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TO COMPARE THE DELINEATION OF FETAL BRAIN LAMINATION BETWEEN T2-WEIGHTED SINGLE-SHOT FAST SPIN ECHO AND ECHO PLANAR IMAGING FLUID- ATTENUATED INVERSION RECOVERY IMAGES--A CROSS-SECTIONAL STUDY

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Absract

The human cerebrum undergoes age-specific lamination changes during development. Notably, the subplate zone stands out as the most significant transient area, where major afferent systems temporarily settle, form synapses, and engage in essential cellular interactions critical for future cortical development. Our research utilized magnetic resonance imaging (MRI) to track the developmental history of this key cortical layer (the subplate zone) and other laminar regions of the fetal cerebral wall from 26 to 32 weeks post-ovulation. The study revealed that alterations in the MRI lamination pattern of the fetal cerebral wall are largely attributed to changes in the subplate zone. This zone is vital for creating important connections between the thalamus and cortex, coinciding with the period when the cortical mantle starts forming sulci and gyri. The present study was conducted on 50 patients and focused on the comparison of fetal brain lamination (Subplate) between T2-weighted SSFSE and EPI-FLAIR sequences to help guide the decision on the utilization of neuroimaging in the diagnostic workup referred to the Radiodiagnosis Department in Government Rajindra Hospital, Patiala.

INTRODUCTION

The subplate zone, along with the marginal zone and cortical plate, forms the foundational structure of the mammalian cerebral cortex in fetuses. Ivica Kostović and Mark E. Molliver first identified the subplate as a distinct transient fetal zone in 1974[1]. This transient structure is crucial for normal cortical development. In the developing human brain, three primary layers are evident in the cerebral wall: the ventricular zone or germinal layer next to the ventricles, which generates neuronal and glial progenitor cells; the intermediate zone or fetal white matter; and the outer developing cortex. Migratory neuroblasts initially exit the ventricular zone via somal translocation to create the preplate, a two-layered structure comprising the outer marginal zone below the pial surface and the inner subplate where most early-generated cells reside. The cortical plate develops within these layers. While the subplate is a temporary structure, the marginal zone remains into adulthood as layer 1 of the cortex. Subplate neurons are among the earliest postmitotic neurons of the cortex, forming before the cortical plate. Most of these neurons undergo programmed cell death before birth, although there is growing evidence of their extended survival into postnatal life.

The subplate's presence is essential for normal corticogenesis. Its existence below the layered cortical plate is a key indicator of cortical immaturity during the preterm phase. Initially, the subplate is quite thick and distinguishable from the cortical plate due to its significantly lower MRI signal intensity It is stated in the Policies, Guidelines, and Recommendations for MR Imaging Safety and Patient Management issued by the Safety Committee of the Society for Magnetic Resonance Imaging in 1991 that —MRI may be used in pregnant women if other nonionizing forms of diagnostic imaging are

inadequate or if the examination provides important information that would otherwise require exposure to ionizing radiation.‖[2] While the cortical plate (CP), or future cortex, is easily identifiable, MRI evaluation of other brain layers is challenging due to poor T2 contrast between the subplate and the underlying intermediate zone (IZ), which become indistinguishable after 24-26 weeks of gestation. Cortical tissues are marked by decreased water content and increased cell density, resulting in decreased signals on T2-weighted images and increased signals on T1-weighted images. The germinal ventricular zone and cortical plate appear as low signal intensity bands on T2-weighted images and high signal intensity bands on T1-weighted images. Compared to standard fetal T2-weighted single-shot fast spin-echo (SSFSE) sequences, echo planar imaging (EPI) fluid-attenuated inversion recovery (FLAIR) sequences provide a more reliable differentiation of fetal brain tissue compartments. The EPI-FLAIR sequence distinctly identifies the subplate from the intermediate zone throughout gestation (18–38 weeks), enhancing contrast in all brain regions compared to T2-weighted SSFSE (mean signal intensity ratio between subplate and intermediate zone). Fetal MRI is a well-established method for assessing and ruling out fetal central nervous system pathologies, particularly in the brain parenchyma. Early MRI machines often caused claustrophobia, but recent advancements have made them much more comfortable for patients. In vivo, fetal MRI offers detailed insights into brain structure, correlates with functional maturation, and aids in the early detection of brain damage.

AIMS AND OBJECTIVES

1. To study the fetal cortical subplate in normal pregnancies.
2. Comparison of T2WI-SSFSE and EPI-FLAIR sequences for subplate layer visualization in the fetal brain.

