Role of diffusion-weighted magnetic resonance imaging in detection of neonatal hypoxic-ischemic encephalopathy

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Background
Hypoxic-ischemic encephalopathy (HIE) is a critical pediatric disease with challenges in diagnosis. Many diagnostic tools have been used to diagnose this condition. Among all these tools, MRI with the advanced sequence; diffusion-weighted imaging (DWI) plays a more vital role in early detection of this condition. In this research we emphasized the role of DW-MRI in the diagnosis of HIE.

Aim of work
The aim of this work is to evaluate the role of DW-MRI in detection and grading of HIE.

Patients and methods
This is a prospective study performed for 1 year (from January 2017 to January 2018). The studied group included 20 full-term neonates admitted to NICU of Assiut University Hospital with provisional diagnosis of HIE. All patients underwent brain imaging by conventional and DW-MRI.

Results
There was a moderate significant agreement between conventional MRI and DWI ($P = 0.023$) regarding both diagnosis and grading of HIE.

Conclusion
MR-DWI is the preferred modality of imaging in diagnosis and grading of hypoxic-ischemic injury due to its high sensitivity and easy interpretation with no need for contrast administration.

Keywords:
apgar score, diffusion-weighted imaging, hypoxic-ischemic encephalopathy, magnetic resonance imaging, transcranial ultrasound

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Introduction

Hypoxic-ischemic encephalopathy (HIE) is a critical disease resulting in high neonatal morbidity and mortality [1] reaching 23 and 25%, respectively, with incidence reaches about 2.5 per 1000 term neonate and 7 per 100 preterm neonate [2]. It occurs due to decreased oxygenation in the blood (hypoxia) and insufficient cerebral blood flow (ischemia) leading to loss of normal cerebral autoregulation and brain injury [3].

Early and accurate diagnosis is essential to start early treatment and prognosis [1].

Clinical confirmation of ischemic damage is often difficult at this age because of nonspecific clinical features. In addition, clinical evaluation alone is often inadequate to provide an accurate prognosis [4].

Imaging modalities like ultrasound, computed tomography (CT) and conventional MRI play role in detection of brain changes, ultrasound is the first investigation of choice because of the low cost, portability, and availability [5], computed tomography is the least sensitive modality for the evaluation of hypoxic-ischemic injury (HII) because of high water content that results in poor parenchymal contrast resolution of neonatal brain. It also has the disadvantage of radiation exposure [6]. MRI has been established as a sensitive imaging tool to detect neonatal brain injury, and it plays an important role in prediction of neurologic outcome in neonates with HI brain injury, advanced imaging techniques such as diffusion-weighted imaging (DWI) is more sensitive to diagnose acute brain injury allowing early diagnosis and timely intervention [7].

Pathogenesis

Reduction of oxygenation in the blood (hypoxia) and insufficient cerebral blood flow (ischemia) leading to loss of normal cerebral autoregulation and brain injury [2], these circumstances result in HIE and brain damage (neuronal cell death).

Clinical manifestation

At delivery, HIE neonate may have low Apgar score (bradycardia, poor respiratory effort, hypotonia, decreased alertness, weak or absent cry, and abnormal skin color) and metabolic acidosis in cord blood. The infant usually develops seizure within first 24 h of life. Children with periventricular leukomalacia may develop spastic cerebral palsy. Basal ganglia and thalamic (BGT) involvement result in extrapyramidal symptoms. Multicystic encephalopathy is associated with quadriplegia, bulbar, and choreoathetoid symptoms [8].

Complication of hypoxic-ischemic encephalopathy

(1) CNS complication:
   (a) HIE may result in neonatal death (15.2%), may be manifested later as cerebral palsy, mental deficiency, and there may be focal or multifocal infarcts [9]
(2) Multiorgan dysfunction:
   Multiorgan systems involvement is a hallmark of HIE. Organ systems involved following a hypoxic ischemic events include the following:
   (a) Heart:
   Reduced myocardial contractility, severe hypotension, passive cardiac dilatation, and tricuspid regurgitation [10]
   (b) Lungs:
   Severe pulmonary hypertension [10]
   (c) Renal:
   Renal failure and significant water and electrolyte imbalances [10]
   (d) Liver:
   Elevated liver function, hyperammonemia, and coagulopathy
   (e) Gastrointestinal dysfunction:
   Poor peristalsis and delayed gastric emptying are common
   (f) Hematologic:
   Disturbances include increased nucleated red blood corpuscles, neutropenia, or neutrophilia, thrombocytopenia, and coagulopathy also noted [11,12].

