ORIGINAL ARTICLE

Evaluating the Correlation between Brain Ultra Sonographic, Brain MRI, and Electroencephalography Findings and the Severity of Asphyxia and Neurodevelopment in Infants with Hypoxic-ischemic Injury

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Abstract

Objective

Hypoxia-ischemia-induced brain injury is a major cause of acute mortality and chronic neurological disability in infants and children. Imaging plays a vital role in diagnosing and treating hypoxic-ischemic encephalopathy (HIE) and as an adjunct to acute conditions and provides valuable information on long-term prognosis.

Materials & Methods

Our study was prospective with 50 neonates aged 34 weeks and older with HIE. Cerebral ultrasound and MRI were performed on the infants, and the pattern of lesions was recorded. A pediatric neurologist examined the infants, and their developmental status was assessed and recorded with electroencephalography (EEG) findings. The data were analyzed.

Results

The sonography pattern was normal in 26 (76.5%) term neonates, and also, the PVL pattern was observed in 10 term neonates. The incidence of observing an edema pattern (17.6%) was significantly different between the term and pre-term infants (P-value = 0.001). MRI findings were normal in 20 (58.8%) term neonates and 11 premature neonates. However, the PVL pattern was observed in MRI performed in six term neonates (6.6%). The watershed pattern (17%) showed that these differences were significant between the term and pre-term infants (P-value = 0/001).

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Conclusion

Normal sonography was significantly higher in neonates with normal neurodevelopment than in patients with normal MRI and EEG findings but with poor neurodevelopment. Also, the probability of having normal MRI results was lower in neonates with moderate to severe asphyxia compared to ultrasound and EEG.

Introduction

Hypoxia-ischemia-induced brain injury is a common cause of short-term mortality and long-term neural morbidity in infants and children (1). Statistics point toward an incidence ratio of 20 cases of systemic asphyxia in every 1000 live births in term newborns. Between 5 to 20 percent of newborns suffering from asphyxia and brain damage from hypoxia-ischemia eventually die in early childbirth (2). At delivery, hypoxic-ischemic encephalopathy (HIE) neonates may have a low Apgar score (bradycardia, poor respiratory effort, hypotonia, decreased alertness, weak or absent cry, and abnormal skin color) and metabolic acidosis in cord blood (3).

Imaging plays an important role in the diagnosis and treatment of HIE. In acute conditions, it can act as a guide for proper management and provide us with helpful information regarding the long-term prognosis of the said cases4. Brain Sonography and MRI are routinely used to observe intracranial alterations in newborns with hypoxic-ischemic injury5. MRI is the most useful of the two in diagnosing hypoxic-ischemic lesions in the brain of the suffering newborn, and it has been, therefore, incrementally used to evaluate such lesions (6, 7). State-of-the-art techniques in MRI, including DWI, can more easily point out both focal and multifocal lesions, such as strokes and white matter damage or any cortical damage, than CT or conventional MRI. The reason is that conventional MRI sequences are normal in the first 48 hours after the hypoxic-ischemic event. In contrast, the DWI and ADC map can demonstrate any possibly existing abnormality sooner and probably in the first 24 hours8, 9. To confirm the diagnosis and determine the size of the lesion, MRI and DWI should optimally be taken on days 3-5 of full-term newborns with encephalopathy (8-10).

MRI is the method of choice in the selective evaluation of newborns with hypoxic-ischemic encephalopathies. However, due to limitations regarding its use, sonography is still the ongoing first diagnostic step in the imaging diagnosis and screening in conditions of hypoxia, especially in newborns severely suffering from encephalopathies. The reason is that such newborns cannot be transported for MRI, and thus, it cannot provide us with crucial first-hand information on

the course of encephalopathy and the site of the lesion (11, 12). Although several lesions can solely be detected in MRI and not in sonography, the latter is the complementary role-playing method besides MRI in evaluating newborns with encephalopathy (13).

The most common findings in brain sonography in newborns with hypoxic-ischemic damage are brain edema with increased echogenicity of the subcortical white matter and increased echogenicity of the brain with or without the ability to differentiate white from gray matter and involvement of basal ganglia. Intraventricular hemorrhage is also detected in such cases. However, this finding is relatively uncommon14, 15. Patterns of injury on MRI are defined based on the predominant site of injury: Watershed predominant, basal ganglia/thalamus predominant, normal, and PV, and involvement of basal ganglia/thalamus in MRI are predictors of abnormal outcome (15).

Although sonography has a lower accuracy than MRI, studies showed compatibility regarding findings in newborns with HIE in both methods3, 16. As mentioned previously, emergent diagnosis and evaluation of the prognosis are vital (17). Therefore, intermittent evaluation with imaging and electroencephalography (EEG) must be done as they may help choose the best appropriate primary intervention, required recovery in cases where necessary, and even predict potential adverse outcomes (18).

