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MR Imaging of hypoxic ischemic encephalopathy – Distribution Patterns and ADC value correlations

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ABSTRACT

Background and purpose: Neonatal hypoxic-ischemic encephalopathy causes hypoxic brain injury. Due to differences in brain maturity at time of insult, severity of hypotension and duration of insult, there are four distinct patterns of brain injury. Magnetic resonance imaging is the most sensitive modality for evaluating these patterns of brain injury. Additional role of Diffusion weighted imaging and ADC values can be useful in the evaluation of such cases. We conducted this study to analyse the usefulness of ADC values in the brain tissue affected by hypoxic-ischemic injury.

Materials and Methods: We conducted a prospective study of all the patients referred to our department for magnetic resonance scanning of brain with history of hypoxic ischemic encephalopathy and clinical features cerebral palsy. 23 Cases with imaging manifestations of hypoxic ischemic encephalopathy were included in the study. We studied distribution patterns of HIE in our cases and calculated the ADC values of involved as well as normal grey and white matter. Further, sensitivity, specificity, predictive values, and likelihood ratios for each dichotomized diffusion and ADC values were obtained Wilson Score method.

Results: The most common distribution pattern in our study was involvement of peri-rolandic area (15 cases, 65%). ADC values were significantly ($p < 0.005$) increased in abnormal white matter. No significant changes ($p = 0.8$) were seen in ADC values of normal and abnormal grey matter.

Conclusions: Due to significant increase in ADC values of affected white matter, ADC value can be used as a marker to detect chronic sequel of hypoxic ischaemic brain injury. Another observation was the perirolandic brain tissue being most common area of involvement in the cases with cerebral palsy.

1. Introduction

Perinatal asphyxia remains significant causes of mortality and long term morbidity inspite of progress advances made by medical science. Almost 20% of neonatal deaths in India is caused by perinatal asphyxia as per data from National Neonatal Perinatal database [1].

Impaired cerebral blood flow leads to fetal cardiac and vascular compromise either in utero or in postnatal period. Intrauterine asphyxia is caused by interrupted placental blood flow and gas exchanges and it is the result of various fetal factors like fetal hemorrage or thrombosis, placental hypoperfusion, impaired maternal oxygenation or disrupted umbilical circulation [2].

Asphyxia in the perinatal period is the most important cause of HIE, causing hypoxemia and hypercapnia which causes reduced reduction in blood pressure and blood flow which in return triggers cascade of harmful events, which are acidosis, release of inflammatory mediators and excitatory neurotransmitters, free radical generation, calcium accumulation, and lipid peroxidation. The accumulated biochemical substances cause failure in vascular autoregulation causing decreased cerebral perfusion. There is biphasic energy failure with initial impairment of cell metabolism is followed by reperfusion prior to eventually leading to neuronal cell death.

Abbreviations: HIE, hypoxic ischemic encephalopathy; MRI, magnetic resonance imaging; DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient; PVL, periventricular leukomalacia; US, ultra sonography; CT, computed tomography

