Section: Anatomy

Original Research Article

AN EXPLORATION OF THE HISTOGENESIS PROCESS INVOLVED IN THE DEVELOPMENT OF THE CEREBRAL CORTEX

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Abstract

Background: Histogenesis within the cerebral cortex is a complex and highly regulated sequence of cellular events that dictate the formation of the brain's neural architecture. The process begins with neuroblast migration from the ventricular zone to their designated positions in the developing cortex. These migrating neuroblasts follow specific patterns, ultimately giving rise to the multilayered structure of the gray matter. The organization of these layers is essential for proper cortical function, including sensory processing, cognition, and motor control. Abnormalities in histogenesis can result in neurodevelopmental disorders. Disruptions in neuronal migration are linked to conditions like lissencephaly, where cortical layers fail to form correctly, causing developmental impairments. Additionally, research into radial glial cells has provided insights into the origins of neurodevelopmental disorders such as autism and schizophrenia. **Materials and Methods:** This study involved 60 fetal cadaveric brains and 40 adult brains. The fetal brains, with gestational ages ranging from 13 to 38 weeks, were dissected to obtain specimens from various regions of the brain. Tissue processing was done, followed by staining with eosin and hematoxylin. **Result:** In fetal brains, by 13 weeks, all three developmental layers—marginal, mantle, and ependymal—were observed. From 14 to 27 weeks, the primitive cortical gray matter is subdivided into outer and inner bands. Between 28 and 38 weeks, differentiation into external granular and pyramidal layers occurred. In adult brains, the neocortex consists of six layers, with laminae III and V prominent in the agranular cortex, and laminae II and IV in the granular cortex. **Conclusion:** The histogenesis of the cerebral cortex is a highly organized process, with neuronal migration beginning as early as 13 weeks and continuing further. Disruptions, including those caused by substances like alcohol or antiepileptic drugs, can lead to neurodevelopmental disorders, highlighting the importance of avoiding harmful substances during pregnancy.

INTRODUCTION

The cerebral cortex is the outermost layer of the brain responsible for processing sensory information, controlling movement, and facilitating thought, perception, and memory. Cortical histogenesis refers to the process by which the cerebral cortex develops into an organized laminar structure, with distinct cell types and synaptic connections, which includes the formation of excitatory and inhibitory neurons, astrocytes, oligodendrocytes, and microglia during embryonic and fetal development.[1]

Cerebral cortical neurons originate from the ventricular zone, which lines the lateral ventricle of the telencephalon. After cell division, postmitotic neurons migrate through the intermediate zone and into the cortical plate, where they will eventually form the six-layered cerebral cortex in the adult brain.[2] Cortical histogenesis occurs within a specific developmental window and is highly sensitive to environmental factors and genetic disruptions, which can lead to neurological disorders if disturbed.[3]

Abnormalities in cerebral cortex development have been implicated in various neurodevelopmental disorders, such as autism, schizophrenia, and intellectual disability.[4,5] Understanding the development of the cerebral cortex can provide insights into the pathogenesis of neurological disorders, such as epilepsy, stroke, and neurodegenerative diseases.[6] Studying the histogenesis of the cerebral cortex can provide clues

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about the evolution of the human brain and the development of cognitive abilities.[7,8]
This study aims to understand the histogenesis processes involved in the development of the cerebral cortex and cortical layering.

