Diagn Interv Radiol 2006; 12:109-114

Clinical outcomes of neonatal hypoxic ischemic encephalopathy evaluated with diffusion-weighted magnetic resonance imaging

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PURPOSE
Detection of early phase neurological deficit in babies with hypoxic-ischemic encephalopathy (HIE) is the most important step to determine the appropriate preventive treatment methods. Diffusion-weighted imaging (DWI) is the most sensitive radiological modality to detect ischemic changes in the brain, in their earliest phase. Herein, we present the results of our study about the role of DWI in the diagnosis and determining the prognosis of HIE in neonates.

MATERIALS AND METHODS
The study included 36 cases (4 preterm, 32 term babies) who were diagnosed with HIE within 24 hours of birth and classified according to modified Sarnat staging. They were examined for the presence of neurological sequelae at 3 and 6 months of age with electroencephalography (EEG), visual evoked potential (VEP), brainstem auditory evoked potential (BAEP), and Denver II developmental screening tests. All 36 patients underwent conventional magnetic resonance (MR) imaging and DWI within the first 24 hours of birth; survivors underwent repetitive imaging exams at the end of the first week and then after a month.

RESULTS
Seventeen stage I cases (47%), 12 stage II cases (33%), and 7 stage III cases (20%) were detected. DWI obtained within the first 24 hours showed high sensitivity (100%) in detecting the permanent neurological sequelae but with very low specificity (20%). The negative predictive value of DWI in this period was 100%; however, in DWI obtained at the end of the first month, not only its sensitivity was preserved, but its specificity reached 80%. The negative predictive value of DWI in this period was preserved and the positive predictive value improved. The importance of DWI in detecting sequelae at the end of the first month was also demonstrated by McNemar ($p = 0.250$) and Kappa (Kappa = 0.719) tests. There was no difference between conventional MR imaging and DWI in detecting sequelae at the end of first month.

CONCLUSION
DWI is superior to other imaging modalities in detecting ischemia; not only because of its high sensitivity in the early phase, but also because of its high sensitivity and specificity in the late phase. Moreover, with its high negative predictive value, DWI can be used for excluding the possibility of sequelae development in the early phase of HIE cases for medico-legal purposes.

Key words: • diffusion-weighted imaging • magnetic resonance imaging • hypoxic-ischemic encephalopathy

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Received 13 November 2005; revision requested 9 March 2006; revision received 12 April 2006; accepted 14 April 2006.

Perinatal asphyxia is the most important cause of neurological morbidity and mortality in preterm and full-term neonates (1). In the past, asphyxia was known as natal encephalopathy, fetal encephalopathy, and asphyxic encephalopathy. In 1980, the term hypoxic ischemic encephalopathy (HIE) came into use for all phases of ischemic changes. Among all HIE cases, 15%-20% die during the neonatal period and 30% of those who survive suffer from neuro-developmental disorders, such as cerebral palsy and mental retardation (2). There are several methods for the diagnosis of asphyxia, including biochemical tests like cerebrospinal fluid (CSF) analysis, or electrophysiological tests like electroencephalography (EEG), brain stem auditory evoked potentials (BAEP), visual evoked potentials (VEP), and somato-sensorial evoked potentials (SEP) (3). The imaging modalities that are used for diagnostic purposes include cranial and color Doppler ultrasound, closed infrared spectroscopy, computed tomography (CT), conventional diffusion-weighted imaging (DWI), and perfusion magnetic resonance (MR) imaging (4, 5). Detection of neurological deficit in the early phase in babies with HIE is the most important step to determine the appropriate preventive treatment methods. DWI is the most sensitive radiological modality to detect ischemic changes in the brain in the earliest phase. Herein, we present the results of our study about the role of DWI in the diagnosis and determination of the prognosis of HIE in neonates.

Materials and methods

Patients

The study included 36 patients (male: 20; female: 16) who presented within the first 24 h of birth and were diagnosed with HIE according to the diagnostic criteria of the American Pediatric Academy and American Obstetrical Gynecology College. Three cases were born in our institution and the others were born at different hospitals and then referred to us. Four cases were preterm and 32 cases were full-term. Cases without proof of acidosis in umbilical cord blood and cases with an Apgar score of ≥ 6 were excluded. Consent forms were obtained from the legal guardians of all cases prior to the study.