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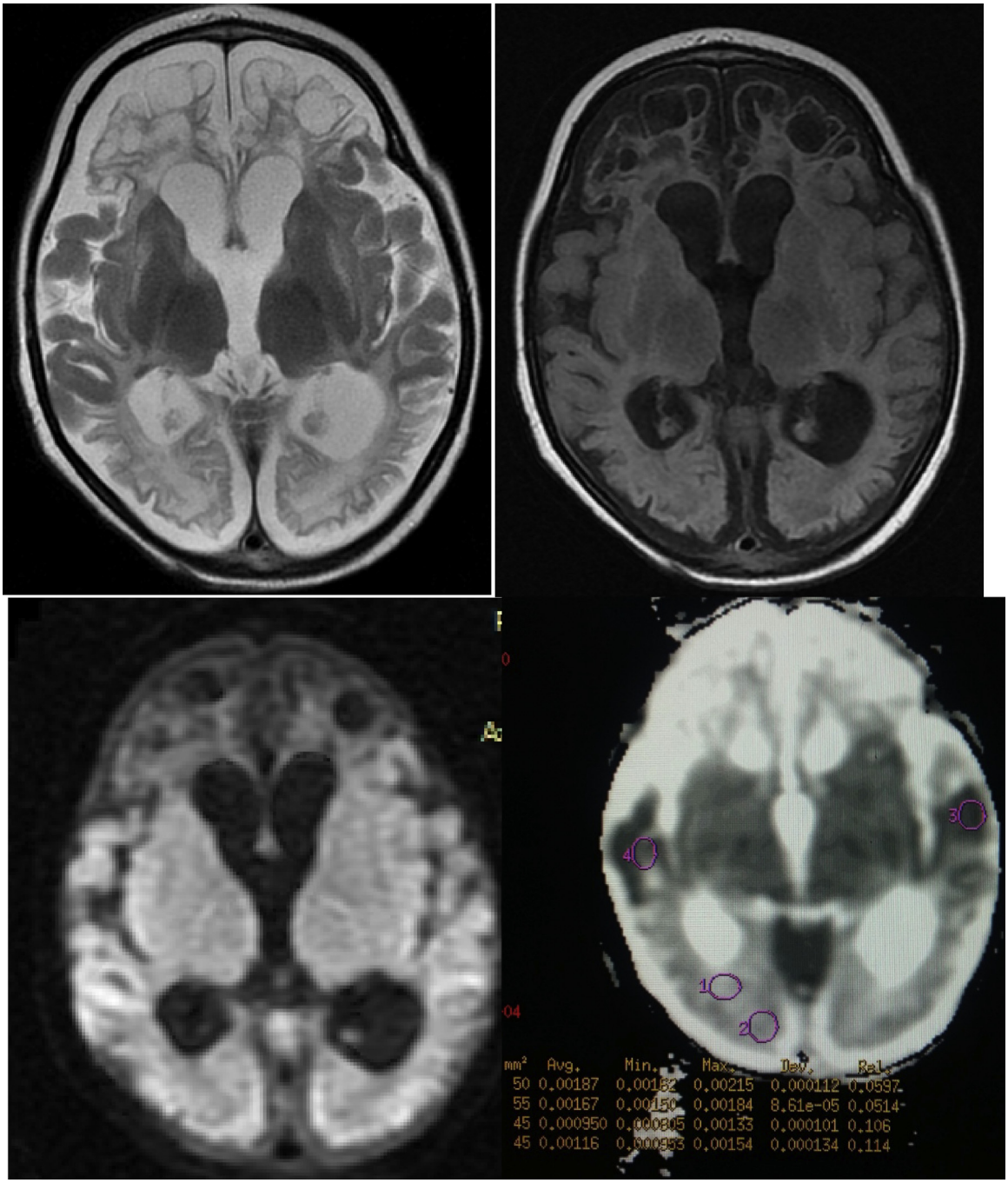

Fig. 1. MR images of the 10 month old male patient of cerebral palsy.Axial T2W(A),T2 FLAIR(B)and DWI (C) images showing bilateral symmetrical areas of cystic encephalomalacia involving frontal lobes which show T2 hyperintense and T1 and FLAIR hupointense (Thin arrows).Bilateral symmetrical areas of gliosis are also seen in frontal and occipital lobes as hyperintense on T2WI and FLAIR. DWI(C) & ADC MAP (D) show no restriction and increased ADC values as shown by ROIs. There is generalised cortical atrophy with ex-vacuo dilatation of ventricular system.

Various neuroimaging modalities like ultrasonography, computed tomography, and Magnetic resonance imaging are used for accurate identification and characterization of the severity, extent, and location of brain injury. Hydranencephaly and porencephaly results when hypoxic insults occur in gestation period generally less than 28 weeks (Figs. 1–3).

Periventricular-intraventricular haemorrhage (PIVH) usually occurs between 28 and 32 weeks. Periventricular leukomalacia (PVL)and subcortical leukomalacia occur in insults usually between 32 and 36 weeks and finally hypoxic-ischaemic encephalopathy of the term newborn [4,5].

The purpose of our study was to evaluate the role of MRI in neonatal hypoxic ischaemic brain injuries can patterns considering the perinatal maturation process of the brain and the severity of an insult.