Patients and methods

Twenty full-term neonates were admitted to NICU of Assiut University Hospital during the period from January 2017 to January 2018. The patients were provisional diagnosed of HIE after exposure to asphyxia. Their age ranged between 3 and 14 days old. All patients were transferred to the Radiology Department by ambulance and oxygen supply and underwent conventional and DW-MRI. The nature of the study was adequately explained to the parents, and an informed consent was obtained from all parents before participating in the study. History, clinical data as well as the clinical diagnosis according to Sarnat staging were obtained for each patient. Written consent was obtained from every neonatal relative included in this Study.

Inclusion criteria

(1) Full-term infants (gestational age >36 weeks)
(2) Within 14 days after birth
(3) Clinical suspicion of neonatal HIE based on:
   (a) Profound metabolic or mixed acidosis (pH>7.0) in umbilical cord arterial blood sample, or 1 h after birth in neonatal arterial blood
   (b) Persistent of Apgar score 0–3 for more than 5 min
   (c) Neurological manifestations in the immediate neonatal period to include; seizures, hypotonia, or coma
   (d) Evidence of multiorgan dysfunction in the immediate neonatal period.

Exclusion criteria

(1) Major congenital malformations
(2) Congenital infection
(3) Preterm neonates
(4) Metabolic disease
(5) When transfer of a neonate or doing MRI is technically difficult.

MRI examination

All patients were examined on a 1.5 T MRI scanner (Achieva; Philips medical systems, Best; The Netherlands) with a head coil. For sedation the neonates received chloral hydrate, 50–70 mg/kg 10–20 min before imaging.

Image acquisition

MRI protocol

A standard MRI protocol was applied to all participants in the research including the following steps and pulse sequences:

(1) T1WI: axial plain, TR/TE 450/15 ms, slice thickness 4 mm with interslice gap of 8 mm and matrix: 256×168
(2) T2WI: axial plain, TR/TE 4750/110 ms, slice thickness 4 mm with interslice gap of 8 mm and matrix: 224×224
(3) DWI: axial plain, TR/TE 5000/90 ms, slice thickness 4 mm with interslice gap of 8 mm and matrix: 112×96 at b values (0 and 1000) followed by computer-generated apparent diffusion coefficient (ADC) mapping of the brain.

MRI demonstrates five classical patterns of injury in hypoxic-ischemic encephalopathy in the term infant according to the site

The clinical pattern and imaging manifestations of HIE in term infants depend on the duration and severity of the hypoxic or ischemic insult.

(1) BGT pattern:
   (a) It is seen most commonly following a history of acute/profound asphyxia
   (b) Affecting the ventrolateral thalami and posterior putamina, peri-rolandic (somatosensory) cortex, and hippocampus often accompanied by internal capsule injury with loss of posterior limb of the internal capsule T1 hyperintensity
   (c) BGT pattern of injury is associated with severe long-term motor disability and cerebral palsy [13]
   (d) DWI is useful in the early days following a hypoxic-ischemic event and often depicts restricted diffusion within the first 24 h that gradually increases over the next several days [14]
(2) Watershed ischemia pattern:
   (a) This pattern is associated with a history of prolonged/partial hypoxic-ischemic insult and neonatal hypoglycemia [15]
   (b) Ischemia to the anterior cerebral artery/middle cerebral artery and middle cerebral artery/posterior cerebral artery watershed zones with predilection for the parasagittal cortex and parieto-occipital lobes
   (c) In the acute phase, this pattern of injury is often seen as corresponding restricted diffusion in the cortex and subcortical white matter
(3) White cerebrum (global injury):
   (a) History of prolonged HIE episode
   (b) Occurs with severe reduction in cerebral perfusion or hypoxia
   (c) Clinical and imaging manifestations are catastrophic
   (d) There is widespread injury to the BGT and diffuse involvement of the cortex and white matter, a severe pattern known as total brain injury, the normal-appearing cerebellum is useful
   (e) In these cases, the cerebral hemispheres demonstrate diffusely restricted diffusion and appear relatively hyperintense compared with the cerebellum, a finding known as the 'white cerebrum' sign [16]
(4) Scattered white matter injury:
   (a) Occurs with punctate ischemic
   (b) Periventricular distribution of punctate ischemic lesions on DWI usually associated with a more benign clinical course [17]
(5) Cerebral infarction: also termed perinatal arterial ischemic stroke and not dissimilar in MRI appearance to adult territorial embolic stroke [13].