Clinical and laboratory evaluation

Physical examinations for the vital signs, body weights, and for excluding organomegaly were performed at the very first presentation of the cases immediately after birth. Detailed circulatory, respiratory, and neurological systems examinations were performed. Encephalopathy was scored according to the American Pediatric Gross Assessment Record (APGAR) and modified Sarnat staging system (mild: stage I; moderate: stage II; severe: stage III) (Sarnat HB and Sarnat MS, 1976). Additionally,

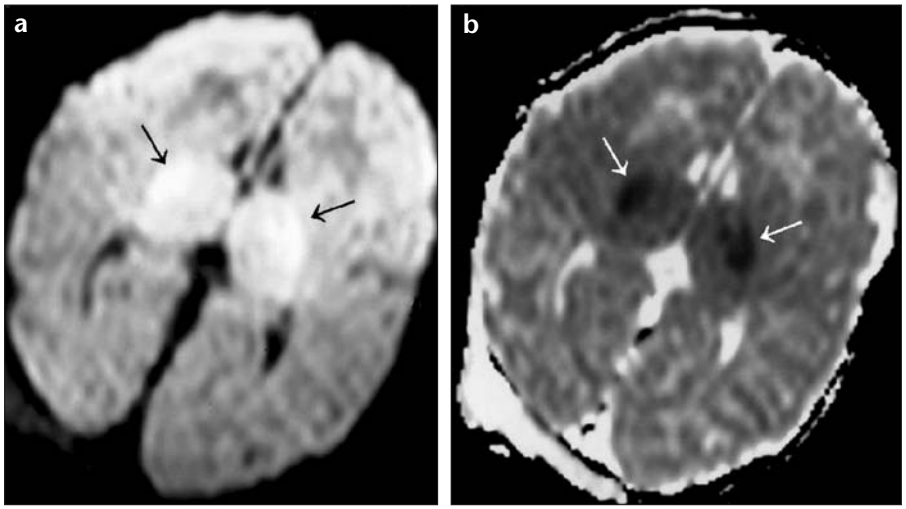

Figure 1. a, b. Stage I hypoxic ischemic encephalopathy. Diffusion restriction representing acute ischemia is seen on DWI (diffusion-weighted imaging) obtained in the first 24 h. Diffusion-weighted image (b: 1000 s/mm^2) **(a)** shows increased signal intensity at the bilateral thalami, posterior limbs of the internal capsules, and the globi pallidi *(black arrows)*; however, on ADC (apparent diffusion coefficient) map **(b)**, these areas are represented as signal loss *(white arrows)*.

complete blood count (CBC), blood smear, blood gases, and serum biochemical exams were performed.

EEG, VEP, BAEP, and Denver II Developmental Screening Tests (Denver II) were performed in the 3rd postpartum month. If there was any abnormality in any of the above tests, Denver II test with detailed neurological examination was re-performed at 6th month to those cases. The abnormalities detected at this period were considered as neurological sequelae.

Imaging method

Radiological examinations were performed with a 1.5 T Gyroscan NT Intera Master (Philips, Best, The Netherlands). For conventional examinations, axial T1 weighted (TR/TE: 450/10 msec), T2 weighted (TR/TE: 3881/120 msec), and FLAIR (TR/TE/TI: 6000/110/2000 msec) sequences were obtained. DW imaging was obtained using an echo planar imaging (EPI) sequence (TR/TE: 5381/81 msec; slice thickness: 5 mm; slice interval: 1 mm; FOV: 230x230 mm; matrix: 256x256; b-value: 0.500, and 1000 s/mm^2). All 36 patients were examined by conventional MR and DW imaging within the first 24 h of birth and survivors were re-examined at the end of the first week and at the end of first month.

Image analysis

Two experienced radiologists reviewed all images and signal changes suggesting ischemia together and made final shared comments. The 2 radiologists had no knowledge about the patients other than the HIE diagnosis and MR images. Ischemic lesions observed on the conventional MR images obtained at the end of first month were accepted as the gold standard for detecting permanent lesions, as suggested in the literature.

