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Can diffusion tensor imaging predict cerebral palsy in term neonates with hypoxic ischemic encephalopathy?

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Abstract

Background: Hypoxic ischemic encephalopathy (HIE) is a principal cause of pediatric mortality and morbidity, with possible neurologic sequel, such as cerebral palsy. Thus, it is of outmost importance to assess, shortly after birth, the prognosis of neonates with HIE. The purpose of this study was to assess the role of diffusion tensor imaging (DTI) in early prediction of cerebral palsy in term neonates with HIE. The study was carried out initially on 35 full-term neonates admitted to the neonatal intensive care unit (NICU) with manifestations of HIE. Imaging was done at the age of 10.32 ± 1.78 days including conventional MRI and DTI (for detection of white matter injury). Thirty-three infants out of the initially examined 35 were finally evaluated at the age of 1 year with the Bayley Scales of Infant and Toddler Development 3rd edition for development of cerebral palsy. Another MRI brain study was done at 1 year of age to evaluate the final brain imaging features and assess white matter integrity.

Results: Seventeen infants (17/33) were clinically normal while 16 (16/33) acquired cerebral palsy (CP) by the end of the first year. Initial conventional MRI showed false-negative results in 7 patients. Diffusion tensor imaging showed significantly different reduction in fractional anisotropy within the examined brain regions of interest (ROIs) between CP and normal outcome infants mostly at the posterior limb of the internal capsule, centrum semiovale, and corpus callosum with significant cutoff values of ≤ 0.435 , ≤ 0.235 , and ≤ 0.45 , respectively.

Conclusions: Diffusion tensor imaging is a valuable tool for early prediction of CP in HIE neonates.

Keywords: Hypoxic ischemic encephalopathy, Cerebral palsy, Diffusion tensor imaging

Background

Hypoxic ischemic encephalopathy (HIE) is a major cause of neurologic disabilities in term neonates. The incidence of HIE ranges from 1 to 8 per 1000 live births in developed countries and is as high as 26 per 1000 live births in underdeveloped countries [1].

Hypoxic ischemic encephalopathy (HIE) is considered one of the main causes of morbidity and mortality among the neonatal age group, carrying the potential of causing long-lasting neurological damage such as cerebral palsy (CP), convulsions, and mental retardation [2].

Brain cooling and therapeutic hypothermia is considered the treatment of choice in these hypoxic neonates

due to its neuroprotective effect especially in cases of moderate and severe HIE [3].

After applying neuroprotective measures, evaluation of the degree of brain injury is of extreme importance in guiding further neurological care. These data are used to plan adjuvant therapy and rehabilitative procedures and to supply information regarding the future prognostic outcomes [4].

Both objective and accurate markers are needed to assess the prognosis of HIE in full-term neonates. Although ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) can be used to evaluate brain injury, still they are unable to provide a quantitative data regarding the degree of affection of the brain mainly white matter which is very important to reach an accurate prognosis [5, 6].

Conventional MRI usually reveals two main types of brain injury in neonates with HIE; these are abnormalities

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detected at the thalami and basal ganglia (central pattern) as well as damage at the watershed zones of the brain (peripheral pattern). These findings express obvious correlation with late cognitive and motor abnormalities [7]. However, conventional MRI done in first days of life may miss significant brain injuries (especially after brain cooling) with highest diagnostic sensitivity at about 1–2 weeks postnatal [8].

Due to this limitation, conventional MRI should be interpreted with other advanced techniques including diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) [9].

The DTI is a modern advanced technique derived from modification of diffusion weighted imaging (DWI). DTI has proved outstanding performance in evaluating the direction and integrity of white matter tracts of the brain [10].

Estimation of values of fractional anisotropy (FA) by DTI within multiple areas in the brain can provide both quantitative and qualitative data concerning the white matter tracts, can assess white matter abnormalities, and can also provide useful data about white matter repair. Currently, it is believed that DTI can be a valuable tool in the assessment of HIE-related white matter injury providing accurate information concerning the severity and prognosis of the condition [11].

The aim of this study was to assess the additive role of DTI over conventional MRI in early prediction of cerebral palsy in term neonates with hypoxic ischemic encephalopathy.

Methods

Approval for this cross-sectional prospective study was obtained from the local human research ethics committee. All study procedures were carried out in accordance with the Declaration of Helsinki regarding research involving human subjects [12]. Written informed consent was obtained from the parents of each child.

Patients

From September 2015 to March 2016, full-term neonates admitted to the neonatal intensive care unit (NICU) with HIE ranging in severity from moderate to profound according to Sarnat's scoring [13] were referred to the Radiodiagnosis Department for brain imaging. The HIE score based on Sarnat's scoring system is a clinical tool comprising of a set of clinical signs associated with CNS dysfunction that is used to assess the status of a child following birth asphyxia. Depending on the neurobehavioral signs, neonates are divided into stages I, II, and III (mild, moderate, and severe, respectively) [13].