Results

Baseline characteristics

Twenty full-term neonates; 14 (70%) male and six (30%) female (Table 1) with mean ± SD age of 7.7 ± 3.5 days (range, 3–14 days). Mean gestational age was 37.9 ±0.9 weeks (range, 37–40 weeks). Sixteen (80%) neonates had a history of obstructed vaginal delivery and four (20%) neonates with history of cesarean section delivery with exposure to risk factors of asphyxia.

Mean Apgar score reported is shown in Table 2.

Radiological characteristics

Ischemic damage to brain parenchyma was detected by conventional MRI in 13 (65%) studies out of 20 included at this study, while ischemic damage to brain parenchyma was detected by DW-MRI in 18 (90%) studies out of 20 studies included in Fig. 1.

Correlation between Apgar score and MRI findings

Correlation between 5 min Apgar score and MRI findings showed that 10 (50%) of DWI findings revealed mild to moderate HIE while five (25%) neonates of Apgar scoring revealed mild to moderate HIE, on the other hand eight (40%) neonates revealed severe HIE at DWI, while nine (45%) neonates detected severe by Apgar score. Two (10%) neonates

Table 1 The sex of the neonates included in this study (*n*=20)

Parameters	Mean/count	±SD/%	Range (minimum-maximum)
Age (days)	7.7	3.496	3-14
Sex			
Male	14	70	-
Female	6	30	-

Table 2 Clinical profile distribution among study population according to Apgar score at 5 min (N=20)

Parameters	Mean/count	±SD/%	Range (minimum-maximum)
Apgar score at 5 min			
Apgar score	4.45	2.625	0-9
Apgar grade [12,18]			
Scores ≥7; generally normal	6	30	-
Score of 4-6; fairly low	5	25	-
Scores ≤3; critically low, needs intervention	9	45	-

revealed normal by DWI, while six (30%) neonates had normal Apgar score (Table 3).

DWI showed better sensitivity in detection of ischemia at different regions as shown in Table 4. Although, *P* values showed insignificant results mostly due to small sample size at this study.

Two cases are discussed in details.

Case I: shown in Figs. 2 and 3.

Conventional MRI: normal findings as shown in Fig. 2a and b.

Table 3 Association between Apgar score grading within 5 min of birth compared with diffusion-weighted imaging grading among study population (*n*=20)

Parameters	Apgar score	DWI	*P*
Normal	6 (30)	2 (10)	0.794
Mild to moderate	5 (25)	10 (50)	
Severe	9 (45)	8 (40)	

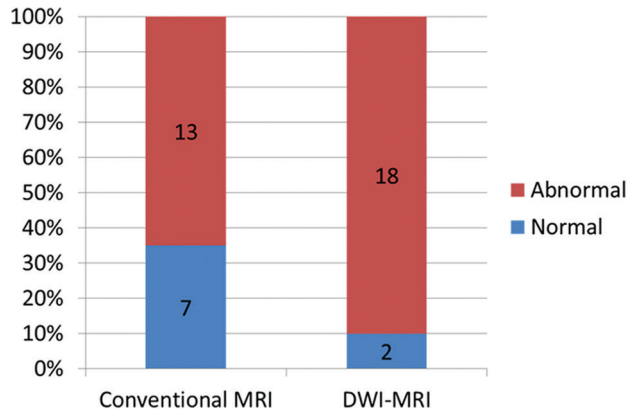
Cohen's kappa (κ) was run to determine if there was agreement between clinical and radiological grading. There was weak insignificant agreement between Apgar and DWI in the grading of HIE, κ=0.037, *P*=0.794.DWI, diffusion-weighted imaging; HIE, hypoxic-ischemic encephalopathy.