Brain sonographic findings are essential in the early and easy prediction of HIE outcomes and assist as a standard in determining the prognosis and the decision regarding whether to start the neuroprotective therapy (19). For instance, one study showed a correlation between brain edema, thalami, and basal ganglia damage as findings in

sonography and spastic quadriparesis and severe damage in mental development in the first year of studied patients (20).

MRI, compared to sonography, is a better method to predict ischemic encephalopathy outcomes and, therefore, will be preferred in the future. With new MRI techniques being introduced, it can increasingly be used as the primary biomarker of outcomes and neural development in neuroprotective strategies3, (15-22).

EEG is also a reliable predictor of outcome in HIE23, 24. A normal EEG in a newborn with HIE is associated with good neurological outcome and abnormality, and the severity of electrographic findings on encephalography for HIE correlated with the extent of the injury on brain magnetic resonance imaging (16, 18).

This study aimed to determine the correlation between brain sonographic, MRI, and EEG findings and the severity of asphyxia and neurodevelopment in newborns with HIE. The purpose was to determine the modality better to use in primary diagnosis, assist with choosing the proper primary intervention, and predict the prognosis and long-term outcomes.

Materials & Methods

This prospective study included 50 newborns with a gestational age of 34 weeks and higher with HIE. A neonatal subspecialty physician determined the dysfunction clinically by taking the required history of the patients and examining them physically. The patients were admitted to the NICU department of the Afzalipoor Hospital in 2018 and enrolled from available cases based on the severity of their encephalopathy using the Sarnat and Sarnat Table. This table is a criterion-based method of classifying HIE, introduced, developed, and first

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used by M.S Sarnat and H.B Sarnat in 197625. In this classification, seven groups are determined via symptoms and signs, and then the severity of their encephalopathy is labeled in three levels, including mild, moderate, and severe, and then documented.

Inclusion Criteria: History of asphyxia/gestational age of 34 weeks and higher

Exclusion Criteria: Suffering from known genetic and structural disorders/metabolic diseases or prior history of trauma in the patient

Brain sonography started at birth was obtained by the neonatal subspecialty, and the pattern of involvement was documented.

Brain MRI was obtained from the cases on the 15th day of birth. A radiology specialist and a resident reported the obtained T1/T2 sequences and DWI, and the involvement pattern was documented.

A pediatric neurologist visited the newborns at 15 days of age monthly, and their developmental status was evaluated using the Bayley Criteria and documented with the EEG taken from them.

The Bayley Criteria is a standard method for evaluating the neural development in newborns and infants, which was first used by Nancy Bayley, an American psychologist, to assess the development of infants and newborns in the age range of 1-42 months (26). In this method, children are evaluated in five key developmental groups: Cognitive, Social and Emotional, Speech, Motor, and Behavioral.

The patients' information, including date of birth, sex, presence of seizure, brain sonographic findings, brain MRI findings, and EEG findings, was collected using the Radiology Resident and included in the information paper of each patient. The statistics adviser analyzed the obtained data; Qualitative data were analyzed with Chi-squared or Fisher's exact test, and quantitative data were analyzed with Wilcoxon rank-sum test. It was used from logistic regression for the evaluation of relationships.

Results

Our study investigated 50 neonates aged 34 weeks and older with HIE. The results showed that the sonographic patterns were normal in 26 (76.5%) term newborns, while the periventricular leukomalacia (PVL) pattern was noted in 10 pre-term newborns. On the sonography of term newborns, six (17.6%) had the "edema" pattern, and the difference between the two groups was statistically significant (P-value=0.001) (Table 1). Also, the results regarding sonography patterns were not significantly different (P-value=0.721) between males and females (Table 1).

The results also showed that sonographic patterns based on the normality or abnormality of EEGs in the newborns were not significantly contrasting, as 74.1% of those with normal EEGs had normal sonographies, and 53.8% of those with abnormal EEG patterns had normal sonographies (P-value=0.216) (Table 1).

Sonographic findings were normal in 56.4% of newborns with abnormal neural development. The PVL and edema patterns were noted in 28.2% and 12.8% of newborns, respectively. There was no significant correlation between the sonographic findings and the neural development when analyzed statistically (P-value=0.127) (Table 1).

Also, normal sonographies were observed in 66.7% of newborns with asphyxia but in 51.9% of them with severe asphyxia, although not statistically significant (P-value=0.125) (Table 1).

The results showed that MRI findings were normal in 20 (58.8%) term newborns, and the PVL pattern was noted in 11 pre-term newborns. Also, the

watershed pattern was noted on the MRI of six (17.6%) term newborns. These differences were statistically significant between the two groups (P-value=0.001) (Table 2).

Regarding gender, the findings on MRI were not statistically different between the males and females(P-value=0.823) (Table 2).

