Original Article

Brain Diffusion Changes in Perinatal Asphyxia Cases

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Abstract

Background: Prolonged perinatal asphyxia (PA) may cause hypoxic-ischemic damage to the brain. The aim of this study was to investigate the brain diffusion changes of patients with PA and examine the relationship with brain damage. **Methods:** This retrospective study included 55 patients diagnosed with PA, separated into mild and severe PA groups. For the evaluation of brain damage in all the study neonates, brain and diffusion MRI scans were performed using a 3T device. The scans were taken between 5 and 10 days postnatal, after completion of hypothermia treatment, in accordance with the standard clinical protocol of our institution. Apparent diffusion coefficient (ADC) values of the lentiform nucleus, thalamus, frontal white matter, and posterior limbs of the internal capsule were measured. Minitab package programs and SPSS version 20.0 software were used for statistical analysis and graphic drawing. Spearman's rank correlation analysis was used. **Results:** The bilateral lentiform nucleus, thalamus, frontal white matter, and posterior limbs of the internal capsule ADC values were significantly higher in the severe PA group than in the mild PA group. **Conclusions:** In neonates with severe perinatal asphyxia, brain damage can be evaluated on diffusion-weighted imaging (DWI) of the cerebral deep white matter and basal ganglia. DWI, imaging with conventional brain MRI comes to the fore in clinical importance in PA patients.

Keywords: *Brain, diffusion-weighted magnetic resonance imaging, Perinatal asphyxia*

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Introduction

Despite follow-up and monitoring during the perinatal period, perinatal asphyxia (PA) and hypoxic-ischemic encephalopathy (HIE) remain serious problems.[1] Although short-term consequences such as death occur in 15-20% of severely asphyxiated infants, clinical conditions such as seizure, behavioral problems, cerebral palsy, and cognitive and neurodevelopmental disorders may occur in those who develop severe HIE, which determines the long-term prognosis.[2] Although it is more common in developing countries, PA is also seen in 1-5 of every 1000 live births in developed countries.[3]

Prolonged PA may cause hypoxic-ischemic damage to the brain and vital organs.[4] In the first 24-48 hours of an ischemic stroke, sodium, calcium ions, and water pass into the damaged neurons, resulting in cytotoxic cell swelling. Ischemia then peaks within 72-96 hours, leading to increased permeability and disruption of the blood-brain barrier (BBB), resulting in vasogenic edema.[5]

Conventional magnetic resonance imaging (MRI) alone may not be able to show brain damage secondary to hypoxia.[6] Diffusion-weighted imaging (DWI) is an advanced MRI technique based on the diffusion properties of water.[7] By understanding water movement in a pathological event, DWI provides qualitative information and the apparent diffusion coefficient (ADC) provides quantitative information. Moreover, vasogenic edema can be distinguished from cytotoxic edema.[8] Diffusion reflects the size, viscosity, and cellularity of

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the extracellular space. If cellularity increases, limited diffusion is detected, and if tissue damage occurs, relatively free diffusion is detected.[9]

The aim of this study was to compare the ADC values of patients with severe and mild perinatal asphyxia and examine the relationship with brain damage.

Materials and Method

Patient population, ethics approval, and data collection

A total of 55 patients with perinatal asphyxia (31 female and 24 male) underwent brain MRI in the hospital between January 2020 and December 2023.

The study included neonates of gestational age ≥ 36 weeks and ≤ 6 hours after birth, with cord blood gas or blood gas pH value ≤ 7.00 or BD value ≤ -16 mmol/L in the first hour after birth and a 10-minute Apgar score < 5. Neonates with moderate and severe encephalopathy according to Sarnat and modified Sarnat scoring were included.[10] The neonates were excluded from the study if medical records could not be accessed properly; if first six hours after birth passed; if they were born below 36 weeks and under 2000 g; if blood samples were not taken at the first six hours of life and/or blood samples were not taken immediately before the rewarming during therapeutic hypothermia (TH); if a definitive diagnosis could not be established; those with documented other conditions that might have caused neonatal encephalopathy (NE); those with mild NE (no TH required); those who developed a complication and/or had a risk of dying in the first 72 hours of life that might have required interruption and/or discontinuation of hypothermia for any reason; those with congenital metabolic diseases; those with a history of energy deficiency other diseases associated with early encephalopathy in sibling history and/or diagnosed in the family; those with severe head trauma and/or extensive intracranial bleeding, those with severe life-threatening coagulopathy; those with a history of maternal chorioamnionitis or infection, those with trisomy; and multiple organ anomalies.[11]