Table 4 Sensitivity of both conventional and diffusion-weighted MRI in detection of ischemia at multiple areas

	Conventional 13 abnormal (65%)	Total	*P**	DWI	
				Mild to moderate	Severe
Watershed area	2	11	0.004	8	3
DWM	7	9	0.687	5	4
PLIC	5	6	1	1	5
BGT	4	9	0.063	2	7
Corpus	0	5	NA	4	1
Cortex	4	9	0.180	7	2

BGT, basal ganglia-thalamus; DWI, diffusion-weighted imaging; PLIC, posterior limb of the internal capsule.

Figure 1



The percentage of the neonates with normal and abnormal MRI finding in both conventional and DW-MRI. DW, diffusion-weighted.

DW-MRI: there is abnormal high-signal intensity (restricted diffusion) seen at left posterior watershed area and left high parietal region with corresponding reduction in ADC values. Also restricted diffusion was seen at the anterior and posterior fibers of corpus callosum with corresponding reduction of ADC value as shown in Figs. 2c, d and 3.

Case II: shown in Figs. 4 and 5:

Conventional MRI: normal findings as shown in Fig. 4a and b.

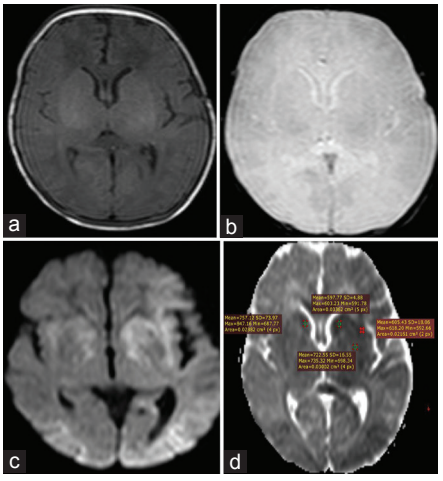
DW-MRI: shows abnormal high-signal intensity (as shown in Figs. 4c, d and 5) at:

(1) Basal ganglia bilaterally (lentiform and caudate nuclei) more significant at the left side with corresponding reduction at ADC value
(2) The ventrolateral aspect of both thalami more significant at the left side and left external capsule with corresponding reduction at the ADC value
(3) Posterior fibers of corpus callosum with corresponding reduction in ADC value
(4) High parietal parafalcine regions and occipital lobes bilaterally with corresponding reduction of ADC values.

Discussion

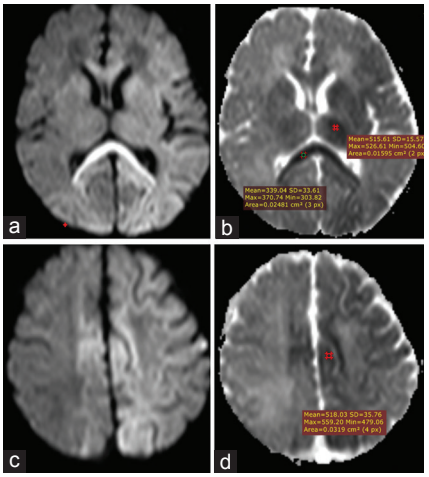
Conventional MRI may be normal despite significant brain injury, especially when imaging is performed early, during the first few days after onset [19].

Figure 2



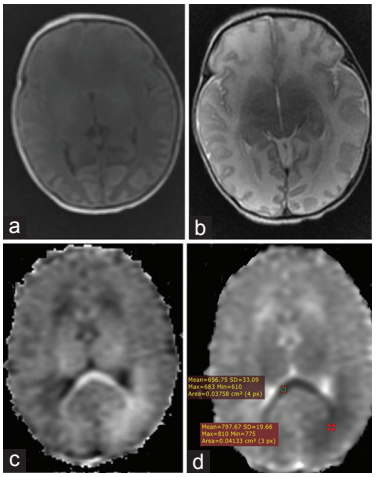
Findings noted in conventional MRI: (a) axial T1W and (b) axial T2 show normal conventional MRI study. Findings noted at DWI correlated with ADC map at the level of BG: (c) axial DWI showing hyperintense signal at both basal ganglia and external capsules more at the left side and (d) ADC map showing corresponding low ADC value at these areas. ADC, apparent diffusion coefficient; BG, basal ganglia; DWI, diffusion-weighted imaging.

