ORIGINAL RESEARCH

Prospective study of diffusion tensor imaging and conventional magnetic resonance imaging in term and preterm neonates with hypoxic ischemic encephalophy and correlation with clinical outcome

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ABSTRACT

Background: HIE is a brain dysfunction caused by a reduction in the supply of oxygen to the brain and other organs (hypoxia), compounded by low blood flow to vital organs (ischemia). Encephalopathy refers to any condition that results from reduced blood and oxygen supply to the brain. HIE is the common cause of cerebral palsy. Cerebral palsy is defined as a group of permanent disorders of the development of movement and posture, causing activity limitation, that are due to non-progressive disturbances that occurred in the developing fetal or infant brain. Early assessment of severity of HIE can help proper parent counseling and early institution of stimulation therapy for better development of infant. So there is a necessity to study the importance of DTI in detecting HIE babies within 14 days of their life.

Aims and Objectives:

- To correlate MRI brain findings and DTI findings in early neonatal period of term and preterm neonates with hypoxic ischemic encephalopathy and its clinical outcome
- It can provide evidence for developing effective measures of prevention, protection, and rehabilitation for damage to the brain

Materials and Method: Prospective study done in 50 newborn babies with hypoxic ischemic encephalopathy under Department of Radiodiagnosis, Govt. Kilpauk Medical College Hospital, Kilpauk, Chennai for a period of 1 year and 3 monthsAll included were underwent conventional MRI sequences and Diffusion Tensor Imaging. All images were screened for any abnormality in the following 6 regions, Corona radiate, anterior and posterior limb of internal capsule, superior longitudinal fasiculus, inferior longitudinal fasiculus andthalamus. **Results:** DTI detected 46 babies out of 50 babies whereas MRI detected 23 out of 50 babies. Study shows DTI has 100% sensitivity and 90% specificity. DTI has a positive predictive value of 91.3% Negative predictive value of 96% and Diagnostic accuracy of 92%. Detailed ROC analysis done for DTI different segments.**Conclusion:** From our study we came to find out that HIE-1 mainly affects the posterior limb of internal capsule and HIE III diffusely affects the white matter, basal ganglia and thalamus. DTI is currently the only way to quantify the maturation and damage of brain development in preterm neonates. Coupled with a good intervention. Treatment system established with clinical development assessment and pathogenic factors, DTI is an important aid to improve the prognosis of nerve development in HIE babies.

Key words:DTI, MRI, HIE, FA, ADC, DDST

INTRODUCTION

HIE is a brain dysfunction caused by a reduction in the supply of oxygen to the brain and other organs (hypoxia), compounded by low blood flow to vital organs (ischemia). Encephalopathy refers to any condition that results from reduced blood and oxygen supply to the brain. Perinatal asphyxia, or birth asphyxia is deprivation of oxygen to a newborn infant that lasts long enough during the birth process to cause injury to the brain[1].

Hypoxic injury occurs before 35 weeks of gestational age results in periventricular leucomalacia. At 40 weeks of gestational age, the degree of hypoxia correlates to the area of the brain that is injured. Mild hypoxia will affect the parasagittal white matter while severe hypoxia affects the putamen, thalamus and paracentral white matter.

Certain signs may appear shortly after birth like organ dysfunction (heart, kidney, lung and liver) denotes possible HIE. Seizure in the first 24 hours of life can also denotes in the possibility of HIE.

Imaging methods attributed to better understanding of pathological events also allows quantitative monitoring of disease progression that may provide decision regarding intervention like stimulation therapy and physiotherapy.

Conventional MRI sequences can help to exclude other causes of encephalopathy such as hemorrhage, cerebral infarction, neoplasm or congenital malformation. Eight months appear to be the earliest time at which MRI findings are correlate well with the developmental outcome. In predicting neurological outcome MRI findings of the neonatal period had the highest negative predictive value[2].

DTI provides qualitative and quantitative information about the Micro structure of white matter that cannot be deducted by the conventional MRI sequences. DTI provides transcending MRI from anatomic images toward functional and embryology based imaging.

DTI enables quantitative analysis and structural analysis that may be created through post processing and reconstructing the course of fibre tracts. Due to incomplete myelination and higher brain water content in term neonates conventional MRI has limited in its ability to detect the presence and extend of injury in stage 1 HIE. Structural changes usually manifested after 4 to 8 months infants with HIE stage 1 and 2.