2. Methods

2.1. Patient selection

We retrospectively identified 24 neonates with HIE born within a 6 month period (October 2016 to march 2017) at our institution facilities. Subjects were identified by using a radiologic database and were

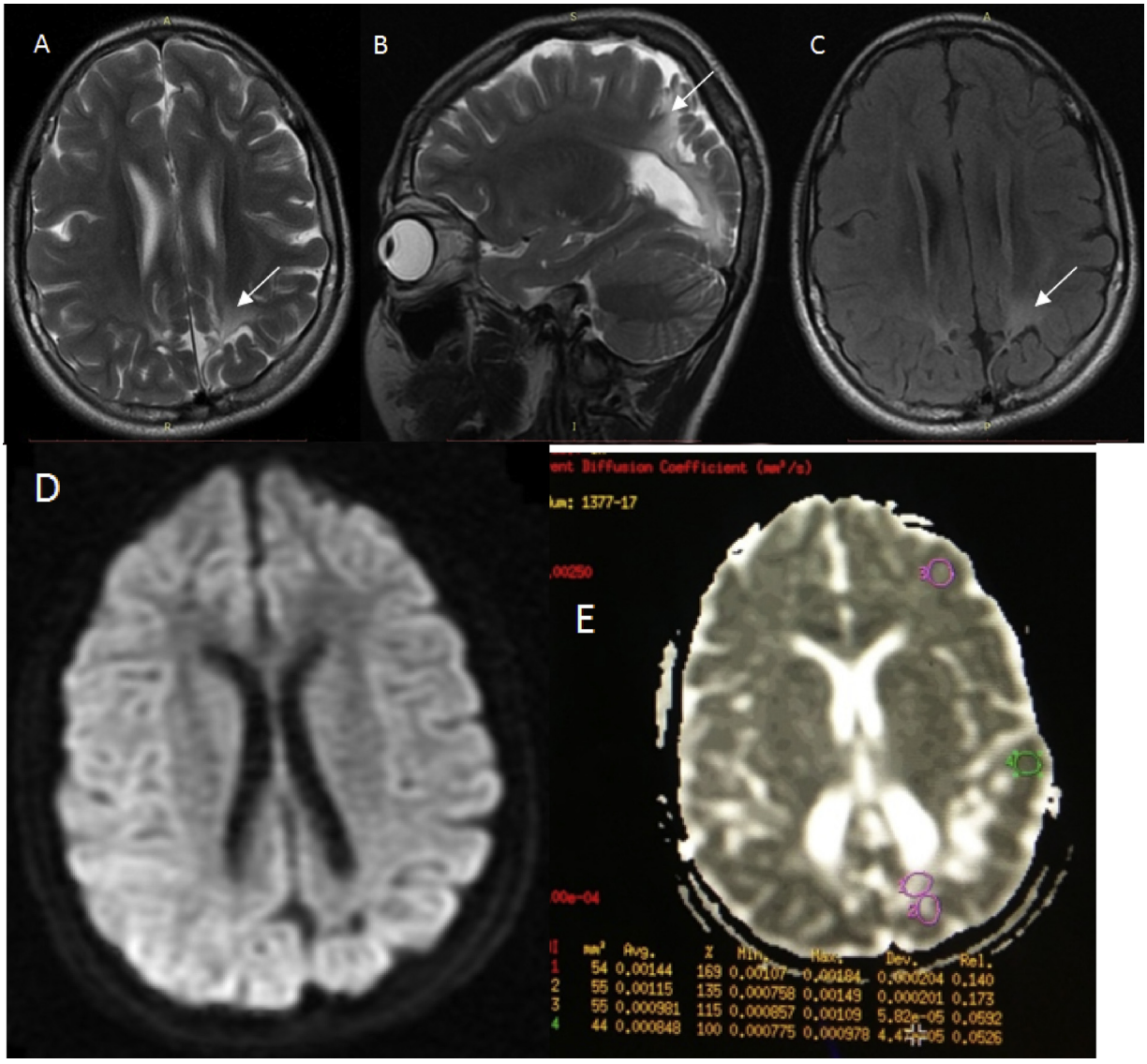

Fig. 2. MR images of a 2 years old child with cerebral palsy. Axial (A) and Sagittal T2WI (B), Axial T2FLAIR (C) images show abnormal hyperintense signal areas with cystic encephalomalacia in bilateral perirolandic and occipital cortex (thin arrows). DWI (C) and ADC map (D) show no diffusion restriction with increased ADC values.

included in the study subjected to clinical records showed perinatal asphyxia and subsequent HIE sequelae, after obtaining a written informed consent from respective parents/guardian. The study was approved by institutional ethics committee.

2.2. Technique -MR Imaging Protocol

A 1.5 T MR scanner (GE Healthcare) was used, with a gradient system that can reach a maximum gradient strength of 21 m T/m in each main direction. The imaging protocol consisted of a spin-echo T1-weighted series (568/18 TR/TE), a turbo spin-echo T2- weighted series (4381/120), and an inversion-recovery series.(3436/18/400 TR/TE/IR). No intravenous Gadolinium based contrast was used. Standard 8-channel birdcage (volume) coil was used. Anaesthesiologists using intravenous Propofol according to weight, after pre-anaesthesia check, sedated the neonates.