Statistical analysis

Data obtained in this study were analyzed with SPSS version 10.0 (Statistical Package for Social Sciences Inc, Chicago, USA). McNemar test which assesses the significance of the difference between two dependent samples was used to compare the existence of sequelae in DWI and conventional MR images of the cases at the end of first month. Kappa statistics were used to assess the agreement among the observers. The predictive value of DWI, performed in different phases for predicting the permanent neurological sequelae development, were calculated by means of accuracy rates.

Results

Seventeen stage I cases (47%), 12 stage II cases (33%), and 7 stage III cases (20%) were detected according to modified Sarnat staging. Ten cases died within the first 6 months. Of those, 3 (17.6%) were stage I, 2 (16.7%) were stage II, and 5 (71.4%) were stage III.

Clinical findings were as follows according to their frequencies; delay in spontaneous respiration (88%), difficult labor (55%), acidosis (53%); convulsion (53%); meconium aspiration (36%), premature rupture of membranes (17%), bleeding (3%), umbilical cord wrapped around the head (3%), non-reactive non-stress test (NST), abruptio placenta (3%); cervical insufficiency (3%), polyhydramniosis (3%), anhydramniosis (3%).

Stage I cases

Within the first 24 h, 14 of the 17 cases (82%) of stage I HIE had diffusion restriction (acute ischemia) that appeared hyperintense in DWI and hypointense in ADC (apparent diffusion coefficients) maps (Figure 1). Three cases of stage I HIE had no pathological imaging findings and DWI of these at the end of first week were unremarkable as well. Two cases died within one week. Diffusion restriction was still prominent at the end of first week in 7 out of 15 cases and there was no restriction in the remaining 8 cases. A total of 14 cases were alive at the end of first month and there was no diffusion restriction on DWI. A diffusion increase representing chronic ischemic changes was detected in only one case and chronic ischemic changes were also noted in conventional MR images of this case. The remaining 13 cases` conventional MR imaging findings were within normal limits in this phase and no sequelae was detected in the neurological examination of these 13 cases.

Stage II cases

Within the first 24 h, 11 of the 12 (92%) of stage II HIE cases had diffusion restriction. DWI was within normal limits in the remaining case. Since 2 patients died and one patient was on continuous mechanical ventilation, DWI could be obtained in only 9 cases at the end of the first week. Diffusion restriction persisted in all but one case. At the end of the first month, among the 10 survivors, 7 cases had diffusion increases in DWI. There was nothing abnormal in the remaining 3 cases. In conventional MR images, there were pathological findings in 7 cases, and normal findings in 3 cases. Five (50%) out of 10 cases were positive for sequelae in neurological examination. All those patients with sequelae, also had diffusion increases and abnormal conventional MR imaging findings.

