DIAGNOSTIC ACCURACY OF 1H-MRS IN PROGNOSTICATION OF PERINATAL ASPHYXIA, KEEPING CLINICAL NEUROMOTOR SCORING SYSTEM IN COMPARISON

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ABSTRACT

Objective: To determine the diagnostic accuracy of 1H- magnetic resonance spectroscopy imaging findings in predicting neurodevelopmental abnorma-lities in term neonates having respiratory distress, using clinical neurological examination as reference standard.

Study Design: Cross sectional validation study.

Place and Duration of Study: Armed Forces Institute of Radiology and Imaging (AFIRI), Pak Emirates Military Hospital, Rawalpindi, from Oct 2017 to Apr 2018.

Methodology: A total of 86 patients were included in study. All term neonates suspected of hypoxic ischemic encephalopathy (HIE) referred for magnetic resonance spectroscopy (MRS) meeting our inclusion criteria were enrolled for study acquisition after taking informed consent from attendants.

Results: Approximately 47 out of 86 patients suspected to have perinatal asphyxia showed raised lactate peaks (resonating at 1.3 ppm) in both watershed and ganglionic regions and at 6 months neurological evaluation showed significantly delayed neurological development and delayed milestones. Seven (8.1%) patients clinically suspected to have birth asphyxia showed no specific detectable spectral spikes at 1.31 ppm. Twenty six (30.2%) patients presenting with delayed cry but no laboratory evidence of birth asphyxia showed no definite evidence of visualization of lactate peaks. Six (6.97%) patients showed normal magnetic resonance spectroscopy who had clinical, biochemical suspicion of systemic ischemic insult and later on showed retarded neurodevelopment at 6 months of age.

Conclusion: Magnetic resonance spectroscopy (magnetic resonance spectroscopy) spectra in patients having high documented clinical and biochemical suspicion of transitory birth asphyxia from any cause, acquired at frontal watershed territory and deep grey matter showed a characteristic spectral resonance of lactate peak not demonstrable in normal term infants at aforementioned locations thus signifying cellular brain injury despite no radiological visible parenchymal infarction.

Keywords: Basal ganglia, Hypoxic ischemic encephalopathy, Lactate peak, Magnetic resonance spectroscopy, Thalamus lesions, Watershed injury.

INTRODUCTION

Perinatal asphyxia or neonatal asphyxia encompasses several different etiologies that lead to brain damage with resultant severe neurological impairment. The commonest of these encountered is secondary to diffuse hypoxic ischemic brain injury referred to as hypoxic ischemic encephalopathy (HIE)[1].

A wide range of disease processes in perinatal period and in utero life can be attributable to impaired cerebral perfusion. However each of these causes neurological deficit of varying severity. Severity of neurological impairment is governed by several different factors. Most important of these include extent of ischemia, time duration before restoration of breathing and gestational age of fetus at the time of insult. These factors influence the outcome of perinatal asphyxia which is being categorized as mild, moderate and severe. Cognitive and behavioral disorders including deafness, hyperactivity, low intelligence and neuropsychiatric disorders are included in mild to moderate HIE (hypoxic ischemic encephalopathy) whilst severe neurological impairment manifests as cerebral palsy, epilepsy and mental retardation[2].

Diagnostic imaging has an important role to play not only in early detection and assessment of severity of hypoxic ischemic brain injury but with the use of appropriate imaging modality it can predict the disease prognosis which may influence the management plan. Both magnetic resonance imaging (MRI) and 1H-magnetic resonance spectroscopy (MRS) have a vital role in disease prognostication. Hypoxic ischemic encephalopathy has different patterns on MRI sequence in term infants. These include basal ganglia, thalamus lesions, watershed injuries, periventricular leucomalacia, sub cortical white matter involvement and ischemic strokes each corresponding to different severity and duration of ischemia[3]. 1H-MRS is a useful method of measuring biochemical markers of ischemia. In a

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normal term neonate, because of lack of brain maturation there is low concentration of N acetyl aspartate (NAA). High levels of NAA and choline (Ch) are noted in basal ganglia and deep white matter attributable to early and rapid maturation. Cerebral ischemia causes triggering of anaerobic glycolysis with increase in lactate levels which is the main product of anaerobic metabolism. Moreover there is a reduction in NAA/Ch ratio with a rise observed in lactate: NAA and lactate: Ch ratio[4,5].