All subjects underwent a neurologic examination at age 10 months by an experienced paediatrician, who was blinded to the results of the imaging studies and to the clinical course of the infant as per protocol.

2.3. Image processing

Images obtained were analysed on the workstation (GE Healthcare). Images were assessed for the presence of ischemic damage by the investigators. Although a history of HIE was given for all subjects, more extensive clinical results were not revealed. Data were analyzed with respect to both, the anatomical site and the time passed after the event of injury. The extent of ischemic damage in each subject was determined according to MRI findings. Three plane anisotropic diffusion weighted images were examined for signal changes not accounted for by normal white matter anisotropy. Conventional MR studies were examined for the findings of HIE, blinded of the diffusion-weighted imaging appearances. The location and extent of involvement (by volume) of ischemic damage on each sequence were noted. Mean ADC values were derived from isotropic ADC maps in three standard locations for each subject. Bilateral regions of interest were manually drawn in the normal appearing gray and white matter as well as involved gray and white matter to calculate ADC values. Results were compared with normal values in published literature.

Data was analyzed with respect to both injury location and chronicity. Areas of presumed damage showed changes in either

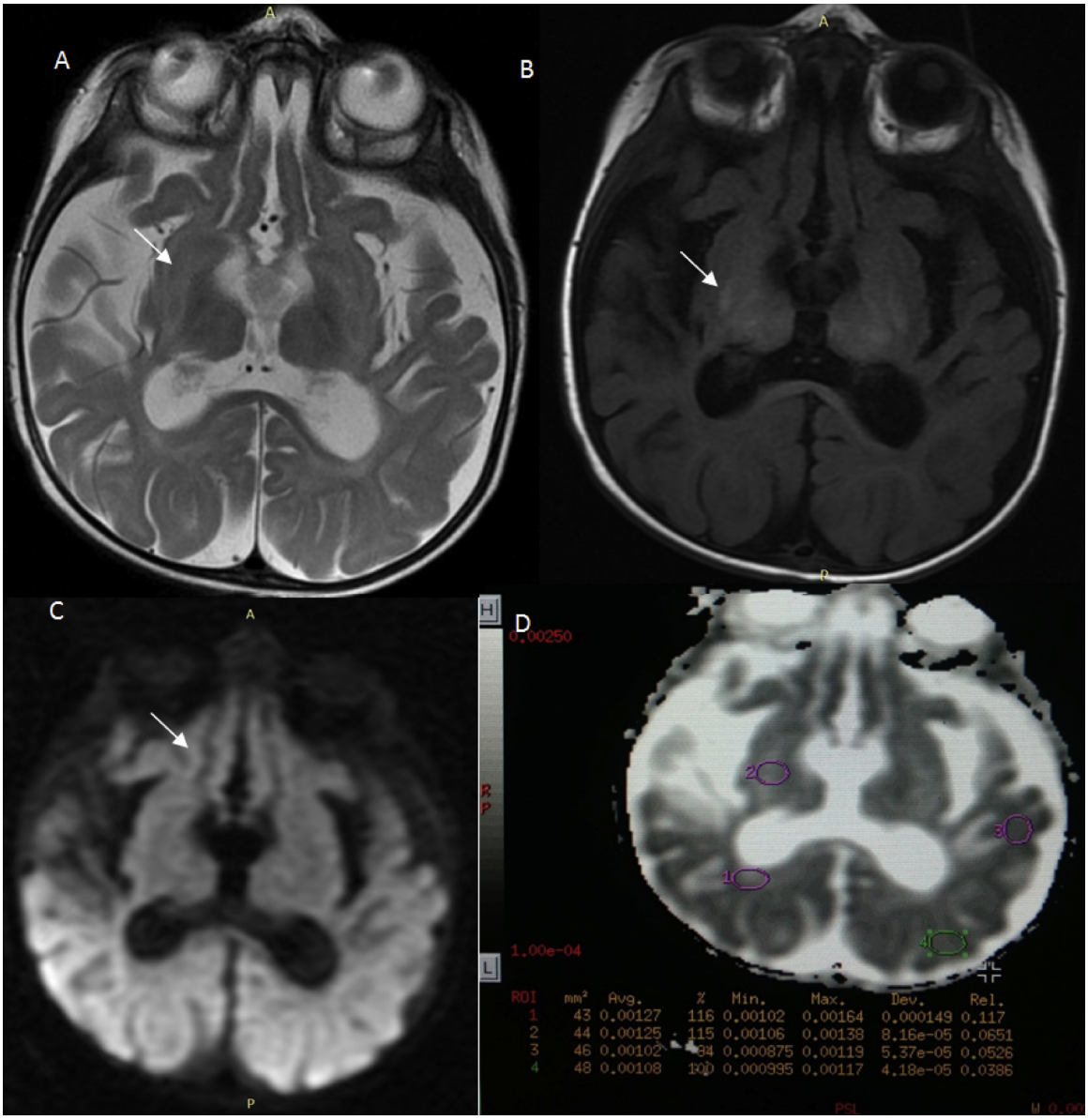

Fig. 3. MR images of a 4 months old child with cerebral palsy and history of birth asphyxia. Axial T2W (A), T2FLAIR (B) show symmetrical marked atrophy of perirolandic white matter with ex-vacuo dilatation of lateral ventricles Abnormal T2, T2FLAIR hyperintense signal is seen in bilateral basal ganglia and thalamic regions (thin arrows). DWI and ADC maps show no diffusion restriction and increased ADC values in the affected grey and white matter (as shown by round ROIs).

conventional MR signal or ADC value, or both. The ability of each imaging technique to detect the full extent of ischemic damage was assessed. The effect of image timing on the ability of diffusion-weighted imaging to detect ischemic damage was considered for all examinations and also separately for deep gray matter and cortical injuries.

We also evaluated the ADC values in the damaged brain issue due to hypoxic ischemic insult in the past and normal brain tissue in both gray and white matter.we analysed whether any significant difference exists between the two normal and abnormal damaged brain tissue. We also studied whether the ADC values are comparable to that of chronic infarct in adults.

3. Results

We analysed 23 studies (Table 1). Mean age of the patient was 7 months. Out of 23 cases, 22 cases had positive history of birth asphyxia. 16 were term born and 7 were preterm born babies. 9 babies were born of home delivery while rest of the cases were born at a hospital.

Table 1
Distribution of MRI findings among term and pre-term neonates.

MRI findings	No. of cases	
	Pre-term	term
Cystic encephalomalacia	1	1
Basal ganglia involvement	2	0