Inclusion criteria included (a) full-term neonates (37–42 weeks gestational age) (b) exposed to perinatal hypoxic conditions based on history of difficult or

prolonged labor, placenta previa, cord prolapse, and/or severe hemorrhage; the perinatal period commences from the 28th week of gestation to the 1st 7 days following delivery. Pre-term neonates (less than 37 weeks gestational age) and neonates with suspected neuro-metabolic diseases, neonatal sepsis, traumatic birth injuries, kernicterus, and congenital brain malformations were excluded. Cases with no available follow-up imaging after 1 year were also excluded.

The study initially included 35 neonates: 19 males and 16 females with mean gestational age of 39.0 ± 2.0 weeks and mean birth weight of 3470.3 ± 500.8 g. Apgar score done at 5 min ranged from 2 to 7. The patients' conditions tended to be unstable in the first week, so initial MRI was conducted at the age of 10–14 days with mean age of 10.32 ± 1.78 days. All neonates included in the study underwent initial imaging protocol including conventional MRI and diffusion tensor imaging (DTI). All neonates received brain cooling in the first 3 days of their lives (which is considered a routine protocol done in the NICU of our tertiary care referring hospital) prior to doing the initial MRI examinations.

Owing to loss of contact with their parents shortly after the first examination, two patients were discarded from our study, so 33 patients out of the initially examined 35 neonates were evaluated clinically and by imaging after 1 year from the first exam (from September 2016 to March 2017) for development of cerebral palsy.

MRI acquisition protocol

Examination was done on 1.5 T GE Signa machine (General Electric Healthcare, Piscataway, NJ). MR images were acquired with the following protocols:

- (a) *Conventional MRI protocol* included 3D T1-weighted sequences (repetition time (TR) 6.6, echo time (TE) 2.6, inversion time (TI) 600, number of excitations (NEX) 1, flip angle 25, matrix 192×192 , 1.2 mm slice thickness, with 0 mm gap) acquired in an axial plane and reconstructed in coronal and sagittal planes, fast spin echo (FSE) T2-weighted axial sequences (TR 4400, TE 120, NEX 2, matrix 384×320 , 3 mm slice thickness, with 1.0 mm gap), and diffusion-weighted imaging (DWI) with single shot, b value = $1000 \text{ mm}^2/\text{s}$ (TR 8000, TE 78.8, NEX 1, field of view (FOV) 220×220 , matrix 140×140 , slice thickness 2.5 mm with 0.6 mm gap).
- (b) *DTI* acquired with pulsed field gradients in 21 directions with single-shot echo-planar imaging (TR, 7800 ms; TE, 102 ms; 40 sections; b value, 0/1000 s/mm^2 ; 3-mm sections, no gap; FOV, 18×36 cm; and 128×256 acquisition matrix).

MRI data analysis and imaging evaluation

MRI data were reviewed for each neonate blinded to the clinical data apart from suspicion for HIE. The following steps of imaging evaluation were followed:

- a. MRI assessment for signs of HIE which included the following:
 1. Signs of acute profound HIE (severe hypotension)—loss of T1 hyperintensity of the posterior limb of the internal capsule (PLIC) with restricted diffusion within the metabolically active areas of the brain including the ventrolateral thalami, posterior putamina, perirolandic regions, and corticospinal tracts (CST) along the anterior aspect of the brain stem as well as the hippocampi [14].
 2. Signs of partial prolonged HIE (mild to moderate hypotension)—loss of gray-white matter differentiation with restricted diffusion of the cortex and subcortical white matter along the intervascular watershed areas between the anterior and middle as well as middle and posterior cerebral arterial territories [14].
- b. DTI assessment (steps were done on GE workstation “Advantage 4.6”) for signs of white matter injury:
 - (a) Generation of fractional anisotropy maps by registration of DTI images to the non-diffusion volume in order to reduce distortion sequel to eddy currents followed by removal of any extra-cerebral tissues by brain extraction process.
 - (b) Analysis of the FA maps using ROI approach where multiple (around 3 mm) regions of interest (ROIs) were placed on the PLIC, the supraganglionic white matter mainly within the centrum semiovale, optic radiations, and occipital white matter (OWM) bilaterally.

Outcome assessment

Imaging assessment

Follow-up imaging after 1 year from the first examination included the following:

1. Conventional MRI including 3D T1, axial T2, and axial FLAIR sequences.
2. Diffusion tensor imaging (DTI) with tractography to identify the integrity of white matter mainly the corticospinal tracts (along their course from

centrum semiovale through PLIC and down to the brain stem) which are the main tracts affected in cases of cerebral palsy.