DTI imaging demonstrates abnormal Fractional anisotrophy and mean diffusivity values in HIE infants even when they shows near normal conventional imaging. An altered pattern of age related changes in Fractional anisotrophy and mean diffusivity and accurate assessment of micro structural damage also been demonstrated with DTI[3].

HIE is the common cause of cerebral palsy. Cerebral palsy is defined as a group of permanent disorders of the development of movement and posture, causing activity limitation, that are due to non-progressive disturbances that occurred in the developing fetal or infant brain. Early assessment of severity of HIE can help proper parent counseling and early institution of stimulation therapy for better development of infant. So there is a necessity to study the importance of DTI in detecting HIE babies within 14 days of their life.

Hypoxic ischemic encephalopathy (HIE) is one of the dreadful birth complication. In developed countries it occurs in 1.5 to 2.5 per 1000 live births.Lawn J *et al.*, 2005 discovered that the incidence is up to 10-fold higher in developing countries and globally, 23% of the 4 million annual neonatal deaths are due to birth asphyxia.

During the prenatal, intrapartum or postnatal period, HIE can occur due to inadequate blood flow to the infant's brain occurring as a result of a hypoxic-ischemic event.

As says by **Liska A, *et al***.and **Azzopardi D, *et al*.** by the age of 2 years, 60% of infants with HIE will experience severe disabilities including cerebral palsy, mental retardation and seizures. Even with advances in obstetric care and fetal monitoring the incidence of HIE has not declined[3, 4, 5, 6].

HIE is spectrum with clinical manifestations of brain dysfunction. Exact cause is not appreciable always [7]some causative factors are placenta previa, abruptio placenta, maternal hypotension, uterine rupture, cord prolapse, breech presentation and shoulder dystocia.

In perinatal HIE in early postnatal life manifestations include poor umbilical cord gases (pH < 7.0 or base deficit ≥ 12 mmol/L)[8], presence of meconium stained fluid, abnormal fetal heart rate tracings[9], low Apgar scores [10], respiratory support within the first several minutes of postnatal life[11].

ANOTHER SARNAT STAGING CRITERIA OR AN ADAPTED VERSION IS ALSO FOLLOWED TO DESCRIBE THE SEVERITY OF ENCEPHALOPATHY WITHIN THE FIRST SEVERAL POSTNATAL DAYS OF LIFE TO ASSESS THE SEVERITY OF THE INSULT

AIMS AND OBJECTIVES

To correlate MRI brain findings and DTI findings in early neonatal period of term and preterm neonates with hypoxic ischemic encephalopathy and its clinical outcome.

DTI is currently the only way to quantify the maturation and damage of brain development in preterm neonates.

In the early stage, it can identify damages that cannot be screened byMRI.

It can provide evidence for developing effective measured of prevention, protection and rehabilitation for damage to the brain.

MATERIALS AND METHODS

STUDY DESIGN: Prospective Study.

DATA COLLECTION: Newborn babies with APGAR score of less than 7 with history of birth asphyxia referred for MRI to our department.

STUDY CENTRE: Departmentof Radiodiagnosis, Govt.Royapettah hospital and Kilpauk Medical College Hospital. Kilpauk,

SAMPLE SIZE: 50.

DURATION OF STUDY:1 Year and 3 months from July 2017 to September 2018

STATISTICAL ANALYSIS: Descriptive statistical analysis.

INCLUSION CRITERIA

Term and preterm new born babies with APGAR SCORE of less than 7.

EXCLUSION CRITERIA

New born with congenital anomalies.

SYNDROMIC BABIES

Infants with metabolic disorders.

ASSOCIATED HYPERBILIRUBINEMIA

One time MRI & DTI images were taken with 1.5 Tesla GE superconductive magnet. All included babies were subjected to the study within 14 days of life. Prior written consent was obtained from all parents. Data collection was performed in the included study group using a proforma.

Proforma includes parents name, gestational age, date of birth, birth weight, term or preterm, day on which MRI was taken, mode of delivery, APGAR score, HIE stage, address, mobile number, findings in conventional MRI, findings in DTI and clinical assessment during serial follow up.

METHODOLOGY

The study was begun after obtaining institutional ethical committee clearance. All the included cases were subjected to imaging after obtaining written consent.

