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ROLE OF MAGNETIC RESONANCE IMAGING AND MAGNETIC RESONANCE SPECTROSCOPY IN EPILEPTIC CHILDREN WITH A HISTORY OF PERINATAL ASPHYXIA: A COMPREHENSIVE STUDY

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Abstract

Introduction: Perinatal asphyxia (PA) is a significant cause of neurological morbidity, with epilepsy being a common sequel. Advanced neuroimaging techniques like Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) are crucial for evaluating brain injury in these children. ***Objective:*** To characterize the structural and metabolic brain alterations in children with epilepsy and a history of PA. ***Methods:*** This cross- sectional study was conducted at Popular Diagnostic Center (Badda), Ibne Sina Diagnostic & Consultation Center (Uttara), Popular Diagnostic Center (Shantinagor), Dhaka, Bangladesh, from July 2018 to December 2019. A total of 153 children with epilepsy and a documented history of PA were enrolled using purposive sampling. All participants underwent detailed clinical evaluation and neuroimaging comprising brain MRI and single- voxel MRS. The collected data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23.0. ***Results:*** Analysis of 153 children revealed structural brain abnormalities on MRI in 89.5%, primarily periventricular leukomalacia (41.2%), which correlated with seizure type ($p=0.008$). MRS showed significant metabolic derangements, including reduced NAA/Cr and elevated Cho/Cr ratios ($p<0.001$). A lactate peak was detected in 52.3% of those with abnormal MRIs and was strongly associated with drug-resistant epilepsy ($p=0.003$), indicating severe, ongoing metabolic dysfunction. ***Conclusion:*** The combined application of Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy effectively delineates the structural and metabolic sequelae of perinatal asphyxia in the epileptic brain, providing crucial biomarkers for prognosis and management in affected children.

Keywords: Epilepsy, Magnetic resonance imaging, Magnetic resonance spectroscopy, Neuroimaging, Perinatal asphyxia, Seizure, Sequelae

INTRODUCTION

Perinatal asphyxia (PA), a condition characterized by impaired gas exchange leading to fetal hypoxia and acidosis, remains a significant cause of global neonatal mortality and long-term neurological morbidity [1]. Despite advances in obstetric and neonatal care, it continues to be a major public health concern, particularly in developing nations, with an estimated incidence of 2 to 10 per 1000 live births [2,3]. The hypoxic-ischemic insult during this critical period can trigger a cascade of cellular events, resulting in selective neuronal injury to vulnerable regions of the developing brain, such as the basal ganglia, thalamus, and cerebral white matter [4]. One of the most prevalent and debilitating sequelae of PA is the development of epilepsy [5]. The risk of epilepsy in children with a history of hypoxic- ischemic encephalopathy (HIE) is substantially higher than in the general pediatric population, with studies reporting incidences ranging from 15% to 40% depending on the severity of the initial injury [6,7]. The resulting epilepsy is often difficult to manage, frequently presenting as drug-resistant seizures that significantly impair the child's neurodevelopmental progress and quality of life [8]. Understanding the underlying neuropathological substrates is therefore crucial for prognostication and developing targeted therapeutic strategies. In this context, neuroimaging has become an indispensable tool. Magnetic Resonance Imaging (MRI) is the gold standard for visualizing the structural consequences of PA, allowing for the detailed characterization of brain injuries, including patterns like periventricular leukomalacia (PVL), watershed infarctions, and lesions in the deep gray matter nuclei [9,10]. Conventional MRI provides exceptional anatomical detail, but it may not fully capture the ongoing metabolic dysfunction that underpins epileptogenesis. Magnetic Resonance Spectroscopy (MRS), a non-invasive technique that quantifies cerebral metabolites, offers a powerful complement to structural imaging. By measuring key neurometabolites such as N-acetylaspartate (NAA, a marker of neuronal integrity), choline (Cho, involved in membrane turnover), creatine (Cr, a reference for energy metabolism), and lactate (Lac, an indicator of anaerobic glycolysis), MRS provides a unique window into the biochemical milieu of the brain [11,12]. In the setting of PA, MRS can detect persistent metabolic alterations that may not be evident on MRI, serving as a sensitive biomarker for the severity of the initial insult and the risk for subsequent neurological sequelae, including epilepsy [13]. While numerous studies have utilized either MRI or MRS in the acute neonatal phase of HIE, there is a relative paucity of research that comprehensively integrates both these advanced modalities in older children who have already developed epilepsy as a direct consequence of PA. Most existing literature from the 2014-2019 period focuses on early prediction of outcomes in neonates, leaving a gap in the characterization of the chronic, established brain injury in the epileptic pediatric brain. Therefore, this study was designed to bridge this gap by conducting a comprehensive evaluation of both the structural (via MRI) and metabolic (via MRS) profiles of the brain in children with epilepsy and a documented history of perinatal asphyxia [14]. We aimed to systematically describe the spectrum of MRI abnormalities, quantify the associated metabolic derangements via MRS, and explore the correlation between these neuroimaging findings and the clinical characteristics of epilepsy in this specific patient population.