Clinical assessment

Sensori-neural and psychomotor integrity was assessed clinically by using the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley III scale) [15], performed by an expert pediatric neurologist. The Bayley scale is the most widely used tool which assesses developmental functioning in infants and young children between 1 month and 42 months. The Bayley III scale is based upon assessment of three major areas of development including cognitive scale, communication or language scale, and motor scale. The outcome of HIE is thus graded, according to the cognitive, language, and motor composites, into normal (v. good or good outcome = Bayley III score ≥ 85 in all 3 domains) and adverse outcome (fair or poor = Bayley III score < 85 in any domain). The primary purposes of Bayley III are to identify children with developmental delay and to provide information for intervention planning [15].

Statistical methodology

Data were collected and entered to the computer using SPSS (Statistical Package for Social Science) program for statistical analysis (ver 21). Data were entered as numerical or categorical, as appropriate. The Kolmogorov-Smirnov test of normality revealed significance in the distribution of some variables, so the non-parametric statistics was adopted. Data were described using minimum, maximum, mean, standard deviation, and 95% confidence interval (CI) of the mean for the normally distributed data. Data were described using minimum, maximum, median, and interquartile range for not-normally distributed data. Comparisons were carried out between two studied independent not-normally distributed subgroups using the Mann-Whitney *U* test. Comparisons were carried out between more than two studied independent not-normally distributed subgroups using the Kruskal-Wallis test. Chi-square test was used to test the association between qualitative variables. Area under the ROC (AUC) curve was carried using MedCalc Software version 14. Comparison of area under the ROC (AUC) curves was done using Delong's method. Percentage of agreement was assessed by kappa coefficient. An alpha level was set to 5% with a significance level of 95%, and a beta error accepted up to 20% with a power of study of 80%.

Results

Demographic data

Seventeen neonates (51.5%) were males while the remaining 16 (48.4%) were females. Among the studied

neonates, 18 (54.54%) were born by cesarean section (CS) while the other 15 (45.45%) were born through normal vaginal delivery (NVD). According to severity, 21 cases (63.6 %) were Sarnat stage II or moderate degree of HIE, while the remaining 12 cases (36.3%) were Sarnat stage III or severe degree of HIE (Table 1).

Final outcome (clinical and radiological outcome) at the age of 1 year (the golden reference)

Seventeen infants were clinically normal at the end of the first year, all of whom showed normal follow-up MRI examinations while the other 16 infants acquired cerebral palsy: 6 of whom showed MRI central pattern of affection with involvement of the thalami, putamina, and posterior limbs of the internal capsules (having clinically dystonic CP) and the other 10 showed peripheral pattern of injury with periventricular leukomalacia (having clinically spastic CP).

Initial conventional MRI and DWI findings as compared to the final outcome

Initial conventional MRI was normal in 24 neonates, 17 of whom proved on follow-up after 1 year to have normal outcome both clinically and radiologically, while the other 7 showed false-negative results as they developed spastic CP by 1 year with their follow-up MRIs showing periventricular leukomalacia.

Conventional MRI was initially abnormal in the other 9 neonates, 6 showed central pattern of affection (T1 hyperintensity of the putamina and thalami with loss of T1 hyperintensity of the posterior limbs of the internal capsules), proved on follow-up to have dystonic CP, while the other 3 neonates showed watershed pattern with smudging of the gray-white matter interface at the watershed regions bilaterally and proved on follow-up to have PVL and spastic CP. The DWI was normal for all neonates at the time of examination.

Table 1 Distribution of the studied neonates according to demographic data, mode of delivery, and HIE Sarnat staging ($n = 33$)

	Number	Percentage
Sex		
Male	17	51.5
Female	16	48.4
Delivery		
CS	18	54.54
NVD	15	45.45
HIE Sarnat staging		
Stage II	21	63.6
Stage III	12	36.3

CS cesarean section, NVD normal vaginal delivery

Thus, the initial conventional MRI showed sensitivity of 56.25%, specificity of 100%, positive predictive value (PPV) of 100%, negative predictive value (NPV) of 70.83%, accuracy of 78.79%, and overall moderate agreement with follow-up reaching 57% (Table 2).

Initial DTI results as compared to the final outcome

FA values were lower in patients with CP outcome compared to those with normal outcome in nearly most ROIs as shown in Table 3. The FA values were significantly lower within the PLIC in patients with dystonic CP outcome. Spastic CP patients also showed significantly lower FA within the centrum semiovale. Corpus callosum genu and splenium FA values also showed significant lower FA values in CP outcome patients as compared to normal outcome infants. No significant difference was noted as regards FA values within the optic radiations as well as the occipital white matter (OWM).

ROC curve analysis was performed to study the significant cutoff values of FA discriminating between CP and normal outcome showing centrum semiovale cutoff value ≤ 0.235 , and genu and splenium of the corpus callosum cutoff value ≤ 0.45 with best significance being PLIC cutoff value ≤ 0.435 (Table 4 and Fig. 1).

All seven neonates with false-negative initial conventional MRI results had significant reduction of FA values (below the aforementioned cutoff values) within the measured white matter regions.

