggest that neural plate folding is not an autonomous process inherent to the neural plate itself but that it also depends on extrinsic forces generated by non-neuroepithelial tissues lateral to the neural plate ***(Smith and Schoenwolf, 1997)***.

The mesencephalic flexure appears, and allows a first subdivision of the brain into three major divisions in the still unfused neural folds,the forebrain or prosencephalon, the midbrain or mesencephalon, and the hindbrain or rhombencephalon, At stage 10, the two subdivisions of the forebrain, the telen-cephalon and the diencephalon, become evident (Fig.4 and Fig.5) ***(Jirasek, 2004).***

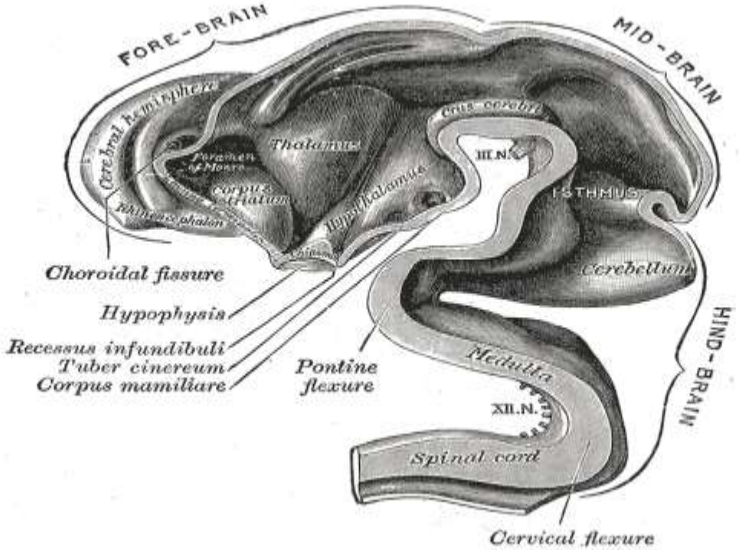

Fig. (4): Interior of brain of human embryo of five weeks. ***(Gray, 2000)***