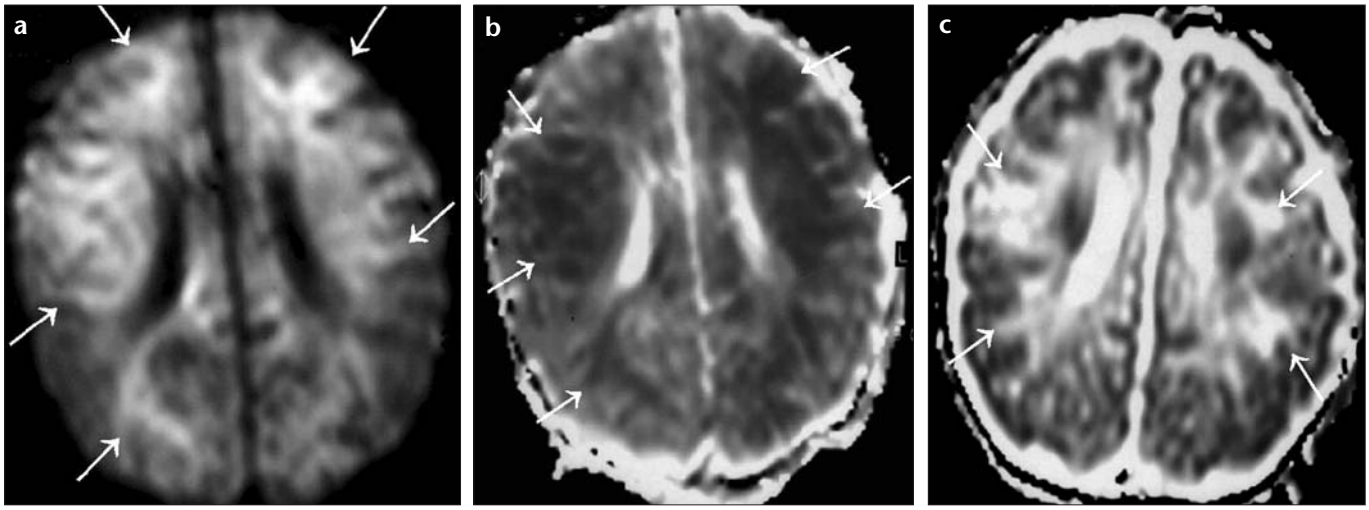

Figure 2. a-c. Stage III hypoxic ischemic encephalopathy. Diffusion-weighted imaging (DWI, b: 1000 s/mm^2) obtained within the first 24 hours shows **(a)** bilateral frontal, parietal, and occipital white matter hyperintense signal *(arrows,* **a***)*; while in ADC map **(b)**, they appear hypointense *(arrows,* **b***)*. In late phase these areas are represented with high signal intensity on ADC map *(arrows,* **c***)* corresponding to diffusion increase due to chronic ischemic changes.

Stage III cases

Within the first 24 h, all 7 stage III HIE cases had diffusion restriction. Since 3 patients died and one patient was on continuous mechanical ventilation, DW images could be obtained in only 3 cases at the end of the first week. Diffusion restriction persisted in all cases. Those 3 cases were alive at the end of the first month. In the DW images, diffusion increases were seen suggesting chronic ischemic changes in these 3 cases (Figure 2). Pathological findings suggesting chronic ischemic changes were also detected in conventional MR images of these cases. One of the stage III cases died between the 3- and 6-month follow-up. Only one of 2 living stage III cases had neurological sequelae at the 6th month.

Table 1. Distribution of lesions detected with MR imaging, according to their locations in hypoxic ischemic encephalopathy cases at different stages.

		1st day DWI	1st week DWI	1st month DWI	1st month MRI
	Location of the lesion	Number of cases with lesions			
Stage I	White matter	9	5	1	1
	Basal ganglia	2	1	-	-
	Thalamus	3	-	-	-
	Other	3	1	-	-
Number of cases with lesions		14	7	1	1
Stage II	White matter	9	7	5	7
	Basal ganglia	-	1	1	1
	Thalamus	4	1	1	1
	Other	5	4	1	4
Number of cases with lesions		11	8	7	7
Stage III	White matter	5	3	3	1
	Basal ganglia	-	-	1	-
	Thalamus	2	2	1	1
	Other	3	1	1	1
Number of cases with lesions		7	3	3	3

DWI: diffusion-weighted imaging MRI: magnetic resonance imaging

Distribution of DWI and conventional MR imaging findings and their locations according to different HIE stages are summarized in Table 1. While examining the role of DW imaging in determining the chronic course, there was no statistically significant difference between the first month DW imaging findings and the presence of neurological sequelae (McNemar test, p = 0.250), but there was a concordance between DW imaging findings and the presence of a neurological sequelae in Kappa test (Kappa value = 0.719). There was no statistically significant difference between the first month conventional MR imaging and the presence of a sequelae (p = 0.125), and there was an almost complete correlation between the 2 parameters (Kappa value = 0.643). Again, there was no statistically significant difference in determining sequelae between the first month DW and conventional MR imaging.

The two by two table for diagnostic accuracy estimations of DW imaging in first 24 h and at the first month used in determining sequelae in HIE cases and diagnostic accuracy ratios for the latter parameters are given in Tables 2 and 3. According to those tables, DW images

obtained within the first 24 h showed high sensitivity (100%) in detecting neurological sequelae with a very low specificity (20%). The negative predictive value of DW imaging in this period appeared to be 100%. However, in DW images obtained at the end of the first month, sensitivity was preserved, but the specificity reached 80%. The negative predictive value of DW imaging in this period was preserved (100%) and the positive predictive value improved (60%).