The MRI results, when assessed regarding the normality or abnormality of EEGs, showed significant contrast between the two groups, as 63% of those with normal EEGs had normal MRIs and 26.9% of those with abnormal EEGs had normal MRIs (P-value=0.019) (Table 2).

Of those with desired neural development, 78.6% had normal MRI, and 14.3% had the watershed view. In those with undesired neural development, 33.3% had normal MRI, and 33.3% had the PVL view, showing a significant correlation between MRI and neural development (P-value==0.017) (Table 2).

In those with moderate asphyxia, 44.4% had normal MRI, and in those with severe asphyxia, 29.6% had normal MRI. Also, MRIs were normal in all those with mild asphyxia, and these differences were statistically significant (P-value=0.004) (Table 2).

However, no significant correlation was observed between the newborns' neural development and gestational age. Moreover, 70.6% of the term neonates had undesirable neural development, while 78.9% of the pre-term newborns had undesirable neural development (P-value=0.508) (Table 3).

Neural development also had no significant correlation with gender. Undesirable neural development was observed in 73.1% of male newborns but 74.1% of female newborns (P-value=0.934) (Table 3).

Desirable neural development was observed in 48.1% of those with normal EEG patterns, whereas it was observed in only 3.8% of those with abnormal EEGs, significantly different (P-value=0.001) (Table 3).

In newborns with mild asphyxia, only one (12.5%) had undesirable neural development, whereas 66.7% and 96.3% of newborns with moderate and severe asphyxia had undesirable neural developments, respectively, which was significantly different (P-value=0.001) (Table 3).

Also, the EEG results had a significant correlation with the severity of asphyxia as in those with moderate asphyxia, 88.9% had normal EEG patterns, whereas, in those with severe asphyxia, 88.9% had abnormal EEG patterns (P-value=0.001) (Table 4).

Table 1. Comparing Sonographic Patterns Based on Gestational Age, Gender, EEG, Neurodevelopment, and Severity of Asphyxia

Brain us		Normal	PVL	BGT(Basal Ganglia-Thalamus)	Edema	P-value
Gestational Age	Term	26(76.5%)	1(2.9%)	1(2.9%)	6(17.6%)	0.001
	Pre-term	8(42.1%)	10(52.6%)	0(0)	1(5.3%)	
Gender	Female	16(61.5%)	5(18.5%)	0(0%)	4(14.8%)	0.721
	Male	16(61.5%)	6(23.1%)	1(3.8%)	3(11.5%)	
EEG	Normal	20(74.1%)	3(11.1%)	0(0%)	4(14.8%)	0.216
	Abnormal	14(53.8%)	8(30.8%)	1(3.8%)	3(11.5%)	
Neural Development	Normal	12(85.7%)	0(0)	0(0)	2(14.3%)	0.127
	Abnormal	22(56.4%)	11(28.2%)	1(2.6%)	5(12.8%)	
Severity of Asphyxia	Mild	8(100%)	0(0)	0(0)	0(0)	0.125
	Moderate	8(57%)	2(11.1%)	0(0%)	4(22.2%)	
	Severe	14(51.9%)	9(33.3%)	1(3.7%)	3(11.1%)	

Table 2. Comparing MRI Patterns based on Gestational Age, Gender, EEG, Neurodevelopment, and Severity of Asphyxia

Brain MRI		Normal	PVL	BGT(Basal Ganglia-Thalamus)	Watershed	P-value
Gestational Age	Term	20(58.8%)	20(58.8%)	20(58.8%)	6(17.6%)	0.001
	Pre-term	4(21.1%)	11(57.9%)	3(15.8%)	1(5.3%)	
Gender	Female	12(44.4%)	6(22.2%)	5(18.5%)	4(14.8%)	0.823
	Male	12(46.2%)	8(30.8%)	3(11.5%)	3(11.5%)	
EEG	Normal	17(63%)	5(18.5%)	1(3.7%)	4(14.8%)	0.019
	Abnormal	7(26.9%)	9(34.6%)	7(26.9%)	3(11.5%)	
Neural Development	Desirable	11(78.6%)	1(7.1%)	0(0)	2(14.3%)	0.017
	Undesirable	13(33.3%)	13(33.3%)	8(20.5%)	5(12.8%)	
Severity of Asphyxia	Mild	8(100%)	0(0)	0(0)	0(0)	0.004
	Moderate	8(44.4%)	4(22.2%)	1(5.6%)	5(27.8%)	
	Severe	8(29.6%)	10(37%)	7(25.9%)	2(7.4%)	

Table 3. Examining Neural Development Based on Gestational Age, Gender, EEG, and Severity of Asphyxia