For the evaluation of brain damage in all the neonates included in the study, a brain MRI scan was performed using a 3T MRI device, at 5-10 days postnatal, after completion of hypothermia treatment, in accordance with the standard clinical protocol. The radiologist, blinded to the clinical status of the neonates, interpreted the MRI studies of these newborns and reported the severity of brain injury according to the MRI scoring system: basal ganglia/watershed score (BG/W score) 0 points for "normal," 1 point for "abnormal signal in the basal ganglia or thalamus," 2 points for "abnormal signal in the cortex," 3 points for "abnormal signal in the cortex and basal nuclei," and 4 points for "abnormal signal in the entire cortex and basal nuclei."[12] The MRI scoring was performed from the T1, T2, and diffusion-weighted images. The extent of brain damage was defined according to this scoring system, then the patients were separated into two groups of mild (MRI score 0-2) and severe PA (MRI score 3-4).[13] Based on this scoring system, we divided neonates into mild (grade 1: MRI score 0-2) and severe PA (grade 2: MRI score 3-4) groups.

MRI examination

All the brain MRI scans were performed on a 3T device (Siemens Magnetom Skyra, Erlangen, Germany) using a head/neck coil. Routine noncontrast brain MRI and DWI images were examined. All subjects underwent the same imaging protocol. The T1, T2, T2 tirm TRA dark-fluid sequences were acquired with the following parameters: T1 se tra sequence voxels size 0.9 × 0.9 × 5.0 mm, TR 370 ms, TE: 11 ms; T2 tse tra sequence voxels size 0.6 × 0.6 × 5.0 mm, TR 4540 ms, TE: 109 ms; T2 tirm TRA dark-fluid sequence voxels size 0.7 × 0.7 × 5.0 mm, TR 9140 ms, TE: 81 ms; T2 tse COR sequence voxels size 0.7 × 0.7 × 3.0 mm, TR 4060 ms, TE: 94 ms; T1 se SAG sequence voxels size 0.8 × 0.8 × 5.0 mm, TR 375 ms, TE: 11 ms. The diffusion-weighted sequences were acquired. ADC maps were created using the software.

Four different neuroanatomical locations were determined bilaterally in the brain for the neonates. These were automatically calculated from the regions of interest (ROIs) drawn on the ADC map by an experienced radiologist. A circular ROI was placed bilaterally on the frontal periventricular white matter, lentiform nucleus, thalamus, and posterior limbs of the internal capsule [Figure 1]. Similar ROIs were selected in all patients by a single radiologist blinded to the patient's clinical status. The mean values were calculated for each region.

The Local Ethics Committee granted approval for the study (decision number: 24.02.65, dated 18.03.2024).

Statistical analysis

Minitab package programs and SPSS version 20.0 software (SPSS Inc.) were used for statistical analysis and graphic drawing. Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test, and then the student's *t*-test or Mann-Whitney U-test was applied depending on distribution and homogeneity. Relationships between data were examined with the Pearson correlation test, and correlation coefficients (r) were extracted from Spearman analysis. The resulting

data were summarized in tables as a number, percentage, median (minimum-maximum), mean, and standard deviation (SD) values. A value of $P < 0.05$ was accepted as statistically significant.

Results

Evaluation was made of a total of 55 newborn infants with perinatal asphyxia, with an average age of 5-10 days. No statistically significant difference was detected between the severe and mild PA groups in terms of gender, birth week, and birthweight ($P > 0.05$).