Discussion

HIE secondary to perinatal hypoxia can cause serious complications, such as cerebral palsy, mental retardation, and convulsions. The morbidity and mortality rates are high in this disease and its prevalence increases proportionally as the level of development decreases in a population. Perinatal asphyxia can be prevented in developed countries by means of appropriate diagnostic and treatment methods (6).

Early diagnosis of acute ischemia in HIE is extremely important in minimizing or even preventing permanent brain damage. Several imaging methods have been tried for early and correct diagnosis. Cranial ultrasound is one of the first used methods that show the ischemic areas as hyperechoic; but, this finding is not visible within the first 24 h of life. The sensitivity of this method was calculated as 30.5% (7). Cranial CT, as the primary diagnostic tool in emergency neurological imaging, may not be able to show ischemic damage before 48 h (8). Conventional MR imaging can supply better and earlier information than CT and ultrasound. Nevertheless, damaged areas cannot be demonstrated before 8-12 h with conventional MR imaging either. DW imaging can detect these hypoxic ischemic changes within a couple of minutes of their occurrence (4, 5, 7, 9). Bozzoa et al. (10) compared 12th hour CT and DW imaging findings and found diffusion restrictions in 10 cases that had unremarkable CT images. Soul et al, used DWI and conventional MR imaging to evaluate HIE patients (11). In this latter study, DW imaging performed at the 6th hour detected ischemic changes which became even more significant at the 32nd hour, whereas in conventional MR imaging, there was no finding at the 6th hour, and initial findings could only be detected at 32nd hour. As demonstrated by the above-cited researchs, DW imaging is superior to the other imaging modalities in detecting early phase ischemic changes, including conventional MR imaging. Therefore, DW imaging has become a routine imaging tool in the imaging of strokes.

Schaefer et al. (12) and Warash et al. (13) studied the relationship between early phase DW-perfusion MR imaging findings and chronic cerebral ischemic changes. In the first study, the sensitivity and specificity of DW imaging was found to be 94% and 96%, respectively. In the second one, retrospective evaluations of patients with neurological sequelae were performed and early phase ischemic findings were detected in 11 out of 12 cases with DW imaging; however, only 4 of them were detected with conventional MR imaging. Ischicava et al., (14) performed experimental studies on rats in which they artificially generated various levels of hypotensive ischemia and then tried to detect a correlation between the ADC changes, and mortality-clinical course. Kluytmans et al., (15) showed a similar relationship in stroke cases. Among our cases, 17 had DW imaging within first 6 h. In the present study, the sensitivity and specificity of DW imaging in the early diagnosis of ischemia was 96% and 75%, respectively. The sensitivity of DW imaging in detecting the presence of a sequelae was 100%, both in the first 24 h and first month. However, the specificity was 80% at the end of the first month. DW imaging was able to detect all cases with neurological sequelae in the late phase. With respect to the literature, DW imaging is more effective in determining chronic ischemic changes and

Table 2. Diagnostic accuracy estimations of diffusion-weighted imaging (DWI) in the first 24 h and at the first month for determining the presence of sequelae in hypoxic ischemic encephalopathy cases.

1st day			
	Sequelae		
DWI	Positive	Negative	Total
Positive	6	16	22
Negative	0	4	4
Total	6	20	26
1st month			
	Sequelae		
DWI	Positive	Negative	Total
Positive	6	4	10
Negative	0	16	16
Total	6	20	26

Table 3. Diagnostic accuracy ratios of diffusion-weighted imaging (DWI) in the first 24 h and at the first month for determining the presence of sequelae in hypoxic ischemic encephalopathy cases.

	DWI	
Parameter	1st day	1st month
Sensitivity	100	100
Specificity	20	80
Positive predictive value	27	60
Negative predictive value	100	100

prognosis as compared to other imaging modalities.

DW imaging is especially effective in the early phase of ischemic changes. Moreover, there are researchs in the literature claiming that some of the lesions detected with DW imaging may regress or disappear with appropriate treatment. In the experimental study of Rumpel et al. (16), they observed that the areas of diffusion restriction pointing at cytotoxic edema does not necessarily mean irreversible brain damage. Kidwell et al. (17) showed that in 9 out of 20 ischemic cases, diffusion restricted areas recovered completely at follow-up. Singhal et al. (18) showed that even with a diffusion restriction, mild hypoxic damage could recover without any chronic changes. In our study, 93% of all stage I and only 30% of stage II HIE cases were recovered. None of the lesions in stage III HIE cases were recovered. These results correlated with the literature claiming that diffusion restriction in DW imaging is not necessarily indicative of permanent damage.