1H-MRS used in conjunction with MRI is a non invasive imaging modality that can help in early detection of cerebral ischemic changes. These not only determine the severity and duration of ischemic insult but also accurately measures in vivo pathological cerebral markers in the setting of ischemia which can reliably predict disease severity and outcome. Considering a very high prevalence of HIE (hypoxic ischemic encephalopathy) in Pakistan (47.69%) 6 and non-availability of other important investigations helpful in prognosticating the outcome, Magnetic resonance spectroscopy (MRS) if judiciously applied can predict disease outcome well before time. This valuable information can be used in future for adequately utilizing hypothermic treatment options in hypoxic ischemic encephalopathy (HIE). Moreover sensitivity of 1H-MRS compared to other imaging modalities in diagnosing hypoxic ischemic encephalopathy (HIE) is far better in the early neonatal period.

MRS volume selection, using the point-resolved spectroscopy (PRESS) technique to acquire the MR spectra from approximately 5.5 cm^3 of tissue is highly sensitive in assessment of biochemical markers. The spectrum for each location is acquired with a TR of 2 seconds, a TE of 288 milliseconds, and a total of 128 acquisitions. The main target of MRS timing and voxel placement is for lactate detection and spectral contamination from extra cranial adipose tissues is minimized. Doublet peaks are centered at 1.31 ppm.

METHODOLOGY

This cross sectional validation was conducted at Armed Forces Institute of Radiology and Imaging (AFIRI), Pak Emirates Military Hospital, Rawalpindi, from October 2017 to April 2018.

A total of 86 patients were included in the study. The sample size was calculated by using WHO sample size calculator taking sensitivity 88%[6], specificity 88%[6], Expected prevalence 47.69%[7], Desired precision 10% for sensitivity and 10% for specificity, and confidence interval of 95%. The recommended sample size would be approximately 86 cases. Non-probability consecutive samplig technieque was used.

METHODOLOGY

All term neonates suspected of HIE referred for MRS meeting our inclusion criteria were enrolled for acquisition study after taking informed consent from attendants. The study was conducted after approval from the Hospital Ethics Committee and all the data was collected after informed written consent from the newborns attendants. A total of 86 suspected patients of hypoxic ischemic encephalopathy fulfilling the inclusion and exclusion criteria were selected in the study by consecutive sampling method. All the patients were referred to the Armed forces institute of radiology and imaging (AFIRI) for suspected diagnosis of hypoxic ischemic encephalopathy. These patients subsequently underwent clinical neuromotor examination at 6 month of ages by a consultant pediatrician blinded to the results. Multi voxel proton spectra, was acquired by placing two voxels, one in the deep gray matter nuclei, including the thalamus and lentiform nucleus, and the other in the intervascular watershed zone frontal lobe. These were acquired in conjunction with an MR imaging study of the entire brain. These images were guided by the MRS volume selection, which was performed using the point-resolved spectroscopy (PRESS) technique to acquire the MR spectra from approximately 5.5cm^3 of tissue for both regions. The spectrum for each location was acquired with a TR of 2 seconds, a TE of 288 milliseconds, and a total of 128 acquisitions. The main target of MRS timing and voxel placement was maximized for lactate detection and minimized the spectral contamination from extracranial adipose tissues. Same parameters and voxel size were used for spectral acquisition in deep grey matter nuclei and subsequently in white matter. Doublet peaks were centered at 1.31 ppm. Inversion of the peak was considered as a confirmatory sign of presence of lactate at site of voxel placement. After acquisition, the MRS data were transferred off-line and analyzed. All of the spectra was analyzed by a 1 radiologist. The MRS data was Fourier-transformed and the peak areas integrated for the choline, creatine, Nacetylaspartate (NAA), and lactate resonances and ratios of lactate/choline, lactate/NAA and NAA/choline were calculated for each voxel.