Figure 3



Findings noted at DWI correlated with ADC map at the level of BG: (a) axial cut of DWI showing abnormal high-signal intensity at splenium of corpus callosum and ventrolateral aspect of the left thalamus and (b) ADC map there is also corresponding low ADC value at these areas. Findings noted at DWI correlated with ADC map at high parietal level: (c) axial cut of DWI showing abnormal high-signal intensity at high parietal parafalcine regions and (d) ADC map showing corresponding low ADC value. ADC, apparent diffusion coefficient; BG, basal ganglia; DWI, diffusion-weighted imaging.

Figure 4



Findings noted at conventional MRI: (a) axial T1W and (b) axial T2W show normal conventional MRI findings. Findings noted at DWI and ADC map at the level of BG: (c) axial DWI show abnormal high-signal intensity involving the posterior fibers of corpus callosum and the posterior watershed area at the left side and (d) ADC map showing low values at these areas. ADC, apparent diffusion coefficient; BG, basal ganglia; DWI, diffusion-weighted imaging.

DWI is a sensitive imaging modality to detect ischemic changes, in earliest phase; depending on early restricted diffusion within ischemic brain tissue. In addition, it provides quantitative ADC values within brain tissue [20].

Abnormal diffusion was seen in 18 out of 20 neonates who were involved in this study; with a sensitivity of about 90%. These findings are in concordance with results of several previous studies. Dag *et al.* [20] postulated that DWI is superior to other imaging modalities in detecting ischemia with no false-negative DWI results. The negative predictive value (NPV) of DWI in early as well as late phases was 100%.

Similarly, Huang and Castillo [19] and Soul *et al.* [21] reported that DWI was the most sensitive imaging modality for detecting HII in its acute period. Wolf *et al.* [3] found that DWI and ADC measurements are helpful in improving detection and depiction of extent of injury in the setting of acute and/or subacute HIE.

From this study, we can conclude that MR-DWI is the preferred modality of imaging of HII due to its high sensitivity and easy interpretation. This is in addition to being a fast imaging sequence, with no contrast administration. The combination of conventional-weighted images and DWI improve diagnostic value of MRI for evaluation of HIE. ADC values should always be interpreted in combination with visual analysis of both conventional and DWI, and timing of scan needs to be taken into consideration.

Liauw *et al.* [22] reported that DWI and T1WI can be chosen as a first step because of their best performance in individual injury patterns and generally good interobserver agreement. Huang and Castillo [19] suggested MRI protocol for HII including at a minimum (T1WI, T2WI, and DWI with corresponding ADC map).

Conclusion

MR-DWI is the preferred modality of imaging of HII due to its high sensitivity and easy interpretation. This is in addition to being a fast imaging sequence, with no contrast administration. The combination of conventional-weighted images and DWI improve diagnostic value of MRI for evaluation of HIE. ADC values should always be interpreted in combination with visual analysis of both conventional and DWIs, and timing of scan needs to be taken into consideration.

Limitations

The age of neonates at imaging ranged between 3 and 14 days. It would be useful to reduce time to imaging for early diagnosis and management, while the challenges were unstable neonates because of respiratory distress.

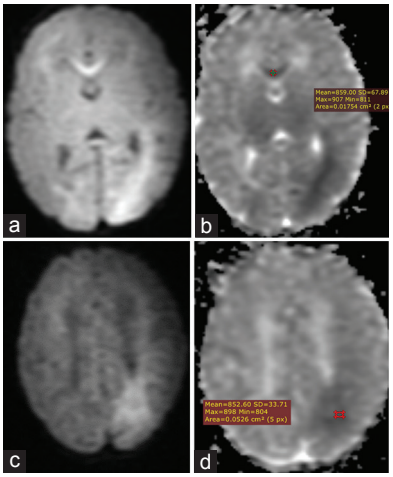
Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Figure 5



Findings noted at DWI correlated with ADC map at lower BG level: (a) axial DWI showing abnormal high-signal at anterior fibers of corpus callosum and (b) ADC map showing low ADC value at this area. Findings noted at DWI and ADC map at the level of corona radiata: (c) axial DWI showing abnormal high-signal at left high parietal region and (d) ADC map showing low ADC value at this area. ADC, apparent diffusion coefficient; BG, basal ganglia; DWI, diffusion-weighted imaging.

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