Example for the difference in DTI/FA between those with normal and CP outcomes is shown in Fig. 2, 3, and 4.

Discussion

Perinatal hypoxia in full-term neonates is a vital cause of long-term neurologic complications ranging from mild behavioral deficits to intractable seizures, mental retardation, and cerebral palsy. With improvements in care of at-risk neonates, more and more children survive. Thus, it is increasingly important to evaluate, soon after birth, the prognosis of neonates with perinatal hypoxic ischemic encephalopathy [16].

In order to answer the question of the title of the study and understand the role of advanced MRI techniques mainly DTI in the prognosis of perinatal HIE, the current study tried to find an answer for the following questions: Are conventional MRI sequences and DWI sufficient for early identification of perinatal HIE and prediction of cerebral palsy? Does DTI have a role in diagnosis and prognosis of perinatal HIE? And lastly, what is the recommended imaging roadmap in cases of perinatal HIE?

Taking into consideration the first question (Are conventional MRI sequences and DWI sufficient for early identification of perinatal HIE and prediction of cerebral palsy?), the current study showed that although MRI is

Table 2 Agreement of the initial routine MRI with final outcome

		Outcome at 1 year		Sensitivity	Specificity	PPV	NPV	Accuracy	Agreement
		Normal	Abnormal [Ⓞ]						
Initial routine MRI	Normal	17	7	56.25	100	100	70.83	78.79	57% (kappa 0.57)
	Abnormal	0	9						
χ^2 (p)		13.148* (<0.001*)							

Kappa coefficient was used for percentage of agreement

χ^2 (p) χ^2 and p values for chi square test for comparing between the two categories, NPV negative predictive value, PPV positive predictive value

*Statistically significant at p < 0.05

[Ⓞ]Abnormal outcome was assessed both clinically as cerebral palsy and by MRI as different patterns of brain injury

still the study of choice in cases of perinatal HIE, yet its main role is evident in cases of acute profound insult with deep gray matter affection pattern. This was clearly evident in the current study as all cases with such pattern (six cases) were accurately detected within the neonatal period and they turned out to have CP by the end of their first year.

On the other hand, conventional MRI as well as DWI showed poor results with high false-negative cases in neonates with mild to moderate hypoperfusion, as seven out of the ten cases (70%) who turned to have periventricular leukomalacia at the end of the first year showed initial normal MRI with even no evidence of diffusion restriction.

Explanation for such false-negative results of conventional MRI and DWI was found in previous studies of Agut et al. [17] and Hayakawa et al. [18], who studied early MRI features of 40 and 17 full-term neonates, respectively, and concluded that despite the higher sensitivity of DWI compared to conventional MRI in the characterization of brain injury in the acute phase of HIE, yet DWI shows restricted diffusion with decrease of ADC values only in the first hours after the anoxic-ischemic event. Low ADC values tend to progressively increase in the first week after the event, resulting in a pseudonormalization of values between days 4 and 6. Being strictly dependent on the timing of the scan, both studies [17, 18] have demonstrated that the diagnostic and prognostic

values of ADC in the subacute stage of HIE are significantly decreased.

This was clearly found in the current study as all neonates were imaged around the tenth day of life, the time of which pseudonormalization of ADC was expected. Such fact resulted in normal appearance of DWI in all cases and lead to reduction in sensitivity, negative predictive value, and overall accuracy of routine MRI (including conventional MRI and DWI) to 56.25%, 70.83%, and 78.79%, respectively. In other words, conventional MRI sequences and DWI are likely not sufficient alone in early diagnosis of all cases of perinatal HIE especially in cases with moderate hypoperfusion or partial prolonged insult.

“Does DTI have role in diagnosis and prognosis of perinatal HIE?” was the second question for which we tried to find an answer.

DTI carries extra information about directional diffusivity (both longitudinal and radial) and fractional anisotropy (FA) which can improve the detection of disruption of white matter tracks. It is thought that reduced FA values are linked to cell death and loss of structural components of white matter fibers. Rutherford et al. [19] reported that apoptosis was more noticeable than necrosis in children in the subacute stage of HIE, which could explain why FA values decreased, but ADC values were normal.

Our results verified that FA values had high diagnostic and prognostic values. In particular, FA values were

Table 3 Fractional anisotropy (FA) values in newborns compared with final outcome after 1 year