Li et al. (19) compared the DW imaging findings in ischemia with histopathological changes in an experimental study. They reported that one could see widespread neuronal necrosis in areas detected as normal with DW imaging and normal brain parenchyma in locations.with abnormal DW imaging findigs. Also in our study, we concluded that visually detected nonmathematical evaluations in DW images might not reflect the prognosis of ischemic lesions.

In the related literature, it is said that DW imaging may not be diagnostic for early stroke in lacunar infarcts located in the brain stem and deep grey matter. It was reported that some of those lesions can only be observed in the late phase and some can never be observed (20, 21). Additionally, in early phase DW imaging, when brain perfusion decreases but cytotoxic edema and infarct do not yet occur, lesion can be missed, whereas diffusion restriction can be detected only in the late phases. Rather than showing the inaccuracy of DW imaging, these findings suggest that in time, the living tissues with hypoperfusion finally end up with infarct (22). In our study, there were no false negative DW imaging results. The negative predictive value of DW imaging in early and late phases was 100%. We think that this result was related to the extent of infarctions in our cases and the relatively long time interval between asphyxia and DW imaging. If we had obtained our DW images within a couple of minutes, there would have been unavoidable false negative results. We concluded that DW images were obtained after the infarction occurred in the brain in our cases. In the light of literature and our data, DW images obtained just a couple of minutes after the detection of neurological findings can be misleading; therefore, if there is an inconsistency between the neurological deficit and infarct areas, DW imaging must be repeated.

Ischemic changes in HIE initially affect the myelinization areas, including periventricular white matter, basal ganglia, internal capsules, and brain stem, which need the most oxygen (23). Vermeulen et al., (24) in their study to evaluate the locations of ischemic damage and the stage of HIE with using DW imaging, showed that periventricular white matter appeared to be involved in advanced HIE cases. All of the 5 advanced stage HIE cases with damage at this location died. Kaufman et al. (25) performed a similar study using conventional MR imaging. They realized that basal ganglia were not involved in mild HIE cases and concluded that the involvement of this area is relevant to the stage of HIE. An experimental study in which moderate hypoxia was created artificially in newborn rats showed that the cerebral cortex, thalamus, and basal ganglia are the most affected locations of the brain (26). However, in our study, there was no such relationship between the stage of HIE and involvement locations. White matter and basal ganglia involvement were present in all stages at different rates.

Knowing that diffusion restriction is not necessarily indicative of permanent damage, we concluded that the imaging findings in early phases might not always reflect prognosis. However in our study, DW images were evaluated visually. Measurements of the ADC values may give an idea of the prognosis of this disease by determining the severity of damage indirectly. Furthermore, advanced studies can clarify this latter subject.

The present study had some restrictions, such as limited number of cases, uneven stage distribution of the cases, lack of a control group, lack of ADC measurements, and choosing the b-value 1000 s/mm², instead of 750 s/mm². Robertson et al. (27) emphasized that conversely to the adult population, the max b value should be 750 s/mm² in neonates. They said that ADC values of neonates are higher than adults, and, therefore, using a higher b value decreases imaging quality by decreasing the signal/noise ratio. If we had used the b value as 750 s/mm², the imaging quality would have been better and more significant results would have been obtained. Additionally, if the ADC measurements had been done, possible qualitative visual reviewing mistakes due to reviewer error would have been eliminated and our results would have been repeatable and comparable to control groups. Apart from clinical researchs, ADC measurements of every neonate with HIE appears to be a challenge in routine clinical applications due to the time consuming nature of the process.

In conclusion, DW imaging is the preferred modality of imaging due to its fast imaging speed within seconds, and contrast material and radiation free nature. It is superior to the other imaging modalities in detecting ischemia, not only because of its high sensitivity in the early phase, but also due to its high sensitivity and specificity in the late phase. Furthermore, with its high negative predictive value, DW imaging can be used for excluding the possibility of sequelae development in HIE cases and, therefore, may be used for detecting sequelae not directly related to labor for medico-legal purposes.

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