Of the total 55 patients, 31 were girls (56.4%) and 24 were boys (43.6%). Twenty-eight were in the mild PA group (16 girls (57.1%) and 12 boys (42.9%)) and 27 were in the severe PA group. (15 girls (55.6%) and 12 boys (44.4%)) [Table 1].

The mean ADC values of the severe PA and mild PA groups are shown in Table 1.

In the severe PA group, the mean ADC values of the right-side lentiform nucleus, thalamus, frontal white matter, and posterior limb of the internal capsule were 1093.89 ± 58.57, 1033.33 ± 71.76, 1644.74 ± 146.57, and 1085.93 ± 107.14 (mean ± SD × 10^{-6} mm²/s), respectively. In the mild PA group, the mean ADC values of the right-side lentiform nucleus, thalamus, frontal white matter, and posterior limb of the internal capsule were 1037.43 ± 100.69, 972.11 ± 80.56, 1517.89 ± 239.32, and 1017.11 ± 91.74 (mean ± SD × 10^{-6} mm²/s), respectively. The right-side lentiform nucleus, thalamus, frontal white matter, and posterior limb of the internal capsule ADC values were significantly higher in the severe PA group than in the mild PA group (All of $P < 0.05$). [Table 1].

In the severe PA group, the mean ADC values of the left-side lentiform nucleus, thalamus, frontal white matter, and posterior limb of the internal capsule were 1094.96 ± 56.30, 1014.93 ± 61.40, 1656.93 ± 189.26, and 1080.67 ± 51.24 (mean ± SD × 10^{-6} mm²/s), respectively. In the mild PA group, the mean ADC values of the left-side lentiform nucleus, thalamus, frontal white matter, and posterior limb of the internal capsule were 1027.00 ± 109.04, 963.14 ± 89.88, 1526.00 ± 236.57, and 1026.21 ± 88.88 (mean ± SD × 10^{-6} mm²/s), respectively. The left-side lentiform nucleus, thalamus, frontal white matter, and posterior limb of the internal capsule ADC values were determined to be significantly higher in the severe PA group than in the mild PA group (All of $P < 0.05$). [Table 1].

In the mild PA group, a strong positive correlation was detected between the right-side lentiform nucleus and the right-side thalamus, frontal white matter, and posterior limb of the internal capsule (r = 0.939, $P < 0.001$; r = 0.891, $P < 0.001$; r = 0.932, $P < 0.001$, respectively).

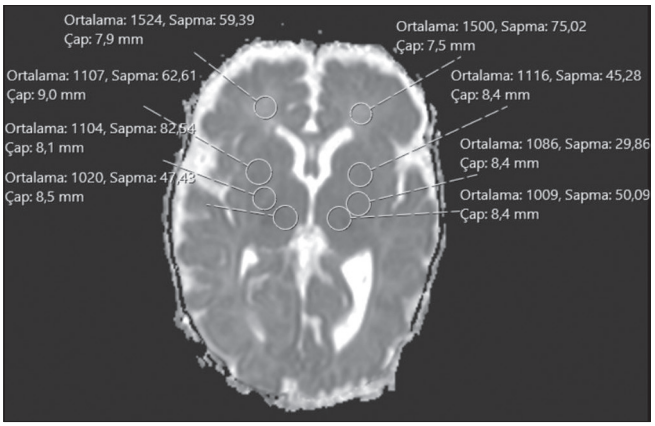

Figure 1: Apparent diffusion coefficient values in the 4 distinct localizations of the brain bilaterally in patients with mild and severe perinatal asphyxia

Table 1: ADC values (×10^{-6} mm²/s) of 4 brain regions of mild and severe perinatal asphyxia groups for each side and demographic characteristics