Outcome at 1 year	FA values of the newborns at first examination							
	Centrum semiovale		PLIC		Genu of CC	Splenum of CC	OWM	Optic radiation
	Right	Left	Right	Left				
Normal outcome (17)	0.27 ± 0.02	0.28 ± 0.03	0.45 ± 0.02	0.46 ± .02	0.54 ± 0.02	0.56 ± 0.02	0.23 ± 0.01	0.30 ± 0.01
Cerebral palsy (16)	0.18 ± 0.04	0.20 ± 0.04	0.35–0.03	0.36 ± 0.04	0.45 ± 0.08	0.46 ± 0.09	0.22 ± 0.04	0.29 ± 0.04
Test of significance, p value	$Z_{(MW)} = 4.304, p = 0.000*$	$Z_{(MW)} = 4.022, p = 0.000*$	$Z_{(MW)} = 4.862, p = 0.000*$	$Z_{(MW)} = 4.378, p = 0.000*$	$Z_{(MW)} = 2.937, p = 0.003*$	$Z_{(MW)} = 3.112, p = 0.002*$	$Z_{(MW)} = 0.605, p = 0.576$ NS	$Z_{(MW)} = 0.805, p = 0.455$ NS

Data are expressed as mean (SD), Mann-Whitney U test

CC corpus callosum, FA fractional anisotropy, OWM occipital white matter, PLIC posterior limb of internal capsule, NS statistically not significant (p > 0.05)

*Statistically significant (p < 0.05)

Table 4 ROC curve analysis of DTI/FA values for discrimination of occurrence of cerebral palsy

Index	AUC (95% CI)	Z (p value)	Cutoff value ^(N)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (%)	NPV (%)
Centrum semiovale	0.949 (0.811–0.995)	9.275 (< 0.0001*)	≤ 0.235	93.75 (69.8–99.8)	94.12 (71.3–99.9)	93.7	94.1
PLIC	1.000 (0.894–1.000)	0 (< 0.0001*)	≤ 0.435	100.00 (79.4–100.0)	100.00 (80.5–100.0)	100.0	100.0
OWM	0.581 (0.397–0.750)	0.789 (0.4303 NS)					
OR	0.511 (0.332–0.688)	0.103 (0.9182 NS)					
Genu of CC	0.811 (0.637–0.925)	4.107 (< 0.0001*)	≤ 0.45	56.25 (29.9–80.2)	100.00 (80.5–100.0)	100.00	70.8
Splenium of CC	0.814 (0.637–0.929)	3.911 (< 0.0001*)	≤ 0.45	60.00 (32.3–83.7)	100.00 (80.5–100.0)	100.0	73.9

AUC area under the curve, CC corpus callosum, CI confidence interval, NPV negative predictive value, OR optic radiation, OWM occipital white matter, PLIC posterior limb of internal capsule, PPV positive predictive value, NS statistically not significant ($p > 0.05$)

*Statistically significant ($p < 0.05$)

remarkably decreased in most of the dense white matter tracts, mainly the corpus callosum and posterior limbs of the internal capsules (PLIC) as well as the centrum semiovale (CSO). Significant differences in FA values were detected between newborns with CP outcome and those with normal outcome with detectable cutoff values of FA within the corpus callosum, PLIC, and CSO averaging ≤ 0.45 , ≤ 0.435 , and ≤ 0.235 , respectively. Significant predictive power of FA within the PLIC had the highest value of accuracy (AUC 1.0) showing 100% sensitivity, specificity, and negative and positive predictive values. Again, all neonates with normal appearing MRI who developed periventricular leukomalacia later on (false-negative

cases) showed initially abnormally reduced FA values within the examined brain regions.

Diagnostic accuracy of DTI in neonatal HIE was previously documented by Barkovich et al. [20], who studied sequentially ten neonates with encephalopathy within the first 2 weeks of life and found that DTI-derived parameters were consistently abnormal even at times where MRI were completely unremarkable.

Similar results were also obtained by Ward et al. [21], in 20 neonates with HIE as they observed that FA stayed reduced, while ADC pseudonormalized with time. At the same time, the authors stated that FA decreased not only in severe basal ganglia and white matter injury but reduced in all moderate basal ganglia and white matter injuries. The authors' assumption was that FA represents an important marker in neonates, mainly in moderate HIE predominantly when results of ADC values are normal.

As regards the prognostic role of DTI, the current results were also matching with the previous study of Brisaud et al. [22], who studied 22 full-term neonates with HIE and found that FA values in PLIC areas showed best correlation with outcome, where the lower the FA values in the PLIC, the worse the infants' neurologic outcome. Cutoff value for FA within the PLIC in their study was 0.38 (lower than the cutoff in the current study).

The only explanation which we found for such difference in FA values in the PLIC is brain cooling application which was adopted in all of our examined neonates, as a routine protocol done in the NICU for neonates with moderate or severe perinatal HIE, while not routinely mentioned in the other studies. Brain cooling is a neuroprotective therapy that reduces the extent of brain injury via at least the following three mechanisms. Firstly, hypothermia results in a graded reduction in cerebral metabolism that reduces accumulation of excitotoxic neurotransmitters, and suppresses oxygen free radical release. Secondly, it has a particular role in suppressing apoptotic processes in the developing brain (i.e., programmed cell death). Thirdly, there is good evidence that cooling can suppress the release of pro-