MATERIALS AND METHODS SOURCE AND METHOD OF COLLECTION OF DATA

The main source of the study was patients from Rajindra Hospital Patiala. The pregnant females (26-32 weeks) who were coming for routine Antenatal checkups from the Department of Obstetrics and Gynaecology. A minimum of 50 cases were intended to be taken up for study to derive a significant result and statistical analysis.

Study Design:

Cross sectional study. Inclusion Criteria: Singleton pregnancy (26-32 weeks) Exclusion Criteria: 1. Unknown gestational age (GA) 2. Any Congenital Malformations and multiple gestation

METHODOLOGY:

This study was conducted on 50 pregnant females (26-32 weeks) who are coming for routine ultrasound examination in department of Radiodiagnosis, Government Medical College and Rajindra Hospital, Patiala. An informed and written consent was obtained from all patients before enrollment. The patients were referred to Department of Radiodiagnosis from Obstetrics and Gynaecology department of Government Medical College and Rajindra Hospital, Patiala for routine ultrasound examination. EQUIPMENT: The study was performed on Siemens magnetom aera 1.5T MRI machine. STUDY ANALYSIS: Descriptive studies were presented in terms of mean and standard deviation. Qualitative data were presented as frequency multivariate analysis. Other sub stratified analysis were carried out as appropriate.

OBSERVATIONS

This cross-sectional study was carried out on 50 pregnant females(aged 18-38 years) coming for routine ultrasound examination to the department of Radiodiagnosis, Government Medical College and Rajindra Hospital, Patiala. They were subjected to an MRI examination. The observations were as under:-

The gestational age range included in our study was from 26 weeks 32 weeks. The maximum number of patients (pregnant mothers) were in the gestational age of 26-27 weeks (44%). The second-highest number of patients were in the gestational age of 31 weeks-32 weeks (16%). The mean gestational age of the patients in our study was 28.17±2.05.

TABLE-1

Comparison of Subplate visualization between T2-SSFSE and EPI-FLAIR sequence

		26^{+0} – 26^{+6} Weeks			27^{+0} – 27^{+6} Weeks			28^{+0} – 28^{+6} Weeks			29^{+0} – 29^{+6} Weeks			30^{+0} – 30^{+6} Weeks			31^{+0} – 31^{+6} Weeks			32^{+0} – 32^{+6} Weeks		
		T2-SSFSE	EPI-FLAIR	p value	T2-SSFSE	EPI-FLAIR	p value	T2-SSFSE	EPI-FLAIR	p value	T2-SSFSE	EPI-FLAIR	p value	T2-SSFSE	EPI-FLAIR	p value	T2-SSFSE	EPI-FLAIR	p value	T2-SSFSE	EPI-FLAIR	p value
Frontal Lobe	Not Visualized	11 (55%)	0 (0%)	0.007 (7.29)	7 (87.5%)	0 (0%)	0.039 (4.27)	4 (80%)	0 (0%)	0.014 (6.02)	3 (75%)	0 (0%)	0.001 (12.29)	3 (75%)	0 (0%)	0.001 (24.01)	5 (83.3%)	0 (0%)	0.009 (6.83)	3 (100%)	0 (0%)	0.025 (5.00)
	Partially Visualized	9 (45%)	2 (10%)		1 (12.5%)	3 (37.5%)		1 (20%)	2 (40%)		1 (25%)	2 (50%)		1 (25%)	3 (75%)		1 (16.7%)	4 (66.7%)		0 (0%)	3 (100%)	
	Completely Visualized	0 (0%)	18 (90%)		0 (0%)	5 (62.5%)		0 (0%)	3 (60%)		0 (0%)	2 (50%)		0 (0%)	1 (25%)		0 (0%)	2 (33.3%)		0 (0%)	0 (0%)	
Temporal Lobe	Not Visualized	11 (55%)	0 (0%)	0.007 (7.29)	6 (75%)	0 (0%)	0.015 (5.95)	3 (60%)	0 (0%)	0.007 (7.22)	3 (75%)	0 (0%)	0.001 (48.02)	3 (75%)	0 (0%)	0.001 (48.02)	3 (50%)	0 (0%)	0.001 (8.26)	2 (66.7%)	0 (0%)	0.002 (10.34)
	Partially Visualized	9 (45%)	2 (10%)		2 (25%)	1 (12.5%)		2 (40%)	2 (40%)		1 (25%)	1 (25%)		1 (25%)	1 (25%)		3 (50%)	3 (50%)		1 (33.3%)	2 (66.7%)	
	Completely Visualized	0 (0%)	18 (90%)		0 (0%)	7 (87.5%)		0 (0%)	3 (60%)		0 (0%)	3 (75%)		0 (0%)	3 (75%)		0 (0%)	3 (50%)		0 (0%)	1 (33.3%)	
Parietal lobe	Not Visualized	15 (75%)	0 (0%)	0.001 (14.3)	7 (87.5%)	0 (0%)	0.011 (6.36)	3 (60%)	0 (0%)	0.057 (3.61)	2 (50%)	0 (0%)	0.002 (7.68)	2 (50%)	0 (0%)	0.006 (17.68)	4 (66.7%)	0 (0%)	0.001 (10.34)	3 (100%)	0 (0%)	0.025 (5.00)
	Partially Visualized	5 (25%)	2 (10%)		1 (12.5%)	4 (50%)		2 (40%)	3 (60%)		2 (50%)	1 (25%)		2 (50%)	3 (75%)		2 (33.3%)	4 (66.7%)		0 (0%)	3 (100%)	
	Completely Visualized	0 (0%)	18 (90%)		0 (0%)	4 (50%)		0 (0%)	2 (40%)		0 (0%)	3 (75%)		0 (0%)	1 (25%)		0 (0%)	2 (33.3%)		0 (0%)	0 (0%)	
Occipital lobe	Not Visualized	12 (60%)	0 (0%)	0.003 (8.90)	7 (87.5%)	0 (0%)	0.011 (6.36)	4 (80%)	0 (0%)	0.003 (8.60)	3 (75%)	0 (0%)	0.001 (12.29)	2 (50%)	0 (0%)	0.006 (17.68)	5 (83.3%)	0 (0%)	0.005 (7.84)	2 (66.7%)	0 (0%)	0.002 (10.34)
	Partially Visualized	8 (40%)	2 (10%)		1 (12.5%)	4 (50%)		1 (20%)	3 (60%)		1 (25%)	2 (50%)		2 (50%)	1 (25%)		1 (16.7%)	4 (66.7%)		1 (33.3%)	2 (66.7%)	
	Completely Visualized	0 (0%)	18 (90%)		0 (0%)	4 (50%)		0 (0%)	2 (40%)		0 (0%)	2 (50%)		0 (0%)	3 (75%)		0 (0%)	2 (33.3%)		0 (0%)	1 (33.3%)	