METHODOLOGY

Study population: This cross-sectional study was conducted at Popular Diagnostic Center (Budda), Ibne Sina Diagnostic & Consultation Center (Uttara), Popular Diagnostic Center (Shantinagor)**,** Dhaka, from July 2018 to December 2019.. A total of 153 children, aged between 2 and 12 years, with a clinical diagnosis of epilepsy and a history of perinatal asphyxia were enrolled.

Inclusion criteria: Participants were included based on the following criteria: (1) a confirmed history of moderate to severe perinatal asphyxia, documented by an Apgar score of ≤6 at 5 minutes and/or evidence of hypoxic-ischemic encephalopathy (HIE) in the neonatal period; and (2) a subsequent diagnosis of epilepsy by a pediatric neurologist, with at least two unprovoked seizures.

Exclusion criteria: Children were excluded from the study if they had: (1) epilepsy attributed to other causes such as CNS malformations, metabolic disorders, or traumatic brain injury unrelated to birth; (2) a contraindication to MRI; or (3) an inability to complete the imaging protocol due to uncontrolled seizures or agitation.

Study procedure: A purposive sampling technique was employed. After obtaining informed parental consent, all participants underwent a detailed clinical evaluation followed by a standardized neuroimaging protocol on a 1.5T MRI scanner. The protocol included conventional brain MRI sequences (T1W, T2W, FLAIR) and single-voxel Magnetic Resonance Spectroscopy (MRS) with voxels placed in the basal ganglia and parieto-occipital white matter.

Data analysis: The collected imaging and clinical data were systematically compiled. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 23.0. Descriptive statistics were used to summarize demographic and clinical variables. The relationships between neuroimaging findings and clinical data were analyzed using appropriate tests, with a p-value of <0.05 considered statistically significant.

RESULT

The study analyzed a total of 153 children with epilepsy and a history of perinatal asphyxia. The cohort had a mean age of 5.8 ±2.7 years, with a male predominance (59.5%, n=91). Focal seizures were the most common type, observed in 44.1% of the participants, followed by generalized seizures (35.3%) and epileptic spasms (20.6%). Brain MRI revealed that the vast majority of patients (89.5%, n=137) exhibited identifiable structural abnormalities (Figure 1). The most prevalent finding was periventricular leukomalacia (PVL), present in 41.2% of the children. This was followed by cortical and subcortical atrophy (28.1%) and injuries to the deep gray matter structures, specifically the basal ganglia and thalamus (20.3%). A small proportion of patients (10.5%, n=16) had a normal MRI study. The distribution of these abnormalities showed a significant association with the predominant seizure type ($p = 0.008$). PVL was most frequently linked with focal seizures, while basal ganglia and thalamic lesions were more common in children presenting with epileptic spasms. Magnetic Resonance Spectroscopy provided critical metabolic insights. In regions with visible MRI abnormalities, significant metabolic alterations were consistently detected (Figure 2). The NAA/Cr ratio was markedly reduced (mean 1.28 ±0.31) compared to both normal-appearing regions in the same patients and the control values from normal brain tissue ($p <0.001$). Concurrently, the Cho/Cr ratio was significantly elevated (mean 1.45 ±0.29, $p < 0.001$). A particularly noteworthy finding was the presence of a detectable lactate doublet in 52.3% of the patients with abnormal MRI scans, a metabolite not observed in normal brain spectra. Further analysis of MRS data stratified by MRI findings revealed a clear gradient of metabolic injury. Patients with normal MRI had metabolite ratios closest to normal values. Those with PVL showed moderate derangements, while the most severe metabolic disturbances, characterized by the lowest NAA/Cr and highest Cho/Cr ratios, were observed in the group with basal ganglia and thalamic injuries (Figure 2). The difference in mean NAA/Cr ratios across these different MRI finding groups was statistically significant ($p <0.001$). Furthermore, the presence of a lactate peak was strongly associated with more severe epilepsy, defined as resistance to two or more antiseizure medications ($p = 0.003$).