	Mean±SD		[a]*P*
	Mild perinatal asphyxia group (*n*=28)	Severe perinatal asphyxia group (*n*=27)	
Age (years)	38.17±1,12	38.00±1.03	0.61[a]
Birth weight (kilogram)	3.33±0.41	3,23±0.41	0,54[a]
Gender; *n* (%)			
Male	16 (%57.1)	15 (%55.6)	0.906[b]
Female	12 (%42.9)	12 (%44.4)	
Right			
Lentiform nucleus	1037,43±100,69	1093,89±58,57	0,025[a]
Frontal white matter	1517,89±239,33	1644,74±146,58	0,021[a]
Thalamus	972,11±80,57	1033,33±71,76	**0,004[a]
PLIC	1017,11±91,74	1085,93±107,14	0,017[a]
Left			
Lentiform nucleus	1027±109,04	1094,96±56,30	0,01[a]
Frontal white matter	1526±236,58	1656,93±189,27	0,012[a]
Thalamus	963,14±89,88	1014,93±61,41	0,021[a]
PLIC	1026,21±88,88	1080,67±51,24	**0,003[a]

[a]Student's *t*-test; [b]Pearson Chi-square test;**P<0.01.
PLIC: Posterior Limb of Internal Capsule

In the mild PA group, a strong positive correlation was detected between the right thalamus and the right frontal white matter and internal capsule posterior limb of the internal capsule (r = 0.850, $P < 0.001$; r = 0.862, $P < 0.001$, respectively).

In the mild PA group, a strong positive correlation was detected between the right frontal white matter and the right posterior limb of the internal capsule (r = 0.875, $P < 0.001$).

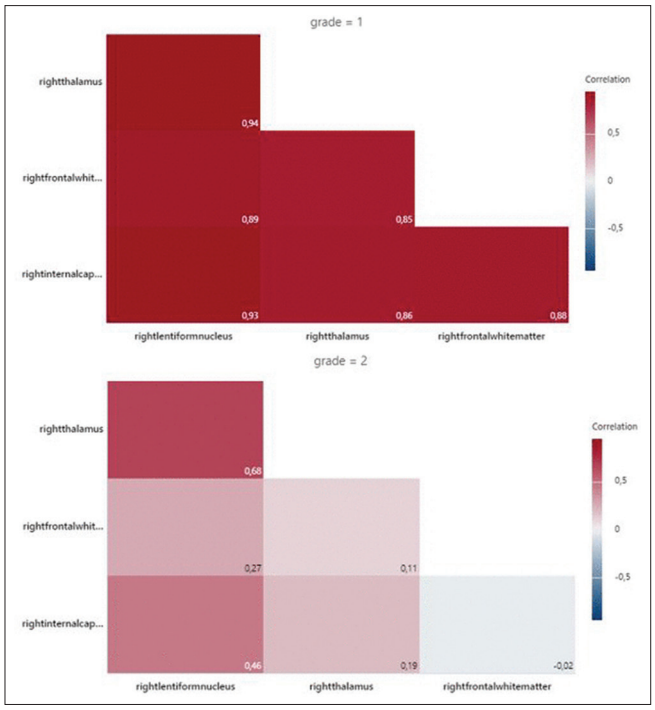

Figure 2: Correlation of ADC values of 4 distinct localizations on the right brain side of patients in the mild and severe PA groups