Neural Development		Desirable	Undesirable	P-value
Gestational Age	Term	10(29.4%)	24(70.6%)	0.508
	Pre-term	4(21.1%)	15(78.9%)	
Gender	Female	7(25.9%)	20(74.1%)	0.934
	Male	7(26.9%)	19(73.1%)	
EEG	Normal	13(48.1%)	14(51.9%)	0.001
	Abnormal	1(3.8%)	25(96.2%)	
Severity of Asphyxia	Mild	7(87.5%)	1(12.5%)	0.001
	Moderate	6(33.3%)	1(3.7%)	
	Severe	12(66.7%)	26(96.3%)	

Table 4. Comparing EEG Results Based on Severity of Asphyxia

EEG	Severity of Asphyxia			P-value
	Mild	Moderate	Severe	
Normal	8(100%)	16(88.9%)	3(11.1%)	0.001
Abnormal	0(0)	2(11.1%)	24(88.9%)	

Discussion

This study showed that normal sonographic findings were significantly more prevalent in full-term newborns than those born prematurely, more than half of whom had abnormal findings. The majority had PVL patterns similar to a study by Bano et al. (3). Abnormal sonographic findings were more pronounced in newborns with severe asphyxia than others (most with severe asphyxia had the PVL pattern). However, normal sonographic findings in these patients based on the severity of their asphyxia were not significantly different. In contrast, in a study by Ghei et al., results based on their brain sonography in pre-term newborns with mild to moderate hypoxic-ischemic injury pointed toward periventricular leukomalacia and germinal matrix hemorrhage and in term newborns in the parasagittal areas (17).

However, sonographic findings showed no differences between males and females or normal and abnormal EEG findings. Abnormal sonographic findings were higher in newborns with abnormal neural development than those with normal development. However, this contrast was not definitive when analyzed statistically.

This study showed that more than half of those with normal EEG patterns had normal MRI, and only 26.9% of those with abnormal EEGs had normal MRI. Also, Obeid et al.'s study showed similar results: The abnormality and severity of electrographic findings on encephalography for HIE correlated with the extent of the injury on brain magnetic resonance imaging (27).

In those with desirable neural development, 78.6% had normal MRI, and 14.3% had the watershed view. Also, in those with undesirable neural

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development, 33.3% had normal MRI, and 33.3% had the PVL view. However, many studies have found that basal ganglia/watershed patterns are an excellent predictor of the neurological outcome (11, 27-29).

In newborns with varying amounts of asphyxia, MRI findings were also relatively and significantly contrasting as those with mild asphyxia had normal MRI findings. Also, approximately half of those with moderate asphyxia had normal MRIs, whereas those with severe asphyxia had abnormal MRIs, and most of the cases with severe asphyxia had PVL patterns. At the same time, it was incompatible with Alexopoulou et al.'s study, showing that severe asphyxial events in term neonates resulted in a primarily central pattern of injury involving the deep gray matter (19).

Normal EEG patterns were significantly more evident in newborns with desirable neural developments than in those with abnormal EEG patterns, and only one patient with desirable development had an abnormal EEG. Also noted is that undesirable neural development was significantly more pronounced in those with moderate and severe asphyxia than in others. EEG patterns also had a significant correlation with the severity of asphyxia, as 88.9% of those with moderate asphyxia were normal. However, in 88.9% of those with severe asphyxia, EEG patterns were abnormal. In a study carried out by Miller et al., normal or slightly abnormal EEG patterns in those with HIE, especially when accompanied by normal imaging findings, were associated with desired outcomes, and those with moderate to severe abnormal EEGs with multifocal or diffuse lesions or with involvement of the profound gray matter were associated with undesirable outcomes18. In Jose et al.'s study, normal EEGs

were associated with good neurologic outcomes, and severe suppressions in EEG patterns indicated more undesirable outcomes16. Our study's results were compatible and showed that abnormal EEG findings in newborns with undesirable neural development were more pronounced and evident, especially in neonates born who had a gestation age of 34 weeks and higher with HIE. Therefore, our study could reconfirm this fact in a different geographic population, indicating that the use of brain MRI as a routine modality in the diagnostic and follow-up approach of neonates with HIE is of significant benefit.

In Conclusion

This study showed that brain MRI was a better modality than ultrasound and EEG for diagnosing and predicting neurodevelopment in neonates with HIE.

One of the limitations of our study was that MRI was difficult to perform during the acute stage since it took almost an hour and needed deep sedation, which is risky in asphyxiated babies. The other limitation was that we sometimes could not match the times of all modalities together for each patient. The strength of our work was that we used three modalities together, and we could be able to compare them for evaluating and distinguishing the best one for predicting neurodevelopment outcomes and early management in newborns with HIE.

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Author's Contribution

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.
Ethics approval: This study was approved by the Ethics Committee of Kerman University of Medical Sciences (License: IR.KMU.AH.REC.1397.058).
Availability of data and materials: The dataset resulting from this article's findings is available upon request to the corresponding author, Mahsa Sirooee Nejad.

Conflict of interest

None

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