Table 1: Demographic and clinical characteristics of the study population (N=153)

Characteristic	Category	n (%)
Gender	Male	91 (59.5)
	Female	62 (40.5)
Seizure type	Focal	67 (44.1)
	Generalized	54 (35.3)
	Epileptic spasms	32 (20.6)
Epilepsy severity	Drug-responsive	84 (54.9)

	Drug-resistant	69 (45.1)

Table 2: Distribution of primary MRI findings and association with seizure type

Primary MRI finding	Total (N=153)	Focal (n=67)	Generalized (n=54)	Spasms (n=32)	p-value
	n (%)				
Normal MRI	16 (10.5)	8 (11.9)	7 (13.0)	1 (3.1)	0.008
Periventricular leukomalacia	63 (41.2)	35 (52.2)	20 (37.0)	8 (25.0)	
Cortical/Subcortical atrophy	43 (28.1)	15 (22.4)	18 (33.3)	10 (31.3)	
Basal ganglia & Thalamic lesions	31 (20.3)	9 (13.4)	9 (16.7)	13 (40.6)	

Data analysis test: Chi-square test

Table 3: Magnetic resonance spectroscopy metabolite ratios stratified by MRI findings

MRI Finding group	n	NAA/Cr ratio	Cho/Cr ratio	Presence of lactate peak
		Mean ± SD		n (%)
Normal MRI	16	1.62 ± 0.18	1.05 ± 0.15	0 (0.0)
Periventricular leukomalacia	63	1.35 ± 0.25	1.42 ± 0.24	28 (44.4)
Basal ganglia & Thalamic lesions	31	1.11 ± 0.22	1.61 ± 0.26	22 (71.0)
p-value		< 0.001	< 0.001	< 0.001

Data analysis test: One-way ANOVA for ratios; Chi-square test for lactate presence

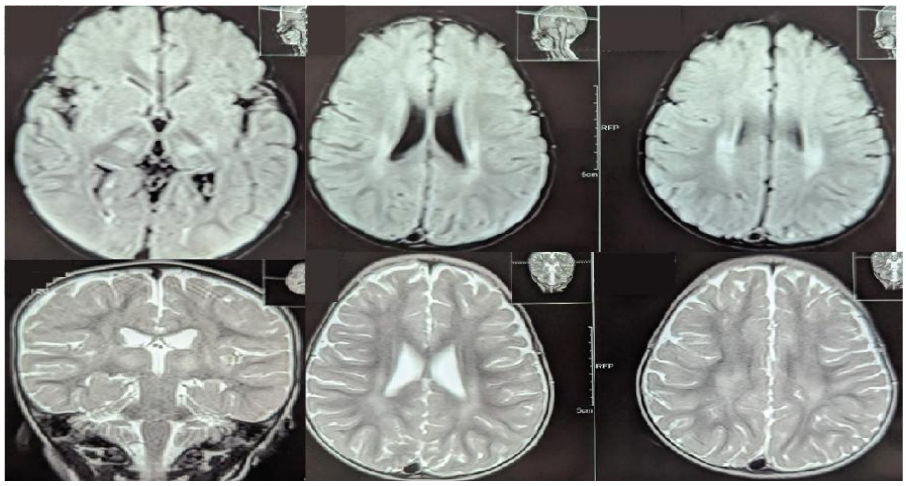

Figure 1: Bilateral symmetrical T2WI/FLAIR hyperintense signal changes at corona radiata, centrum semiovale and thalamus of both cerebral hemispheres.

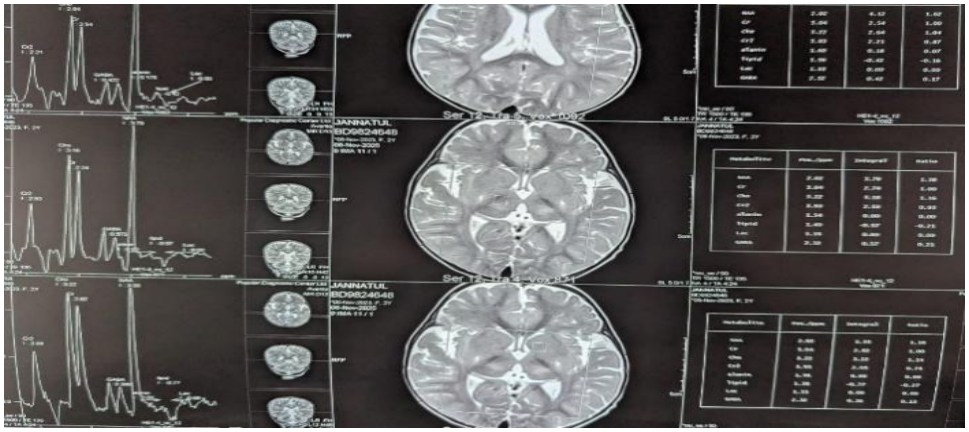

Figure 2 : MRS at left basal ganglia and right thalamic region shows decreased NAA peak,

increased Cho peak, low NAA/Cr ratio and high Cho/Cr ratio.