This study was conducted with full-term and preterm neonates with HIE (23 mild HIE cases, 16 moderate HIE cases and 11 severe HIE cases with a history of neonatal asphyxia).The HIE patients were subdivided into mild, moderate and severe groups according to APGAR SCORE and sarnat and sarnat staging.Twenty newborn babies referred to MRI brain without abnormality were selected for control.

All 50 cases were subjected to conventional MRI and DTI within a maximum period of 14 days from birth. Baby's attenders were well explained about the procedure and are advised to remove metallic pins, jewellery, hearing aids and other metal objects outside the MRI gantry. Babies were positioned comfortably in supine position. Conventional MRI consisted of sagittal and axial T1-weighted and T2-W, diffusion weighted image and FLAIR imaging; DTI was acquired using single-shot Echo-planar imaging (EPI).

IMAGING PROTOCOL

- T1 & T2 sequences in axial plane.
- T1 W sequence in sagittal plane.
- Diffusion weighted imaging in axial plane.
- A single-shot SE EPI was taken once with DTI.
- A cotton ball is stuck into each ear of patients to decrease the influence of noise.
- Sedation if required.
- Image acquisition is completed within 10 mins.

PARAMETERS SET FOR T1

TR (REPETITION TIME): 400-620 ms TE (echo time): 10-30 ms.
FLIP ANGLE:90 degrees Slice Thickness-3mm Matrix-288 x 160.

PARAMETERS SET FOR T2

TR: 8000-9000 ms.
TE: 80-120 ms.
FLIP ANGLE: 90 degrees Slice thickness 3 mm.
FOV: 256 x 256mm.
MATRIX: 416 x 288.

PARAMETERS SET FOR DT1

TR; -12000.
TE; -96.4.

Slice thickness; 3 mm Flip angle-90 degree.
FOV;128X 128mm b=1000s/mm Matrix; 128 x 128for each slice one image without diffusion weighting (b=0s/mm square) and six images with diffusion weighting (b=1000s/mm square) was obtained.

Post processing was done using automated GE software system. FA and ADC were measured in several ROI in brain including both thalamus, corona radiata, anterior and posterior limb of internal capsule, SLF, and ILF.ROI were manually placed in FA map. According to anatomic structure and ADC mapsize of ROI was changed to cover all anatomical structure and to prevent mutual influence of volume effects between neighboring regions.

From our study in selected control babies we found mean FA value for corona radiate is 0.60 anterior limb of internal capsule is 0.60,posterior limb of internal capsule is 0.59,superior longitudinal fasiculus is 0.58, inferior longitudinal fasiculus is 0.54,and thalamus is 0.55.

All babies were followed at 3 months interval for 1

year and developmental milestones were assessed using Denver Developmental scale.

STATISTICAL ANALYSIS-RESULTS

Table 1: Descriptive Analysis

	HIE 1	HIE 2	HIE 3
BIRTH WEIGHT			
<2.5KG	6	7	2
>2.5KG	17	9	9
GESTATIONAL AGE			
<32 Weeks	6	8	3
>32 Weeks	17	8	8
GENDER			
Male	17	9	8
Female	6	7	3
MODE OF DELIVERY			
Normal	17	14	9
LSCS	6	2	2

In our study out of 50 babies, 23 babies belonged to HIE I (46%). 16 babies belongs to HIE II (32%) and 11 babies belongs to HIE III (22%).

Table 2: DTI VS Development Delay ROC values

PARAMETER	SENSITIVITY	SPECIFICITY	YOUDEN INDEX	AUC
corona_radiata_DTI LEFT	62.96	95.65	0.5862	0.853
corona_radiata_DTI RIGHT	92.59	65.22	0.5781	0.845
anterior limb DTI LEFT	66.67	86.96	0.5362	0.791
anterior limb DTI RIGHT	74.07	86.96	0.4622	0.757
posterior limb DTI LEFT	70.37	86.96	0.5733	0.775
posterior limb DTI RIGHT	92.59	60.87	0.5346	0.806
cingulate gyrus DTI LEFT	59.26	86.96	0.4622	0.757
cingulate gyrus DTI RIGHT	92.59	65.22	0.5781	0.845
SLF DTI LEFT	100	60.87	0.6087	0.836
SLF DTI RIGHT	74.07	88.96	0.6103	0.815
Thalamus LEFT	66.87	100	0.6667	0.886
Thalamus RIGHT	74.07	100	0.7407	0.903
IFOF DTI LEFT	62.96	95.65	0.5862	0.853
IFOF DTI RIGHT	92.59	65.22	0.5781	0.845

