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Cellular migration and histogenesis of cerebral cortex with functional correlations in human fetuses at different weeks of gestation

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Abstract
Cerebral cortex in humans is thinnest at 8 weeks of intra-uterine life and becomes thicker progressively along the superolateral and inferolateral walls from frontal to occipital poles. Histogenesis of the cerebral cortex (neocortex) - The layered structure of the adult cerebral cortex forms from the telencephalon as the surface area increases. At first there are 3 zones to the cortex: 1) germinal zone, immediately surrounding the lateral ventricle, 2) intermediate zone, becomes the white matter, and 3) marginal zone, becomes the gray matter. Neuroblasts of the germinal zone divide and migrate into the marginal zone to become neurons and glial cells. The marginal zone is formed by cells migrating a) early, which become the deeper layers of the cortex while those that migrate b) later, form the more superficial layers. Between 6 and 8 months 6 layers are observed in the marginal zone of the neocortex, recognized by cellular and fiber laminate. The 6-layered cortex is further distinguished as having two main divisions: 1) the deeper highly cellular pyramidal layer are layers II - VI and 2) the more superficial molecular layer (layer I) is comprised mostly of fibers. The intermediate zone becomes the white matter of the cerebral hemispheres which is traversed by the processes of the cells migrating toward the surface. At birth the neocortex has a 6-layered structure while cortical areas dealing with olfaction (paleocortex) and the hippocampal formation (archicortex) do not have a six-layered structure. Cerebrum of 32 still born human foetuses of both sexes were procured from the Department of Gynaecology after spontaneous miscarriages and therapeutic abortions. 5 mm tissues from frontal, temporal, parietal and occipital cortices were dissected and kept in 10% Formalin overnight for better fixation. Then they were processed for histological examination using H/E stain. The neurons were granular until 18 weeks of gestation and showed few pyramidal cells at 24 weeks and then they showed sesqui laminar pattern with predominance of Betz cells in frontal and temporal cortex and predominance of granule cells were seen in parietal and occipital cortex. Cell migration and histogenesis of cerebral cortices are important in disorders like epilepsy or epilepsy.

Keywords: betz, cerebrum, histogenesis, formalin, granule cells

Introduction

The histogenesis of the cortex of cerebral hemispheres is reported in literature since 1930. The of cell types show immense complexity, multiplicity and structural heterogeneity in different locations of cerebral cortex which has generated wide study by different authors abroad and nationwide in the past.

The present study has been undertaken to enrich the knowledge of studies done by previous workers of the changes in the cortex of foetal cerebral hemispheres in this eastern India.

By the end of 4th week of Intrauterine life, the telencephalic pallium (cortex), in the human fetus consists of a germinal layer and an ependymal layer, which together form the stratified cellular wall of the neural tube.

By the end of 8th week of Intrauterine life, medullary differentiation is well advanced, and the cells migrate toward the surface to form the mantle layer. Thus, the wall of the cerebral hemisphere consists of the general primitive structure of the neural axis with the germinal or mantle layer on the interior and the marginal or future molecular layer on its exterior.

During 12th week of Intrauterine life, the cortical layer is formed by cells from the mantle layer migrating toward the surface. This cortical layer is thin in the archicortical and paleo cortical regions and thick in the neocortical region.

Various cortical regions differentiate from the cortical layers- the primordial olfactory cortex begins first between 2 and 3 months, and the hippocampus (archicortex) and paleocortex can be seen in this period of gestation which forms a 3-layer cortex forms in these areas. Differentiation of the neocortex extends from the beginning of 12th week of intrauterine life to the end of 24th week of intrauterine life. It is characterized by extensive cellular migrations, resulting in the formation of six layered cerebral cortex.

In the adult, the cerebral cortex forms a layer of gray matter approximately 3 to 5 mm thick

The cellular migration and layering of cells are first seen in insular and parietal cortex. Thus, the somesthetic system which is noticed by the ascending parietal convolutions of the cerebral cortex is functional in the fetus very early before the special senses like sight and hearing. Then cellular migrations appear at the level of the frontal and occipital cortices.

In 24th week of Intrauterine life, the neurons form their processes and in 28th week of intrauterine life the various types of cortical structures are established which are involved

in motor, sensory, associative functions according to the proportion of specialized cells they contain.

Aims & Objectives

Study was done to correlate the Chronological Pattern of Cerebrum development in this geographical eastern region of India & compare the results from other researchers nationwide & worldwide.