Perinatal asphyxia is defined as evidence of cardio respiratory and neurological depression (defined as an APGAR score remaining less than 7 at 5 minutes after birth) and evidence of acute hypoxic compromise

with academia (defined as an arterial blood pH of <7 or base excess >12 mmol/L). Anatomica site for voxel placement in deep gray nuclei voxel includes most of the lentiform nucleus, the ventrolateral thalamus, and the posterior limb of the internal capsule. The spectrum reveals: 1) a small myoinositol peak, 2) a large choline peak, 3) two small creatine/phosphocreatine peaks, and 4) a medium-sized NAA peak[7]. The watershed voxel includes primarily white matter from the intravascular boundary zone. NAA and choline peaks are relatively smaller in the less mature watershed zone than in the more mature deep gray nuclei with minimal or no lactate[8-12]. Abnormal spectrum in Basal ganglia pattern of injury shows a markedly elevated lactate peak centered at 1.31ppm, reduced NAA, Cho and Cr and watershed pattern of injury includes raised lactate peak with reduced NAA, Cho and Cr (less marked as basal nuclei pattern of injury). Comparison of Mr spectroscopic analysis was done with neuromotor scoring system (table-I) graded as Normal (score=0), unclear (score=1), mildly abnormal (score=2 or 3), or severely abnormal (score=4–6). A score of ≥3 will be considered positive abnormality and ≤2 will be considered as negative/absence of abnormality.

Table-I: Neuromotor scoring system and grading assessment[13-15].

Score	Features
0	Normal
1	Abnormal tone or reflexes or primitive reflexes
2	Abnormal tone and reflexes
3	Decreased power in addition to tone or reflex anormality
4	Cranial-nerve involvement in addition to any motor abnormality
5	Cranial-nerve involement and spastic quadriparesis (tone, reflexes, and power affected)
6	Expired

Data were analyzed using SPSS version 25. Mean ± SD was calculated for quantitative variables, frequency and percentage were calculated for qualitative variables 2x2 table. Table was constructed to find out sensitivity, specificity, positive and negative predictive valuse.

RESULTS

A total of 86 patients were included according to the inclusion criteria of the study. All the patients were examined at 6 months of age using neuromotor scoring system and assessment of developmental parameters There were 47 (54.65%) males and 39 (45.34%) females patients who were included in the study. Approximately 47 out of 86 patients suspected to have perinatal asphyxia showed raised lactate peaks (resonating at 1.3 ppm) in both watershed and ganglionic regions and at 6 months neurological evaluation showed delayed milestones. Seven (7) patients clinically suspected to have birth asphyxia showed no specific detectable spectral spikes at 1.3 ppm. Twenty six (26) patients suspected to have delayed cry but no laboratory evidence of birth asphyxia showed no definite evidence of visualization of lactate peaks. Six patients showed normal MRS who had clinical, biochemical suspicion of systemic ischemic insult and later on showed retarded neurodevelopment at 6 months of age (table-II).

Table-II: Assessment of sensitivity of mrs lactate peak in prognosticating severity of hypoxic ischemic insult in term neonates.

Magnetic Resonance Spectroscopy	Clinical Outcome	
	Positive (≥3)	Negative (≤2)
Positive (lactate peak)	47 (54.6%)	7 (8.1%)
Negative (Absent Lactate Peak)	6 (6.97%)	26 (30.2%)

The most consistent abnormality detected on MRS spectrum acquired from watershed territory and basal ganglia was lactate peak resonating at 1.3 ppm shown in fig-1 & 2. Intermediate levels were found in those patients with neurologic examinations scored in the intermediate range The NAA peaks were attenuated in some patients who subsequently had neurodevelopmental stability. It was found that patients with severe detrimental neurodevelopment delay sho-