DISCUSSION

The subplate of the lateral neocortex changes dramatically during fetal development. The monolayer (presubplate) undergoes bilaminar transformation between 15 and 17 GW and in midgestation (17-23 GW), even trilaminar organization in the deep subplate, intermediate (SP proper), and superficial subplate subcompartments. In the stationary phase from 24 to 30 GW, the SP gradually loses sublamination and regresses after 37 GW. However, many SP neurons survive even into adulthood as subcortical white matter interstitial neurons.[3] The importance of subplate neuronal injury in the encephalopathy of prematurity is seen in the form of a decrease in subcortical white matter neurons, presumably subplate neurons, in infants with PVL. Subplate neuronal pathology has been suggested in various other neurological disorders, including epilepsy, autism, and schizophrenia, beyond the neonatal period also. Drug-resistant epilepsy is often accompanied by severe cortical dysplasias, in which large groups of cells are also abnormally located within the cerebral white matter.[4]

Period of gestation:- The gestational age range included in present study was from 26 weeks 32 weeks. The maximum number of patients (pregnant mothers) were in the gestational age of 26-27 weeks (44%). The second highest number of 58 patients were in the gestational age of 31 weeks-32 weeks (16%). The mean gestational age of the patients in our study was 28.17±2.05.

Overall Comparison of subplate visualization between T2-SSFSE and EPI-FLAIR sequence between 26-32 gestational weeks:- In our study, the difference of subplate visualization in all cerebral lobes between T2-SSFSE and EPI-FLAIR sequence was statistically significant from 26-32 weeks. In (26weeks 0 days-26weeks 6 days) gestational age, the p-value was 0.007 in the frontal & temporal lobe, 0.001 in the parietal lobe and 0.003 in the occipital lobe. In (27weeks 0 days-27 weeks 6 days) p-value was 0.039 in the frontal lobe, 0.015 in the temporal lobe, 0.011 in parietal and occipital lobes. In (28 weeks 0 days-28 weeks 6 days), the p-value was 0.014 in the frontal lobe, 0.007 in the temporal lobe, 0.057 in the parietal lobe and 0.003 in the occipital lobe. In (29 weeks 0 days-29 weeks 6 days), the p-value was 0.001 in frontal, temporal & occipital lobes and 0.002 in the parietal lobe. In (30 weeks 0 days-30 weeks 6 days), the p value was0.001 in frontal &temporal lobes and 0.006 in parietal &occipital lobes. In (31 weeks 0 days-31 weeks 6 days), the p-value was 0.009 in the frontal lobe, 0.001 in temporal &parietal lobes and 0.005 in the occipital lobe. In (32 weeks 0 days), the p-value was 0.025 in the frontal & parietal lobe and 0.002 in the temporal & occipital lobe.