Materials & Methods

This study was done to correlate the chronological pattern of spleen development in this geographical eastern region of India, Odisha& compare the results from other researchers nationwide & worldwide. This is a hospital based, observational, cross sectional study conducted at Hi- Tech Medical Colleges & Hospital, Bhubaneswar, India by the Department of Anatomy in collaboration with Department of Obstetrics & Gynaecology from November 2011 to June 2013 on thirty-two aborted human foetuses without obvious congenital anomaly of gestational age between 18 weeks and 40 weeks collected within 6 hours of delivery by spontaneous miscarriages & therapeutic legal abortions. Study samples were arbitrarily divided into groups of biweekly gestational age by duration of amenorrhoea from medical records & ultrasound fetometry after receipt of informed consent from mother and legal guardians. Fetuses were immediately fixed in 10% Formalin for 1-2 hrs. Spleen was dissected by Dissecting Microscope, fixed in 10% Formalin for 48-72 hrs. After fixation by formalin, the tissues were transferred to 30%, 50%, 70%, 90% and Absolute alcohol each for 30 minutes. This ascending grading of the dehydrating fluid was done because when alcohol mixes with water, it produces diffusing current which can damage the tissues. Then the tissues were put in xylol for 24 hours to clear the residual alcohol. These tissues were processed for paraffin sections by tissue blocking (Paraffin Embedding). 3 pots of hard paraffin were taken; paraffin was melted in the incubator at 56 degrees, as hard paraffin is ideal for materials which are to be cut in thin sections about 12 mu. The tissue was put in the first pot containing equal parts of paraffin and xylol and then changed to second and third pots containing only fresh melted paraffin at 90 minutes interval. Then the tissues were mounted in fresh melted paraffin with L-Block. The L-Block was then trimmed to a rectangular shape. Then the L-Block was fixed with the block holder (choke) and the block holder was clamped in the rotary microtome. 5 mu sections were cut in rotary microtome. The microtome was revolved at 40 per min and ribbon was formed. Then the ribbon was put in tissue flotation bath. Albuminised slide was then made by putting a drop of Mayor's albumin (equal parts of glycerine and egg white) and spreading it uniformly by rubbing with finger. The piece of ribbon was then taken on the slide and dried at room temperature. The slide was then put in the warming table. When the paraffin melted the slide was put into xylol for 2-3 minutes because xylol removes paraffin. Then the tissue was put in decreasing grades of alcohol (Absolute alcohol,90%,70%,50% and 30%) then was put in the prepared Harris Alum Haematoxylin (nuclear) stain for 7 minutes and lastly washed with distilled water.2-3 drops of 1% acid alcohol (1cc Hcl in 75% alcohol) was added to remove the excess stain beyond the nucleus. The slide was then put in running tap water for 30 minutes to develop haematoxylin colour (bluish). Then the slides were again dipped in ascending grades of alcohol (30%, 50%, and 70%) and then put in eosin Y (cytoplasmic) stain for 30 seconds. Then the slide was washed with absolute alcohol for a few seconds so that excess of eosin was removed and lastly the slide was placed in xylol. The slide was then taken out from xylol and then put in 1-2 drops of DPX (Adhesive agent) and a cover slip was put on it and pressed slightly so that air bubbles were removed. Sections were then seen in light microscope under low power 10X followed by high power 40X magnification. Thereafter photomicrographs were taken by camera using microscope adapter.

Table 1

Crown-Rump Length & Crown-Heel Length

WEEKS	CRL (in cm)	WEEKS	CHL (in cm)
10	3.1	22	27.8
12	5.4	24	30.0
14	8.7	26	35.6
16	11.6	28	37.6
18	14.2	30	39.9
20	16.4	32	42.4
		34	45.0
		36	47.4
		38	49.8

Observations

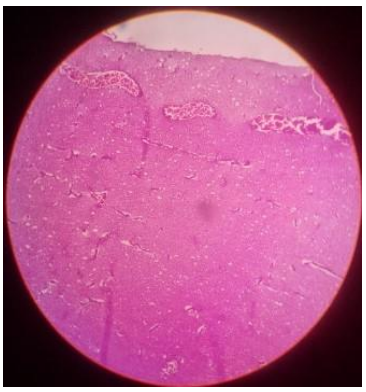

Fig 1

At 18wks gestation, the neuronal cells showed a closely packed stratifcation with migration of all the cells from the ependymal zone to the pial surface. This being very prominent in all the regions of cerebral cortex. Vertical migration is predominant over the collateral migration. The cells are rounded with deep stained nuclei.

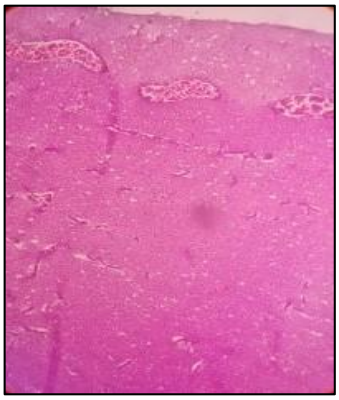

Fig 2

At 24 wks the process of migration is still on. However the typical laminar pattern is not seen. The cells look like rounded granule cells with deeply stained nuclei.