Peri-rolandic involvement	1	12
Watershed zone involvement	3	1
Mixed pattern	0	2
Total	23	

Developmental delay was present in 20 cases, while abnormal speech as an isolated feature was found in 3 cases. Involvement of peri-rolandic brain was the most common imaging finding (15 cases) followed by cystic encephalomalacia, basal ganglia involvement, watershed zone involvement seen in 2 cases each. Perirolandic involvement was seen more commonly in term neonates (12 cases) than in preterm neonates

(3 cases).

We dichotomised the patients into two groups i.e. Term and preterm and applied Pearson chi square test while comparing predominant area of involvement in term and Term born children there was no statistically significant co-relation existed between the two($p = .139$).

We also analysed these groups on the whether these cerebral palsy patients having predominant muscular, developmental or speech involvement, however here also no statistically significant co-relation existed.($p = .219$)

The average ADC values in brain affected area both gray and white matter and contralateral (unaffected) areas both gray and white are shown in Table 1.

Quantitative analysis of ADC values were done by drawing regions of interests over grey and white matter regions, both normal and abnormal. ADC values for normal and abnormal grey matter mean were 0.0013 and 0.0012 respectively. The changes in grey matter ADC values were not statistically significant in the presence of abnormal imaging findings ($p = .819$). ADC values for normal and abnormal white matter were having mean of 0.0009 and 0.0012 respectively. The white matter regions involved by ischaemic insults showed increased ADC values and they were statistically significant($p < .000$) (Table2). As they were all chronic cases with cerebral palsy the average ADC values in affected regions were higher than the contralateral side and values were significant different from other ($P < 0.000$) (Table 2).

4. Discussion

ADC quantitatively denotes assessment correlating with changes on conventional MRI and neuromotor outcome. We have demonstrated that the raised ADC value in chronically affected white and gray matter as well as the appearance of these on conventional MR imaging, is significantly associated with morbidity in a cohort of infants with HIE. The raised ADC values in abnormal white matter is significantly associated with motor cerebral palsy thus it is important confounding factor in our analysis [10,11]. We also found a significant relationship between raised ADC values and neuromotor outcome. Thus there is potential importance of measuring ADC values and its correlation with manifested cerebral palsy in infants with HIE [12–14]. This is in keeping with findings of Wolf et al. [17] In their study, control subjects had ADC values 1.0 m2/ms in the PLIC. None of the infants in our cohort who had severe neuromotor impairment had an ADC value less than 1 m2/ms. Although these findings should be validated with greater cohort numbers and larger outcome data with studies carried out for longer period of time, but their significance is encouraging.