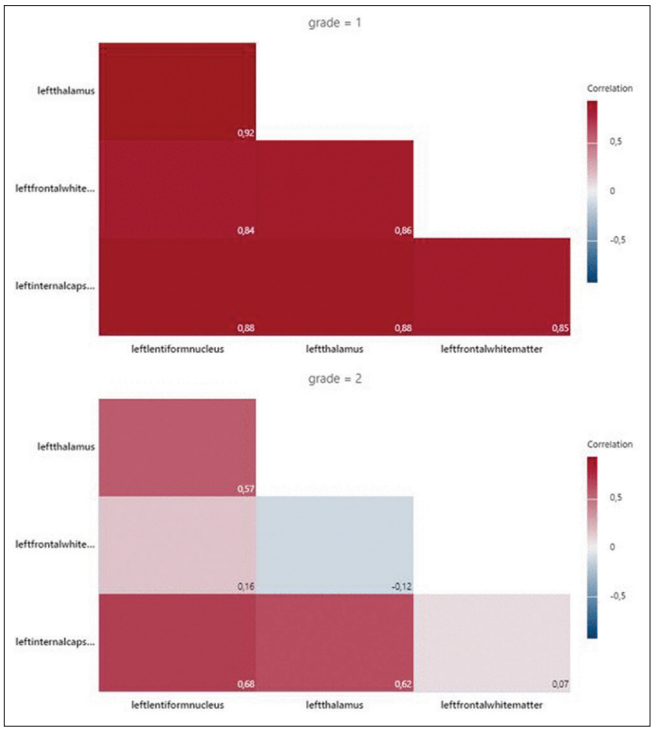

Figure 3: Correlation of ADC values of 4 distinct localizations on the left-brain side of patients in the mild and severe PA groups

In the severe PA group, a strong positive correlation was detected between the right lentiform nucleus and the right thalamus (r = 0.676, $P < 0.001$).

In the severe PA group, a moderate positive correlation was detected between the right lentiform nucleus and the right posterior limb of the internal capsule (r = 0.461, $P = 0.015$) [Figure 2].

In the mild PA group, a strong positive correlation was detected between the left lentiform nucleus and the left thalamus, frontal white matter, and posterior limb of the internal capsule (r = 0.923, $P < 0.001$; r = 0.841, $P < 0.001$; r = 0.884, $P < 0.001$, respectively).

In the mild PA group, a strong positive correlation was detected between the left thalamus and the left frontal white matter and posterior limb of the internal capsule (r = 0.861, $P < 0.001$; r = 0.885, $P < 0.001$, respectively).

In the mild PA group, a strong positive correlation was detected between the left frontal white matter and the left lentiform nucleus, thalamus, and posterior limb of the internal capsule (r = 0.841, $P < 0.001$; r = 0.861, $P < 0.001$; r = 0.854, $P < 0.001$, respectively).

In the mild PA group, a strong positive correlation was detected between the left posterior limb of the internal capsule and the left lentiform nucleus, thalamus, and frontal white matter (r = 0.884, $P < 0.001$; r = 0.885, $P < 0.001$; r = 0.854, $P < 0.001$, respectively).

In the severe PA group, a moderate positive relationship was detected between the left lentiform nucleus and the left thalamus (r = 0.568, $P = 0.002$).

In the severe PA group, a strong positive correlation was detected between the left lentiform nucleus and the left posterior limb of the internal capsule (r = 0.681, $P < 0.001$).

In the severe PA group, a moderate positive relationship was detected between the left thalamus and the left posterior limb of the internal capsule (r = 0j. 620, $P = 0.001$).

In the severe PA group, a strong positive correlation was detected between the left posterior limb of the internal capsule and the left lentiform nucleus (r = 0.681, $P < 0.001$).

In the severe PA group, a moderate positive relationship was detected between the left posterior limb of the internal capsule and the left thalamus (r = 0.620, $P = 0.001$) [Figure 3].

Discussion

In neonates with severe perinatal asphyxia, damage to the cerebral deep white matter and basal ganglia can be evaluated using DWI. In our study, ADC values of bilateral measurements in 4 different regions of the brain were higher in the severe PA group than in the mild PA group.

The ADC values of the bilateral lentiform nucleus, thalamus, frontal white matter, and posterior limbs of the internal capsule were significantly higher in the severe PA group than in the mild PA group.

It has been reported that the ADC values of white matter, basal ganglia, and thalamus in newborns with asphyxia are significantly reduced secondary to severe brain damage.[14] It has also been shown that ADC values were decreased in the perirolandic cortex, the posterior limb of the internal capsule, hippocampus, thalamus, and putamen,[15] and another study found significantly lower ADC values in the posterior limb of the internal capsule, frontal and parietal white matter. Calculating the ADC values, which can increase the visibility of hypoxic-ischemic damage in the acute and/or subacute period, has been shown to provide an objective measurement, and these findings have been attributed to the heterogeneity of injury patterns in patients.[16]

Two groups with favorable and adverse neurodevelopmental outcomes in newborns with hypoxic-ischemic encephalopathy after perinatal asphyxia were compared. The ADC values of the basal ganglia and thalamus measured after diffusion MRI within the first 7 days of life have been found to be significantly lower in PA with poor outcome ($P < 0.05$).[17]