MATERIALS AND METHODS

The study was done on 60 fetal cadaveric brains and 40 adult brains. The fetal brains ranged from 13 weeks to 38 weeks of gestation. The specimens were obtained from the Department of Obstetrics and Gynaecology, Victoria General Hospital, Visakhapatnam, and the Department of Anatomy, Andhra Medical College, Visakhapatnam.
The fetuses were weighed with the help of a digital weighing machine and crown-rump lengths were measured with the help of measuring tape. This calculates the fetal gestational age according to the crown-rump length as per the description of Langman's Human Embryology. Material taken for the histological study is from the prefrontal cortex, temporal, precentral, postcentral, hippocampal, and occipital lobes of cerebral hemispheres of both adult and fetal brains.
The tissue after washing with water thoroughly is fixed in a 10% solution of formaldehyde for 24 hours. Then it is passed through ascending graded alcohol for Dehydration, clearing is done using xylol, and then impregnated and embedded in Paraffin. Sectioning is done using a Rotary Microtome at 6 microns thickness and mounted on slides. The slides are allowed to dry at room temperature overnight. Later they are stained with Haematoxylin and Eosin technique. Photomicrographs of sections were taken at 10X, and 40X magnification, and copies of photographs were obtained and observed the layered pattern of cerebral cortex.

RESULTS

In the present study, at 13 weeks of gestational age, all three developmental layers marginal, mantle, and ependymal layers are seen. The primitive marginal constitutes the primordial cortical gray matter. In the mantle layer neuroblasts are seen. No specific cells were identified in the marginal zone [Figure 1]. The mantle layer has taken more amount basophilic stains because of the presence of neuroblasts.
At 14 weeks, the histological picture [Figure 2] showed the primitive primordial cortical grey matter subdivided into an outer and inner band, separated from each other by a layer of scattered small neuroblasts, which have migrated from the ependymal zone, this less cellular zone constitutes the primordial internal granular layer of the cortex. The primordial internal granular layer is basophilic and the primordial cortical outer and inner band has taken eosinophilic stain.
At 19 weeks, the histological picture shows outer and inner bands with intervening primordial internal granular layers. The intermediate layer shows external and internal layers. It has taken eosinophilic stain.
At 23 weeks, the cortical outer band was divided and differentiated into the external granular II and external pyramidal layer III. The primordial inner band is divided into internal pyramidal layer V and multiform layer VI. The individual layers were not well differentiated.
At 33 weeks, these layers increased in thickness. The characteristic adult six-layered pattern was seen at this stage. All the layers were identified and well differentiated. Pyramidal and stellate cells were identified [Figure 3].

In adult brains

Neocortex

1. **Frontal:** The histological slide was taken from the superior frontal gyrus. It showed small and medium-sized pyramidal cells in Lamina III and V. Lamina II and IV were poorly developed.
2. **Precentral (Agranular cortex) [Figure 4]:** The histological slide was taken from the precentral area. More number of pyramidal cells were observed. The size of the pyramidal cell was larger when compared to the other areas. Lamina II & IV are less developed, containing stellate cells.
3. **Post central (Granular):** The histological slide was taken from post central gyrus it contained densely packed granular cells with small pyramidal cells in Lamina II & IV. Lamina III and V are moderately developed containing small and medium size pyramidal cells.
4. **Parietal:** The histological slide was taken from the superior parietal lobule. More number of granular cells are seen and less number of small pyramidal cells are seen.
5. **Polar:** The histological slide was taken from the occipital lobe. All the layers were present. Small and medium-sized pyramidal cells are present in lamina III and V. Lamina VI is well developed.

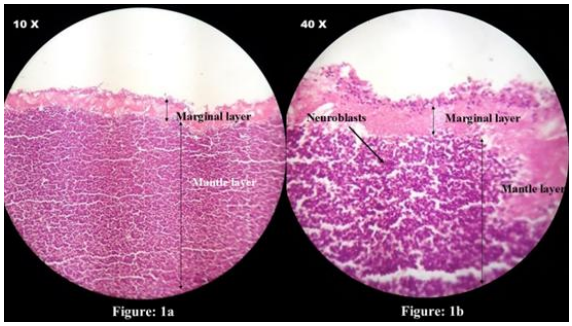

Figure 1: Histology of cerebral cortex of 13 weeks fetus (a) 10X (b) 40X

Allocortex

1. **Archipallium:** The histological slide was taken from the Hippocampal region. The dentate gyrus (DG), is seen as a tightly packed layer of small granule cells wrapped around the end of the hippocampus proper (Fig 5) it shows three layers

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polymorphic, granule cell layer, and molecular layer. The hippocampus showed three layers polymorphic layer, pyramidal layer, and molecular layer.