We demonstrated a strong relationship between the ADC value and observed changes on conventional MRI, this supports the possibility that the signal abnormalities, first reported by Rutherford et al. [8], is related to Wallerian degeneration of the motor pathway after ischemic injury to the parasagittal motor cortex which is commonly seen in HIE insult [2].

Global ischemic insults depending on the severity and duration of insult and the age of the neonate which makes particular brain areas selectively vulnerable to damage. Areas of high metabolic demand containing a high concentration of excitatory amino acid receptors, such as the deep gray matter and perirolandic cortex are commonly damaged in acute severe ischemia. In comparison to this, less severe but more prolonged ischemic insults affect the cortical and sub-cortical watershed regions. We also found in our study that perirolandic involvement remains the most common area involved in the patients of cerebral palsy.

The diffusion-weighted imaging detected isolated cortical injuries, it failed to detect the damage to the deep gray matter and perirolandic cortex. The damage to these areas results in a different cellular response to cortical watershed injuries. On conventional MR T1-weighted signal hypointensity, indicating edema, is seen in watershed damage, T1-weighted hyperintensity is seen in deep gray matter injuries. The exact origin of the T1 signal changes in the deep gray matter remains unclear, but may indicate hemorrhage. Brain damage resulting from neonatal asphyxia is also known as hypoxic-ischemic reperfusion injury, it shows the importance of both ischemia and arterial reperfusion in eventual damage [15–17]. We examined the effect of image timing on our results and we observed possible differences between cortical and deep gray matter injuries [18–20,2], the high ADC values are related probably to definitive ischemia (necrosis).

Published studies have so far addressed the predictive value of ADC measurements in neonates with HI brain damage. Wolf et al. [12] studied 13 term neonates with suspected HIE within 12 postnatal days. ADC values were measured in predefined brain regions; without distinction between abnormal and normal-appearing regions on DWI. Wolf et al. [12] found decreased ADC values in the posterior limb of internal capsule, corona radiata, posterior frontal white matter, and parietal white matter in patients with HIE compared with as compared to controls but predictive value of ADC measurements were not assessed for clinical outcome. This difference in the value of ADC in different portion of brain is probably due to different water composition in different parts of the brain.

Our results demonstrate that diffusion-weighted imaging can detect parenchymal changes from severe chronic cerebral ischemia and hypoxemia with sensitivity of DWI for adult cerebral infarction is 88% to 99%. Our results suggest that this technique is much less sensitive to neonatal HIE and all subjects in this study suffered HIE, with follow-up studies, where available, supporting this. We have assumed that ischemic injuries in all cases occurred around the time of birth. The limited sensitivity of diffusion- weighted imaging probably reflect differences in the pathophysiological response of the neonatal brain to ischemia [22].

As mentioned previously there are limitations to our study as well first being the timing of the MR imaging examinations, taking place up to several months after birth. However, in most cases of perinatal asphyxia, the exact time of the inciting event is difficult to determine. Another limitation is that we did not perform initial imaging at birth around the time of insult normal. Finally, because of the heterogeneity of the group we studied, showing various injury patterns, the number of infants with specific injury patterns was limited. No predictive values of either ADC or DWI could be assessed.

5. Conclusions

We conclude that in neonates with HIE, high ADC values of the abnormal white matter correlate with already manifested cerebral palsy, independently of all imaging findings. In this group of neonates with heterogeneous injury patterns, high ADC values in visibly

Table 2
Analysis of ADC values of normal and abnormal grey and white matter.

	Mean	N	Std. Deviation	p-value
ADC-normal grey matter	.0013057	23	.00170501	
ADC-abnormal grey matter	.0012248	23	.00026868	.819
ADC-normal white matter	.0009830	23	.00014646	
ADC-abnormal white matter	.0012704	23	.00027556	.000

abnormal brain tissue particularly white matter correlated well in cerebral palsy patients.

All ethical standards laid by the institutional committee was taken care,this study was not funded by any external resource and there was no conflict of interest involved.

Conflict of interest

That the author(s) or author(s) institutions have no conflicts of interest.

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