Table 3: MRI VS Developmental Delay

Parameter	Sensitivity	Specificity	PPV	NPV	ACCURACY	Mcnemar p value
corona_radiata_MRI	62.96	69.57	70.83	61.54	66	.6291
anterior limb MRI	40.74	82.61	73.33	54.29	60	0.0118
posterior limb MRI	29.63	73.91	57.14	47.22	50	0.0146
gulate gyrus MRI	18.52	91.30	71.43	48.84	52	.767
SLF MRI	25.93	91.30	77.78	51.22	56	.0001
IFOF MRI	25.93	91.30	77.78	51.22	56	.0001
THALAMUS MRI	40.74	86.96	98.57	55.56	62	0.0044

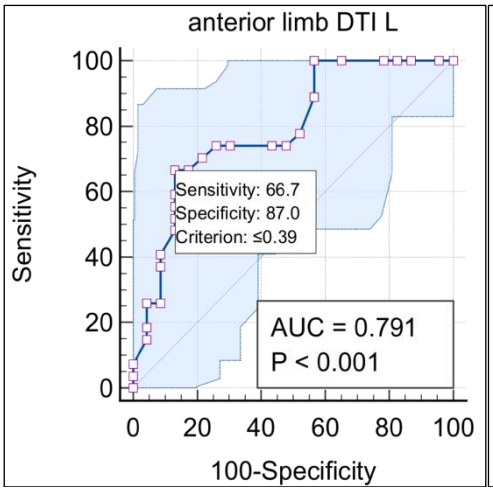
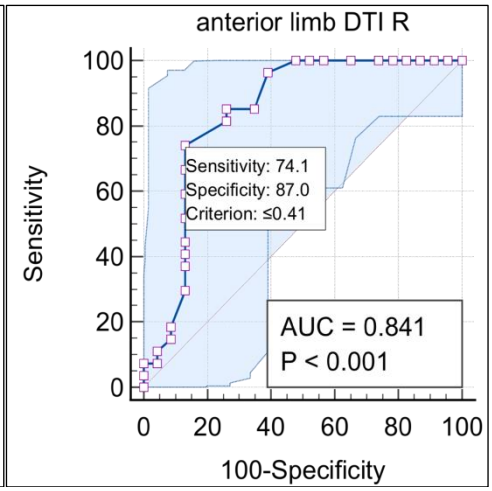


Fig 1



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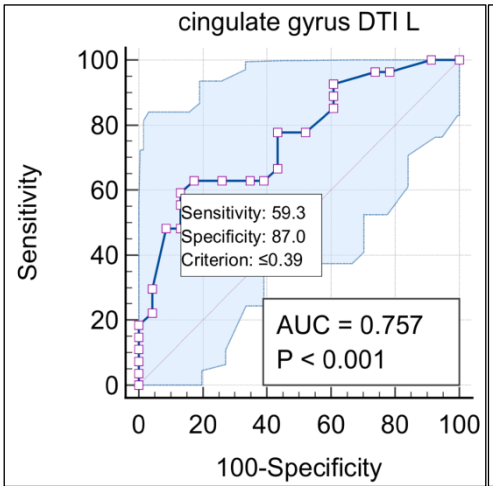

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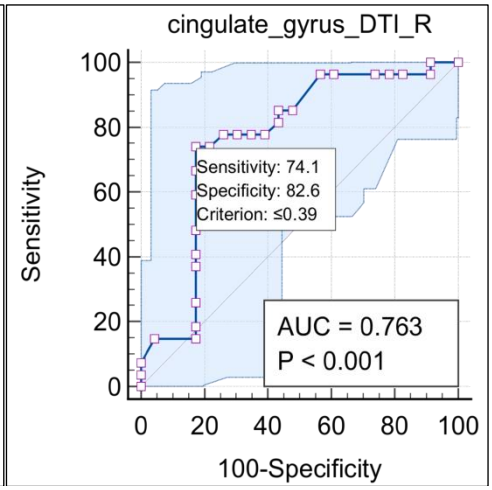