Hypoxic-ischemic encephalopathy, which can lead to neurodevelopmental sequelae and cerebral palsy, is the name given later to cerebral encephalopathy associated with perinatal asphyxia.[18] Hypoxic-ischemic encephalopathy can range from temporary edema to infarction or necrosis. In these conditions, diffusion restriction develops as cytotoxic edema. Deep gray matter, which has high metabolic demands, is typically one of the most severely affected areas. These regions are considered classic, including the lentiform nucleus (globus pallidus and putamen), thalamus, caudate nucleus, and hippocampus. A combined edema (cytotoxic and vasogenic edema) pattern can be observed in some diseases such as hypoxic-ischemic encephalopathy, toxic conditions, infection, or inflammation.[19]

Brain edema due to ischemic stroke is initially caused by cytotoxic edema and the subsequent occurrence of vasogenic edema.[20]

Chien *et al.*[21] observed an increase in ADC in most subacute and chronic stroke patients. In the subacute stroke patient group, there was also observed to be an increase in ADC as time progressed in repeated diffusion measurements starting from the 10th hour. This increase in ADC was attributed to increased vasogenic edema developing hours or days after an ischemic event. In our study, ADC values of 4 different regions of the brain were higher in the severe PA group than in the mild PA group. It was consistent with the above study.

Ischemic stroke can be defined in periods of hyper-acute (0-6 hours), late hyper-acute (6-24 hours), acute (1-7 days), subacute (7-21 days), and chronic stroke (>21 days).[22] When hyper-acute ischemia develops in the brain, ischemic changes can be detected after a few minutes. During the first week (acute days 1–7), the infarcted parenchyma exhibits a low ADC signal, but the ADC values begin to increase by the end of the first week. In the subacute (7-21 Days) period, normalization of ADC may take 10 to 15 days. As the infarction progresses, it progresses to vasogenic edema and encephalomalacia.[23] In our study, increased ADC values in the cerebral deep white matter and basal ganglia are consistent with the timing of the above study.

Cerebral edema that develops after massive ischemic infarction can lead to mortality. The extent, type, and duration of ischemia of edema are associated with deaths occurring in the days after stroke.[24] The edema that occurs in the early stages of ischemia is limited to the intact BBB.[25] Damage to intercellular tight junctions at the endothelial level leads to BBB disruption. After an ischemic event, vasogenic edema progresses with maximum fluid extravasation within a period of 3 days to 2 weeks.[24] As a result of severe PA, fluid transfer to the extracellular space occurs due to damage to the blood-brain barrier. This explains the increase in ADC values in our study, consistent with the studies above.

Increased ADC values in patients with type 2 diabetes have been accepted as an indicator of vasogenic edema in the brain. Etiologically, hypoxia, atherosclerosis, and disruption of the blood-brain barrier are blamed.[26] Vasogenic edema develops as a result of blood-brain barrier disruption and hypoxia that occurs in severe PA. It explains the increase in ADC values in line with the above study.

In the current study, the ADC values measured bilaterally in 4 different brain regions were higher in the severe PA group. In the pathogenesis, increasing severity of brain damage leads to disruption of the blood-brain barrier, and this may also lead to an increase in extracellular water volume.

The primary limitation of this study was the lack of pathological correlation with imaging. A secondary limitation of this study is that comparison of MRI scores with clinical parameters of neonatal encephalopathy could not be made. Other limitations could be said to be the small patient population, and that follow-up MRI examinations could not be performed.

Conclusion

In neonates of severe perinatal asphyxia (PA), cerebral deep white matter and basal ganglia can be evaluated using DWI, which provides information about brain damage. DWI imaging with conventional brain MRI assumes greater clinical importance in PA patients. Nevertheless, there is a need for further studies on this subject using DWI.

Ethics Approval

Harran University Rectorate Non-Interventional Research Ethics Committee granted approval for the study (decision number: 24.02.65, dated: 18.03.2024).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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