2. **Paleopalium:** The histological section was taken from the parahippocampal region. The section showed three layers.

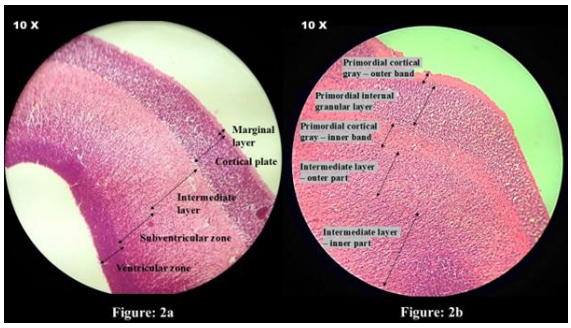

Figure 2: Histology of cerebral cortex of 14 weeks fetus

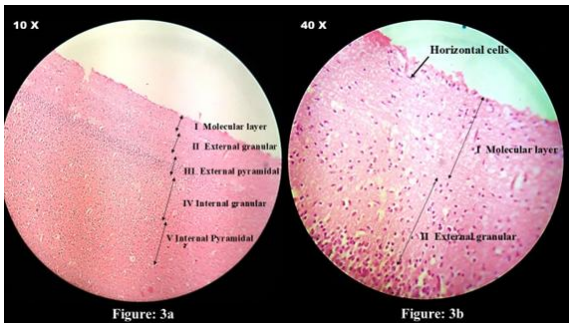

Figure 3: Histology of cerebral cortex of 33 weeks fetus (a) 10x (b) 40x

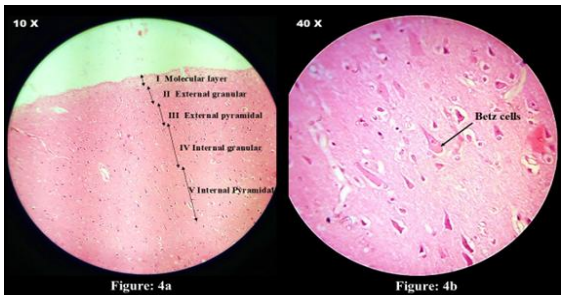

Figure 4: Histology of cerebral cortex in precentral area (a) 10x (b) 40x

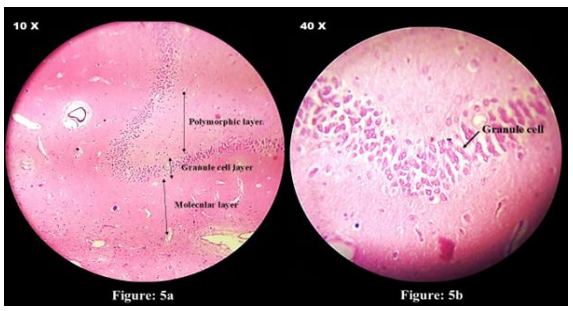

Figure 5: Histology of Dentate gyrus a) 10x (b) 40x

DISCUSSION

A key process in brain histogenesis is cell migration. Neuroblasts, originating near the brain's ventricles, migrate toward the periphery following specific patterns. These migration patterns lead to the formation of multiple layers of gray matter in brain tissue. Radial glial cells play a crucial role in this process, extending long processes from their cell bodies near the ventricular lumen toward the developing cortex's periphery. Postmitotic neurons, typically simple bipolar cells at this stage, wrap around the radial glial cells and use them as guides during migration from their point of origin to the outer regions. In areas of the brain cortex with six layers of gray matter, large neurons in the innermost layer migrate first. Smaller neurons then move through the initial and other previously formed layers, establishing new layers of gray matter at the outer edges. Thus, the outermost layer of neurons is formed last, while the innermost layer is formed first.[9]