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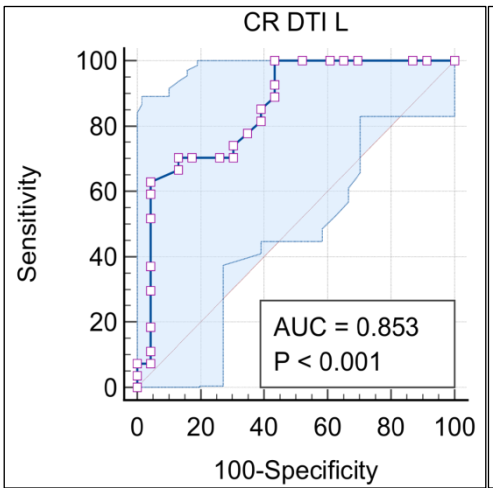

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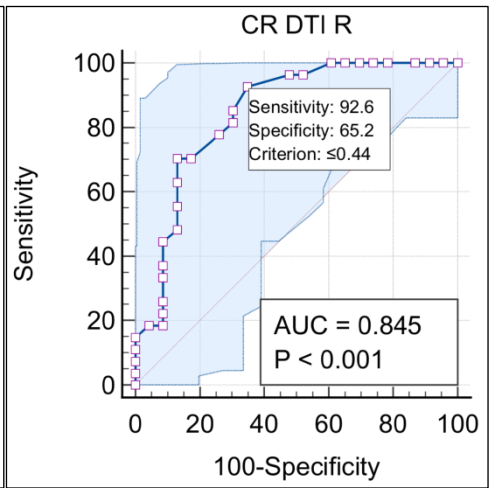

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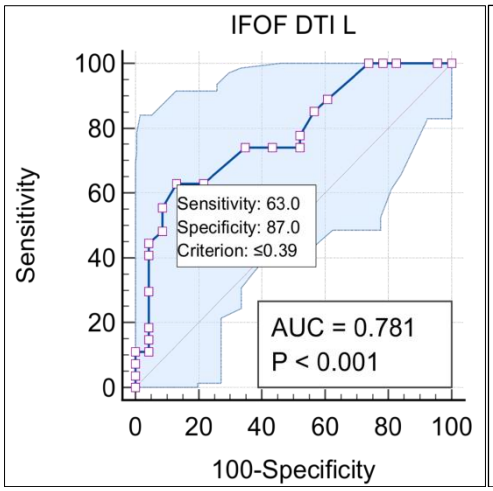

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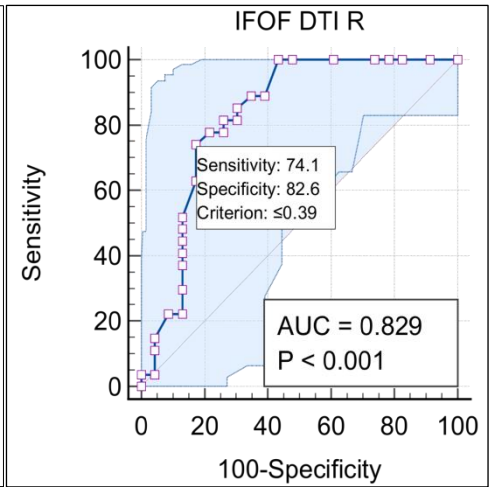

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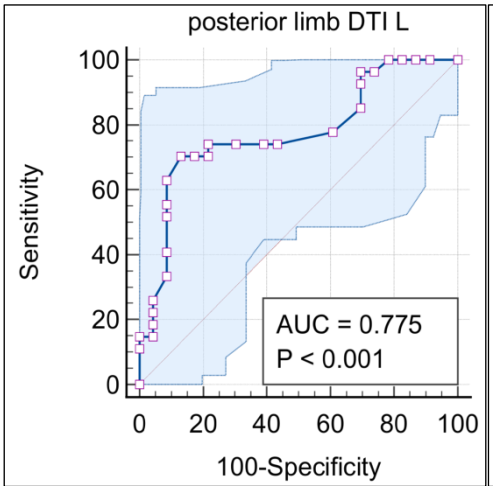