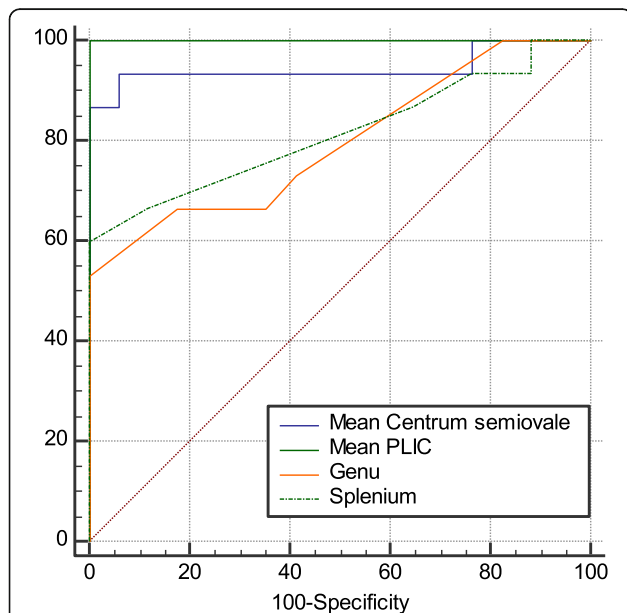


Fig. 1 ROC curve analysis for FA of PLIC (continuous green line), CSO (blue line), and genu and splenium of the corpus callosum (red and dotted green lines, respectively) where FA of PLIC ≤ 0.435 was shown to be the most statistically significant discriminator of occurrence of cerebral palsy with area under the ROC curve (AUC) = 1.000 with $*p < 0.0001$

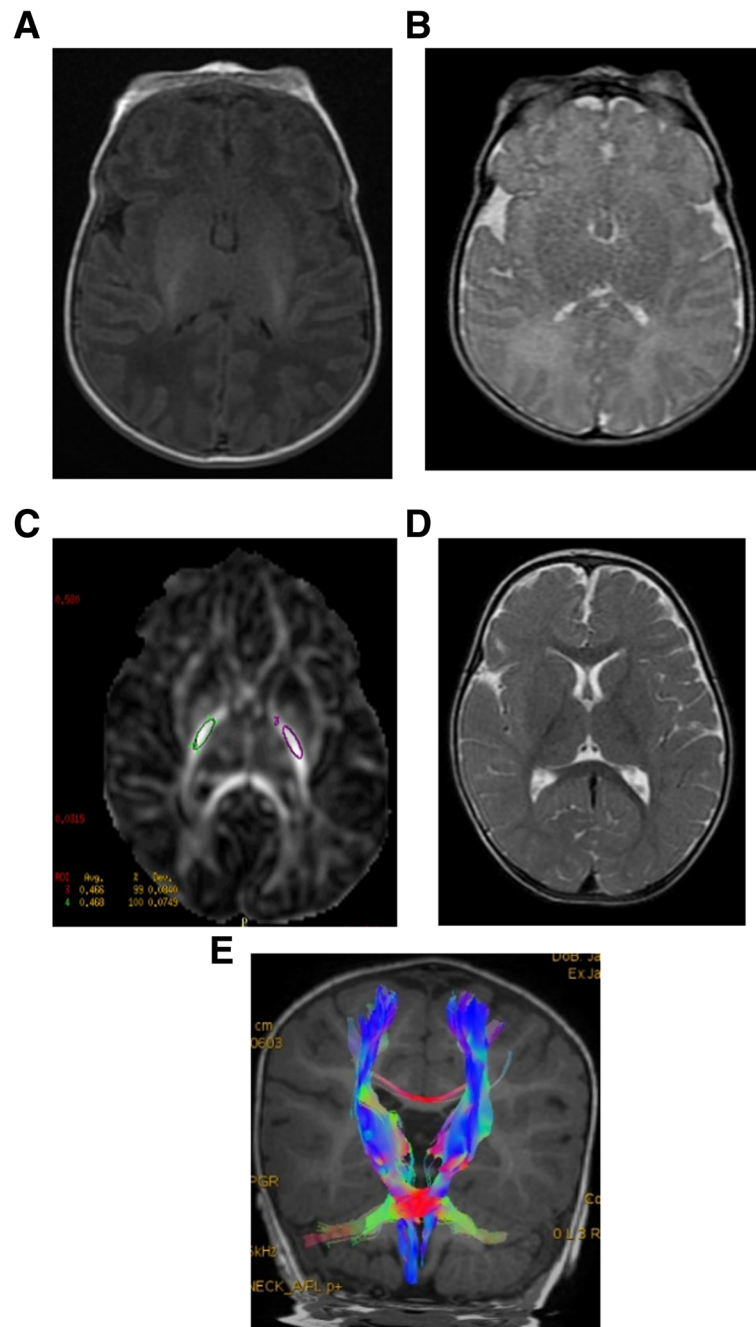


Fig. 2 Ten days neonate presenting with moderate HIE picture, Sarnat II with normal final outcome. Conventional MRI: **a, b** axial T1 and T2 showed preserved PLIC signal and distinct gray-white matter differentiation. DTI: **c** posterior limb of internal capsule FA value = 0.47. Follow-up examination: **d** axial T2 is unremarkable, and **e** tractography showed preserved integrity of the corticospinal tracts

inflammatory cytokines and interleukins, reducing direct neurotoxicity, such via suppression of microglial activation [23].