Cortical layering is a crucial aspect of brain development, where neurons migrate from their origin in the ventricular zone to form the six distinct cortical layers. This process is tightly coordinated, involving radial migration, where neurons travel along radial glial fibers to their final destination in the cortical plate, and tangential migration, where neurons can move parallel to the cortical surface, contributing to layer formation. The inside-out pattern of migration ensures that the innermost layers of the cortex are formed first (Layer VI), and the outermost layers are formed later (Layer I).[10]

According to Angevine and Sidman,[11] when titrated thymidine was incorporated into the cells of neuroepithelial and mantle layers, the neuroblast labeled in the early stages of development were, later found in the infra granular laminae V & VI, subsequently appeared in the granular and supra granular laminae, IV, III & II.

According to Hicks et al,[12] the pathways of the migratory cells were found to be extremely complex. The last neuroblasts to reach the cerebral cortex in late fetal life were those destined to form its outer layers.

According to Berry and Rodgers,[13] the layered arrangement of cells within the cortex was not necessarily due to the successive waves of neuroblast migration but may be determined by the lines of stress resulting from the rapid expansion of the cortex.

According to Patten's embryology,[14] during the 8th week, the wall of the cerebral hemisphere consists of the ependymal zone, mantle zone, and marginal zone from inside to outside. During the 10th week, the intermediate mantle layer is divided into the outer primordial cortical grey and the inner intermediate layer. During the 4th and 5th months, the primordial cortical layer is divided into an outer supra-granular layer, an inner infra-granular layer is an inner nuclear

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layer. During 6th month, the cellular band deep to the granular layer differentiates into V and VI layers. During the 7th month, the supra granular layer has also divided and differentiates into the external granular II and the pyramidal layer III. Thus, a six-layered cortex is differentiated. From the 8th month to term, these layers gradually increased in size and white fibers increased in thickness. By modifications of these six basic layers, the characteristic patterns of the various specialized regions of the neopallial cortex are established. In adults, all six laminae are well-developed. The findings of the present study on histogenesis are similar but lag behind Patten's findings.

According to Von Economo & Koskinas,[15] the structure of the cerebral cortex shows considerable variation from region to region, 1.Granular, 2.Agranular, 3. Frontal (pre-motor), 4. Parietal (post-central), 5.Polar.

Agranular type: It has diminished or lacks granular laminae (II & IV) but always contains scattered stellate cells. The large pyramidal cells are found in the greatest densities. The agranular cortex is often equated with the cortical motor area.

Granular type: Granular layers are maximally developed and contain densely packed stellate cells and dispersed small pyramidal neurons. Laminae II & V are poorly developed.

Frontal type: It contains a large number of small and medium-sized pyramidal neurons in laminae III & V. Granular layers II & IV are less prominent.

Parietal type: It contains small pyramidal cells, granular laminae are wider and contain more of the stellate cells.

Polar type: All six laminae are present but pyramidal layer III is reduced. The multiform layer is more highly organized.

The findings of the present study are similar to the findings of Von Economo & Koskinas.

CONCLUSION

In summary, the histogenesis of the cerebral cortex is a precisely orchestrated event, where neuroblast migration, radial glial guidance, and the layered organization of neurons all play critical roles. Neuronal migration in humans begins as early as 13 weeks of gestation and continues throughout fetal development. Certain drugs like antiepileptic drugs, steroids, retinoids, and substances like alcohol, and tobacco can severely impact neuronal migration during fetal development. Disruption in these processes can lead to a range of neurodevelopmental disorders and brain malformations like lissencephaly, autism spectrum disorders, and schizophrenia. It is crucial to avoid exposure to harmful substances during pregnancy and seek guidance from healthcare providers regarding the safety of medications.

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