Similar results were also observed in a study conducted by L Perkin 2007, in which they observed that subplate diameters ranged from 0 to 4.5 mm. The subplate showed a relatively constant diameter before becoming MR invisible from approximately 28 weeks gestation. After 28 weeks, a measurable subplate was seen in the occipital and frontal lobe but only in 2 and 3 fetuses, respectively. The subplate increased between 20 weeks and 35 weeks gestation ($p = 0.04$) in the temporal lobe. It remained visible throughout the range of study, only disappearing in 2 fetuses at 30 and 32.5 weeks, respectively.[5]

The results were in concordance with a study done by Lana vasung in 2016, for the Quantitative and Qualitative Analysis of Transient Fetal Compartments during Prenatal Human Brain Development. Forty-four postmortem brains of human fetuses and prematurely born infants were included. They described that the volume of SP increases with age between 13 and 30 PCW, reaching the maximum around 30 PCW in most areas of the cerebral hemisphere, occupying up to 45% of the entire telencephalic volume and being almost four times thicker than CP.[6]

The results concordance with a study conducted by J. Corbett-Detig in 2010, where twenty-one subjects were selected from the age range 20.57 to 25.86 gestational weeks (GW) calculated from the last menstrual cycle period. They show that global subplate volume increased in proportion with the supratentorial volume; the subplate remained approximately one-third of the supratentorial volume. They also found both global and regional growth in subplate thickness and a linear increase in the median and maximum subplate thickness through the waiting period. Furthermore, they found that the developing brain's posterior regions-specifically the occipital lobe, ventral occipitotemporal region and planum temporale-underwent the most statistically significant increase in subplate thickness. The thickest region was the developing somatosensory/motor cortex during this period. The subplate growth patterns reported here may be used as a baseline for comparison to abnormal fetal brain development.[7]

EPI-FLAIR enabled better visualization and delineation of the subplate, as determined by a qualitative assessment, with identification of the subplate (GC and SB) being significantly higher with EPI-FLAIR than with T2-weighted SSFSE (significant and highly significant p-value in all lobes between 26-32 weeks of gestation on EPI-FLAIR as comparison with T2-SSFSE in its qualitative analysis). Similar results were observed in the study conducted by Mariana C. Diogo, MD in 2019, where a total of 259 MRI examinations were included in the qualitative analysis and 72 MRI examinations were included in the quantitative analysis in which they concluded that identification of the subplate was superior on EPI-FLAIR images when compared with T2-weighted SSFSE images in all lobes (subplate visualization [complete + partial]: frontal lobe, n = 243 vs n = 117; temporal lobe, n = 244 vs n = 137; parietal lobe, n = 240 vs n = 93; occipital lobe, n = 241 vs n = 97, respectively; P, .001). On T2-weighted SSFSE images, there was consistent visualization of the subplate

until GW 26, after which only partial visualization of the subplate was possible; the subplate was then not visible after GW 35.[8]

CONCLUSION

The subplate zone, a temporary cellular compartment in the embryonic cerebrum, has grown in size and complexity throughout primate evolution, reaching its peak in humans. Understanding the normal changes in the subplate layer and the intermediate zone is crucial. This information can be used in prenatal assessments, addressing white matter injuries from ischemia or infection, and identifying abnormal white matter development associated with brain malformations. The volume of proliferative compartments significantly decreases after 25 weeks post-conception (PCW), while the extracellular matrix-rich, synapse-containing subplate compartment reaches its maximum volume and thickness around 30 PCW before diminishing again. Therefore, the optimal period for evaluating the subplate is between 26-32 weeks, as shown in our study. During mid-gestation, the subplate zone occupies nearly half of the total hemispheric volume, underscoring its importance in human brain development. A decrease in subplate neurons is linked to the development of encephalopathy in premature infants. Additionally, subplate neuronal pathology is found in various neurological disorders, including drug-resistant epilepsy, temporal lobe epilepsy, autism, and schizophrenia. Our study demonstrates that an echo-planar imaging (EPI) fluid-attenuated inversion recovery (FLAIR) MRI sequence enhances the visualization of fetal brain lamination compared to standard T2-weighted single-shot fast spin-echo sequences. Using an EPI-FLAIR sequence could also improve the in-utero detection of anomalies affecting lamination or the subplate. EPI-FLAIR sequences provide a more detailed evaluation of fetal brain maturation later in pregnancy when ultrasound imaging is limited due to skull ossification (after 30 weeks of gestation). Given its advantages and relatively short acquisition time, we recommend including this sequence in routine fetal brain MRI examinations.

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