We believe that brain cooling has protective effect on FA of white matter, limiting its damage, as mentioned before in the study of Chan et al. [24], regarding effect of brain cooling as a neuroprotective method on alteration of brain metabolites on MR spectroscopy.

“What is the recommended imaging roadmap in cases of perinatal HIE?” was our last question. From the aforementioned results, we suggest that conventional MRI with DWI is sufficient for early identification as well as prediction of development of CP in cases of acute profound hypoxia with central pattern of affection. In cases with normal appearing MRI and suspected mild to moderate HIE, doing DTI with emphasis of accurate

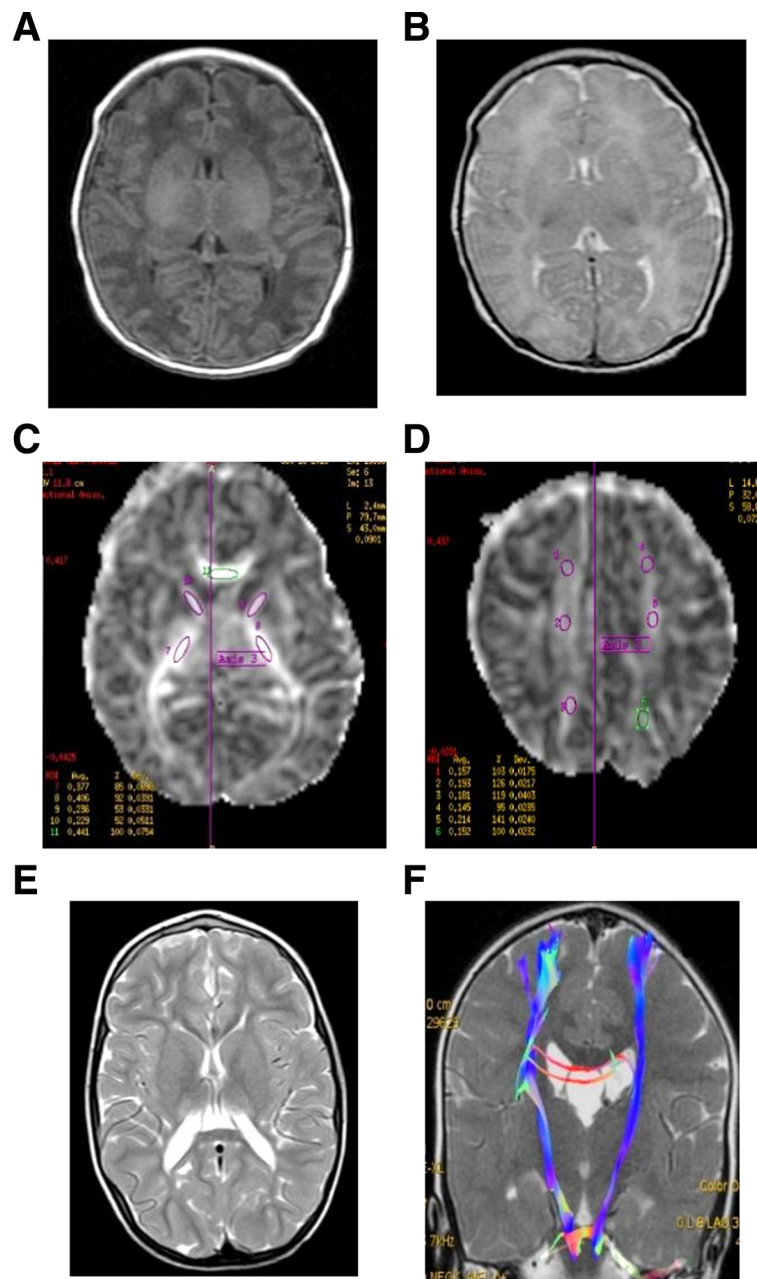
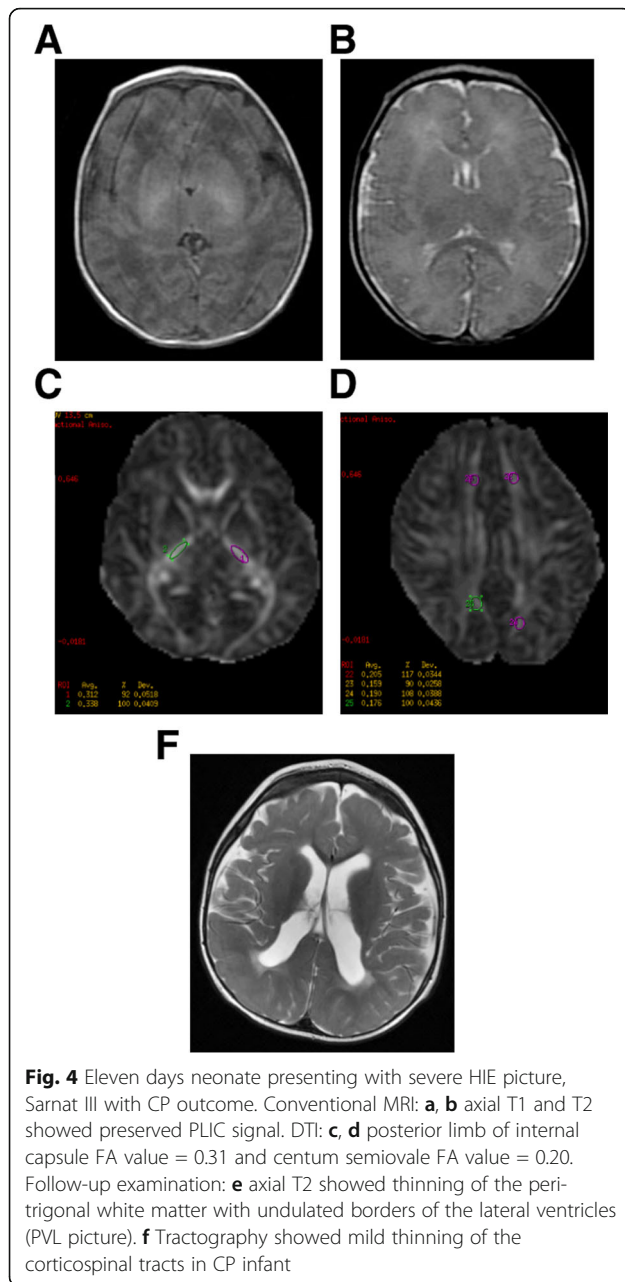