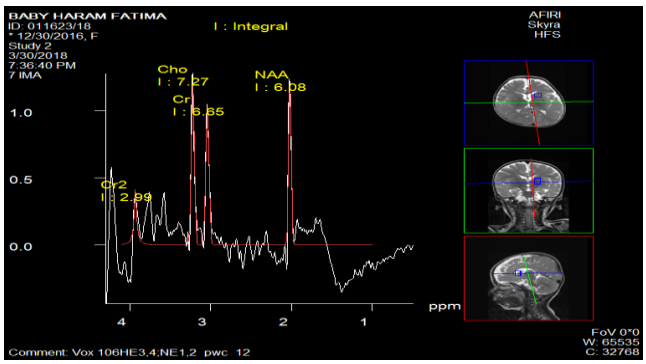

Figure-1: MRS multivoxel performed at AFIRI acquired by placing the voxel in left ganglionic region (grey matter) in a term neonate at 1 week age suspected to have hypoxic ischemic injury showed a prominent lactate peak resonating at 1.3 ppm with characteristic doublet inversion. Moreover there is a persistent choline peak seen resonating at 3.2 ppm which unlike in adults is a physiological spectroscopic observation in newborns attributable to rapid myelination and neuronal growth.

wed raised lactate peak in both grey matter and white matter consistent with severe hypoxic ischemic insult.

Grading Score

Normal (score=0), unclear (score=1), mildly abnormal (score=2 or 3), or severely abnormal (score=4–6).

A score of ≥3 was considered positive abnormality and ≤2 was considered as negative/absence of abnormality.

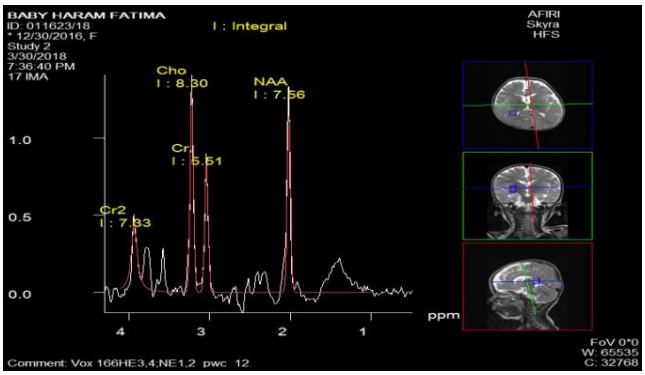

Figure-2: MRS multivoxel acquired at AFIRI by placing the voxel in circulation watershed territory in a term neonate at 1 week age suspected to have hypoxic ischemic injury showed a prominent lactate peak resonating at 1.3 ppm representing areas of anerobic cellular activity as a sequelae of ischemic insult.

DISCUSSION

Peinatal asphyxia is commonly encountered in Asian population and has a considerably high prevalence in Pakistan. Majority of the children who survive the condition later on in their lives develop variable severity of cognitive and behavioral disorders with some remaining vegetative throughout their lives developing cerebral palsy. Non invasive imaging modalities such as MR spectroscopy if recruited earlier can accurately estimate degree of brain damage at a much earlier stage in life and can expedite recruitment of newer emerging medical treatments for stabilizing biochemical alterations[17-20].

There was a difference in our study compared to that of Shu *et al* and of Groenendaal *et al*, who found stronger associations with NAA levels with the difference arising secondary to difference in timing of MRS. The average time at which MRS was carried out in our patients was 6 days; for the patients of Hanrahan *et al* it was <24 hours; and for those of Leth *et al* it averaged <5 days.

CONCLUSION

MRS on account of its non invasive nature and accurate estimation of biochemical markers of anaerobic glycolysis in particular the lactate peak has high sensitivity in early detection of metabolic abnormalities of perinatal asphyxia at a time when the diagnosis may remain uncertain. Early detection of brain damage helps not only in prompt management but also helps the treating physician in foreseeing potentially treatable disease spectrum associated with the condition.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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