Table 4: Association of key MRS biomarkers with drug-resistant epilepsy

MRS biomarker	Category	Drug-responsive (n=84)	Drug-resistant (n=69)	p-value
NAA/Cr ratio	>1.4 (Near-normal)	48	15	< 0.001
	1.0-1.4 (low)	31	38	
	<1.0 (Severely low)	5	16	
Lactate peak	Absent	72	37	0.003
	Present	12	32	

Data analysis test: Chi-square test for trend (NAA/Cr) and Chi-square test (Lactate)

DISCUSSION

This study provides a comprehensive analysis of the structural and metabolic brain alterations in children with epilepsy following perinatal asphyxia (PA). Our findings underscore the high prevalence of neuroimaging abnormalities in this specific patient population, with 89.5% of participants exhibiting clear structural lesions on MRI. This aligns with existing literature that identifies PA as a major etiology of brain injury leading to remote symptomatic epilepsy [6,15]. The predominance of periventricular leukomalacia (PVL) as the most common MRI finding is particularly noteworthy. This pattern reflects the vulnerability of the periventricular white matter in the premature and term infant to hypoxic-ischemic events, disrupting myelination and cortical connectivity, which subsequently serves as a potent substrate for epileptogenesis [9,16]. The significant association between specific MRI patterns and seizure types offers valuable clinical insights. The link between PVL and focal seizures can be explained by the disruption of thalamocortical pathways, creating focal cortical dysmaturity and irritability [17]. Conversely, the strong correlation between basal ganglia and thalamic lesions and epileptic spasms is consistent with the known role of these subcortical structures in the neuronal networks underlying infantile spasms, often classified as a form of "epileptic encephalopathy" [18]. This suggests that early MRI can not only confirm the cause of epilepsy but also help predict the likely electroclinical syndrome, guiding management strategies. Our MRS findings further illuminate the chronic metabolic dysfunction underpinning this condition. The significantly reduced NAA/Cr ratios in affected brain regions are a robust marker of impaired neuronal integrity and viability, a consistent finding in chronic cerebral injury from HIE [12,19]. The elevated Cho/Cr ratios suggest persistent alterations in membrane turnover, likely reflecting ongoing gliosis or demyelination in these established lesions [11]. Crucially, the detection of lactate, a marker of anaerobic metabolism, in over half of the patients with abnormal MRI, even years after the initial insult, is a profound finding. It indicates a lasting shift in cerebral energy metabolism, potentially creating a chronically "stressed" and hyperexcitable neuronal environment conducive to seizure generation [20]. The stratification of MRS data by MRI findings reveals a gradient of injury severity. Patients with normal MRI had near-normal metabolite profiles, suggesting a functionally preserved brain despite the clinical history of PA and epilepsy. In contrast, those with PVL showed intermediate metabolic disturbance, while the most severe derangements were confined to the deep gray matter injury group. This gradient was most apparent in the strong association between severely low NAA/Cr ratios, the presence of lactate, and the clinical phenotype of drug-resistant epilepsy, as detailed in our results. This reinforces the concept that MRS provides a quantitative biomarker of disease burden that is more sensitive than visual MRI analysis alone for predicting clinical severity and therapeutic response [13,21].

Limitations:

The primary limitations of this study include its single-center, cross-sectional design and the use of purposive sampling, which may limit the generalizability of the findings and preclude assessments of causality or longitudinal progression.

CONCLUSION

In conclusion, the combined use of MRI and MRS offers a powerful, synergistic tool for evaluating children with postasphyxial epilepsy. MRI delineates the structural footprint of the initial injury, while MRS reveals the ongoing metabolic dysfunction that correlates with epilepsy severity and drug resistance. These imaging biomarkers are crucial for prognostication and personalizing patient management, highlighting the need for their integration into the standard diagnostic workup for this vulnerable population.

Recommendation:

Future large-scale, longitudinal multi-center studies are recommended to validate these findings. Incorporating advanced MRS sequences and correlating imaging biomarkers with long-term neurodevelopmental outcomes would further enhance prognostic accuracy and guide targeted interventions for this patient population.

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