Fig. 3 Nine days neonate presenting with severe HIE picture, Sarnat III with CP outcome. Conventional MRI: **a, b** axial T1 and T2 showed preserved PLIC signal and distinct gray-white matter differentiation. DTI: **c, d** posterior limb of internal capsule FA value = 0.37 and centum semiovale FA value = 0.20. Follow-up examination: **e** axial T2 showed thinning of the peri-trigonal white matter with approximation of the corticoventricular distance (PVL picture). **f** Tractography showed mild thinning of the corticospinal tracts in CP infant

measurement of FA values within the posterior limbs of the internal capsules is likely to reduce the possibility of missing these cases and increase the accuracy of MRI in early prediction of pathological outcome namely cerebral palsy.

The main limitation of the current study is represented by the relatively limited number of HIE newborns recruited. The present results should be confirmed in a

larger population. For ethical reasons, there was no control group of normal neonates for comparison, as no informed consent could be obtained from parents of normal appearing neonates. Another limitation of this study is noted in most studies of neonatal encephalopathy that exact time of injury was not known in most of the patients. The extent and pattern of injury differ temporally. Particularly in the case of DTI, some regions will



appear more severely damaged and some less damaged, depending on the timing of the examination with respect to the injury. Lastly, and to illuminate the full quantitative assessment power of DTI versus the qualitative power of conventional MRI and DWI, extended follow-up at the age of 2 years (at which complete myelination is acquired) should have been done.

In summary, among imaging-based parameters, DTI values closely correlated with the Bayley scores. Such technique can be carried out in a single individual, which has important clinical significance, as it can accurately and objectively assess the prognosis of full-term

neonates with HIE which can guide the treating clinicians for early intervention.

Conclusion

Application of advanced MRI techniques including DTI in assessment of full-term newborns with perinatal HIE is a more accurate quantitative MR biomarker for prediction of neurodevelopmental outcome mainly cerebral palsy.

Abbreviations

CP: Cerebral palsy; CSO: Centrum semiovale; CST: Corticospinal tract; DTI: Diffusion tensor imaging; FA: Fractional anisotropy; HIE: Hypoxic ischemic encephalopathy; PLIC: Posterior limb of the internal capsule

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Authors' contributions

AB drafted the manuscript. AB and MA edited the images. TO and AO reviewed the clinical part of the work. AN worked on the conception and oversaw the entire project. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Approval for this cross-sectional prospective study was obtained from the Research Ethics Committee of Alexandria Faculty of Medicine (Ethics committee's reference number: 020814, IRB no: 00012098, FWA no: 00018699). All study procedures were carried out in accordance with the Declaration of Helsinki regarding research involving human subjects. Written informed consent was obtained from the parents of each child.

Consent for publication

Written informed consent for publication of this data was given by the parents or legal guardians of the included children.

Competing interests

The authors declare that they have no competing interests.

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