Fig 9

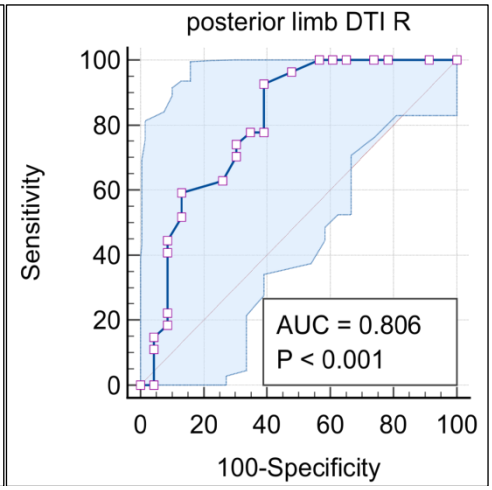

Fig 10

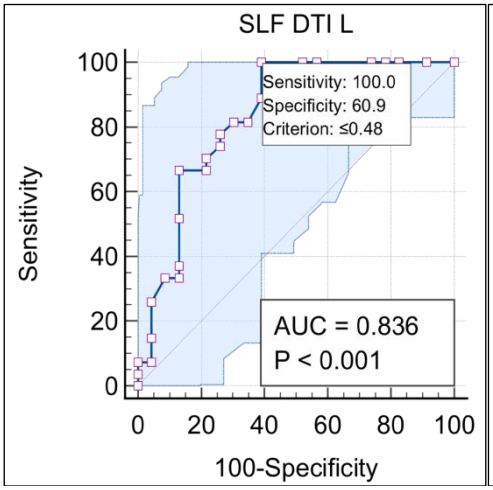

Fig 11

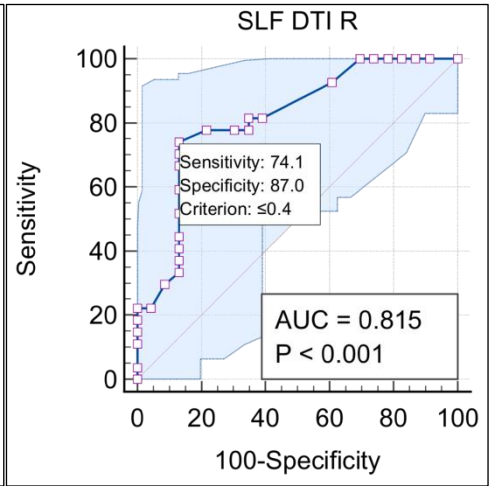

Fig 12

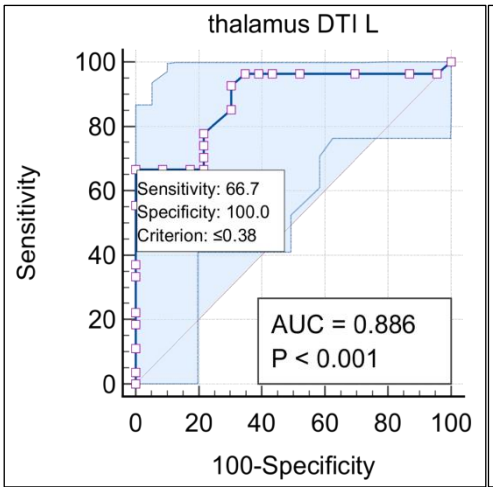

Fig 13

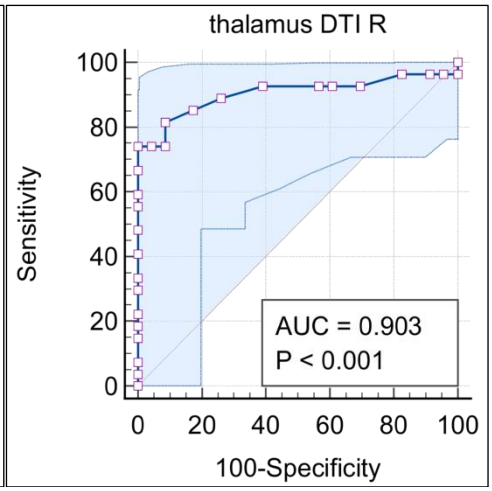

Fig 14

DISCUSSION

In our study there were no significant differences in ADC values among the different stages of HIE, which was consistent with a previous study done by van Laerhoven *et al*., 2013 [62].

In our study, in 5 babies MRI imaging was done within 7 days of life. All the 5 babies showed abnormality in ADC value and also had diffusion restriction. Which was consistent with study done by Winter *et al*., 2007[63].

Who says that ADC values are more useful in the early diagnosis of HIE, and pseudo-normalization of ADC values occur after the acute stageand another study done by Guo *et al*. 2016[64] reported that within seven days after birth, DWI used to detect ADC values showed that the HIE sensitivity was 83%, specificity was 63% and positive predictive value was 83%.