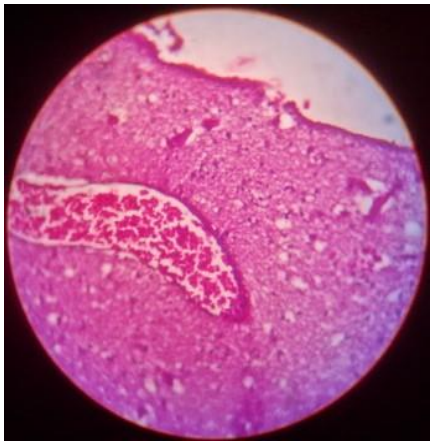

Fig 3

At 33 wks, the cells are assuming the laminar pattern. Predominance of granule cells is seen along with few pyramidal cells.

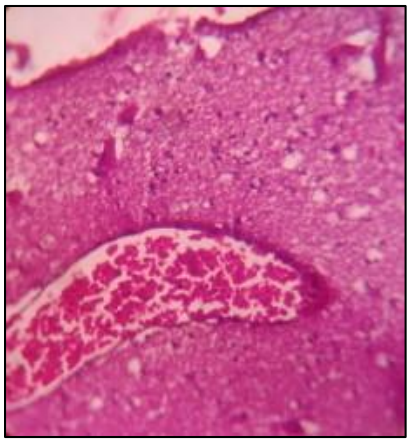

Fig 4

At 40 weeks, the laminar pattern is clearly demarcated. Large pyramidal cells (Betz) are seen in the pre-central gyrus in the frontal lobe. In post-central gyrus, granule cells are predominant with few pyramidal cells. The granule cells and predominantly pyramidal cells are seen which is feature of temporal cortex. The occipital cortex showing very small, rounded granules with deeply stained nuclei, absence of pyramidal cells completely, a feature of koniocortex.

Discussion

Pioneering studies of cell migration in the developing cerebral neocortex were made by Tilney *et al*. 1933 who observed trilaminar sequential structure of cerebral cortex. Economo and Koskinas (1929) also studied the five fundamental types in neocortex and further professed sesquilaminar pattern [1]. Human cerebral cortex is thinnest at 8 weeks of intra-uterine life and becomes thicker progressively along the superolateral and infero- lateral walls from frontal to occipital poles (Sanides *et al.* 1970) [2]. Outer molecular layer is thin with sparse cells adjacent to pia mater named as cajal-retzius cells (Bryan Kolb, Ian Q. Whishaw 2003) [3]. The neurons that are migrating accomplish a vertical and lateral migration from that of the first matured neurons which settled down as layer 6 neurons. Later more superficial layers of cortex are formed from inside out. The transformation into the adult neocortical pattern starts between weeks 25 and 35 as the migration and proliferation of proneurones diminishes. Dendrites begin to differentiate, and synapses begin to develop in the deepest cortical layers, progressing to the most superficial layer. (Huttenlocher, p.r.1987) [4]. The topographic changes in pre-central, post-central, temporal, and occipital cortices do take place between 5-8 months due to unequal growth and heterogeneous differentiation of cortical regions. It has been recognized that the young neurons are guided in their migrations by following the surfaces of radial glial cells, a bipolar cell form of astroglial lineage (Rakic, 1972, 1978) [5, 6]. This areal differentiation occurs concomitantly with the arrival of thalamocortical fibres (Marin - Padilla, 1970: Sidman and Rakic, 1973) [7, 8] but not necessarily because of it (Seil *et al*., 1974) [9]. The embryonic central nervous system consists of five fundamental zones from which the adult organization is derived, though none of the five corresponds directly to any adult component. The geographical names are ventricular zone, subventricular zone, intermediate zone, cortical zone and marginal zone (the Boulder Committee, 1970) **[10]**. Chong *et al*., (1996) **[11]** had provided a template of the normal appearance and the temporal pattern of neuronal migration in the human foetal brain early in the II Trimester as seen with MRI and correlated with histological sections. The presence of germinal matrix and layers of migrating neurons diminished considerably in size by 21 weeks (Bryan Kolb, Ian Q. Whishaw 2003) Clark (2002) **[12]**, made identification of lisencephaly, cerebral hypoplasia, polymicrogyria and heterotopias which are sex-linked inherited disorders. In the present study, the six layered patterns of cortex were clearly appeared at first in the precental gyrus from 30 weeks on wards.

Conclusion

At present, disorders of cell migration can be identified by magnetic resonance imaging, most common disorder is dyslepsia or epilepsy. Brain mapping studies done now a days to days to know the neural regulation in brain can be enriched by knowing the detailed cellular architecture of developing cerebral cortices in human brain. The treatment of Lisencephaly, Cerebral hypoplasia, Polymicrogyria and heterotopias which are sex linked inherited disorders can be useful by knowing the histogenesis of cerebral cortex in human foetuses of various weeks of gestation using the Targeted Drug Delivery system by Nanoparticles in In-Utero in future. This study should be further enriched by Special stains like Cresyl Violet and Ultrastructural studies to know the detailed cell organelles structure in the developing brain.

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Conflicts of interests: None

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