In our study only 5 babies were underwent imaging within 5 days of life. Rest of the 45 babies were imaged after 7 days of life, because of unstable vitals and most of the babies were desaturated without oxygen support. This is agreed with study done by Li *et al*., 2014 [65]says that in the acute stage possibly the babies had severe lesions and unstable vital signs in each group. MRI examination was difficult in the acute phase.

In our study 45 babies were screened after 7 days so life so they had no significant abnormality in diffusion weighted imaging and ADC values.It is consistent with study done by de Vries *et al*., 2011[66] have revealed that the diagnostic value of ADC values in the subacute stage is decreased.

Our study results demonstrated that the FA values had a high diagnostic value. and FA values were markedly decreased in the dense white matter, splenium of the corpus callosum, and posterior limbs of the internal capsules. Decreased FA values are related to cell death and loss of structural components of white matter fibers.as says by Rutherford *et al*. 1998[67] demonstrated that apoptosis was more obvious than necrosis in children in the subacute stage of HIE, this could explain why FA values decreased, but ADC values were normal.

In this study, MRI in 6 cases of moderate HIE children revealed symmetric high-signal intensity in the thalami, but FA values were reduced in the thalami. This type of basal ganglia/thalamus injury can cause athetoid cerebral palsy as says by De Vries *et al*., 2011[65]. and shows the possibility of severe cognitive impairment as says by Li *et al*., 2016[66].

In our study 50 babies were selected with APGAR score of less than 7. All babies were investigated by MRI within 14 days of life. In our study out of 50 babies 33 term babies and 17 preterm babies were included. Among these babies 17 babies were under 2.5 kg birth weight and 33 babies were more than 2.5kg.Among them 40 babies were delivered by normal vaginal delivery and 10 had LSCS. There was no statistical difference in gravidity, parity, gestation, to p-birth weight, sex, mode of delivery.

ROC performed to the following parameter of different segments of DTI with Development delay. The following table reveals that almost most of the segments Right and Left had very good Area under curve and having good Yuden Index good fit to predict the outcome Delayed outcome. Most preferably Thalamus segment Right and Left are having more AUC(0.903 & 0.886) than the other segments.

Parameter	AUC
corona_radiata_DTI LEFT	0.853
corona_radiata_DTI RIGHT	0.845
anterior limb DTI LEFT	0.791
anterior limb DTI RIGHT	0.757
posterior limb DTI LEFT	0.775

posterior limb DTI RIGHT	0.806
cingulate gyrus DTI LEFT	0.757
cingulate gyrus DTI RIGHT	0.845
SLF DTI LEFT	0.836
SLF DTI RIGHT	0.815
Thalamus LEFT	0.886
Thalamus RIGHT	0.903
IFOF DTI LEFT	0.853
IFOF DTI RIGHT	0.845

Whereas the following are the sensitivity and specificity of Conventional MRI for different segments with respect to prediction of Development of Delay. In these segment wise results of Conventional MRI vs. Developmental delay, Corona radiata segment had diagnostic Accuracy 66%, other segment had lesser diagnostic accuracy.

Parameter	Sensitivity	Specificity	ACCURACY	Mcnemar p value
corona_radiata_MRI	62.96	69.57	66	.6291
anterior limb MRI	40.74	82.61	60	0.0118
posterior limb MRI	29.63	73.91	50	0.0146
gulate gyrus MRI	18.52	91.30	52	.767
SLF MRI	25.93	91.30	56	.0001
IFOF MRI	25.93	91.30	56	.0001
THALAMUS MRI	40.74	86.96	62	0.0044

ROC CURVE FOR ALL SEGMENTS (BOTH RIGHT AND LEFT) HAD PRESENTED IN THE RESULTS SECTION, CLEARLY ENDORSED OUR AUC VALUES

CONCLUSION

In summary, DTI is currently the only way to quantify the maturation and damage of brain development in preterm neonates. In the early stage, it can identify damages that cannot be screened by MRI. Thus, it can provide evidence for developing effective measures of prevention, protection, and rehabilitation for damage to the brain. Coupled with a good intervention. Treatment system established with clinical development assessment and pathogenic factors, DTI is an important aid to improve the prognosis of nerve development for preterm neonates, owing to its ability to reflect the damage to cells in white matter and nerve fibers at an early stage and at a microscopic level.

In our study, both the sensitivity, specificity and Area Under curve of ROC are high for DTI compared to conventional MRI.

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