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EVALUATION OF BRAIN ISCHEMIA BY MAGNETIC RESONANCE SPECTROSCOPY

Radiodiagnosis

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ABSTRACT

OJECTIVES : The study aims to determine metabolite abnormalities in complete infarct region of the brain.

METHODOLOGY: 34 patients referred to the department of radiology with imaging evidence of hemispheric ischemic stroke were subjected to MR Spectroscopy on 1.5 Tesla MRI.

RESULTS: Out of 34 cases, in infarct region, elevated lactate was present in 100% , decreased NAA in 94%, while reduced choline was noted in 53% and increased in 47% of study population. In assumed penumbra region, elevated lactate was present in 76% , decreased NAA in 76.5% cases, while reduced choline was noted in 41% and increased in 59% of study population.

CONCLUSION: This study has concluded that lactate was present in both the infarct and penumbra region. NAA was significantly reduced in the infarct region and mild decrease in the assumed penumbra. Choline was decreased and increased in both the infarct region and penumbra region.

KEYWORDS

INTRODUCTION :

Conventional magnetic resonance imaging (MRI) is a well-developed and much-utilized method for visualizing the radiological extent of disorders involving cerebral ischemia. Magnetic resonance spectroscopy (MRS) is a non-invasive in vivomethod that allows the investigation of biochemical changes. [1]The application of MRS to the study of stroke has made possible dynamic studies of intracellular metabolism of cerebral ischemia. The ischemic penumbra is a region of incomplete ischemia adjacent to the zone of complete ischemia, the core of the ischemic infarct[2].As originally defined, it encompasses that portion of the oligemic territory where electrical failure has occurred, but cellular integrity is maintained.[3] The concept of an ischemic penumbra has been a significant impetus for developing pharmacologic interventions in the acute treatment of stroke patients to potentially salvage a peri-infarct region that is at high risk for infarct evolution.[4] The identification of amenable tissue in the hyperacute period is of critical importance because the tolerance of perfusional disturbances is related to its duration, which can determine the progression of ischemia from the core into the oligemic penumbral region.[5]In human studies, it was found that viable tissue in the ischemic penumbra can be found up to 4- 6hrs after stroke hours onset.[6]

Proton magnetic resonance spectroscopy is a technique which provides a noninvasive method for characterizing the cellular biochemistry which underlies brain pathologies and for monitoring the biochemical changes after treatment in vivo. Proton spectroscopy is easier to perform which provides much higher signal-to-noise than either sodium or phosphorus.[9]MRS which is an adjunct to MRI defines neurochemistry on a regional basis and display the quantities as a spectrum. It is considered as a connecting bridge between metabolism, anatomic and physiological studies available from MRI. More the metabolites taller is the peak.[10]

The present study is done for assessment of metabolite abnormalities in the ischemic brain and to determine preservation of N acetyl acetate (neural integrity) with elevated lactate (anaerobic glycolysis) which can act as a potential marker of ischemic penumbra in the absence of perfusion studies.

AIMS AND OBJECTIVES

- The study aims to determine metabolite abnormalities in complete ischemia (infarct) region of the brain.
- To determine the preservation of N acetyl acetate (neural integrity) with elevated lactate (anaerobic glycolysis) which can act as a potential marker of ischemic penumbra in the absence of perfusion studies.

PATIENTS AND METHODS

This study was carried out in the department of radiology of Dr. Pinnamaneni Siddhartha Institute of Medical Sciences and Research foundation, Gannavaram, Krishna District. Totally 34 cases who came for MRI brain to the department of Radiology were evaluated for presence of infarct.. The period of study was done from Nov-2016 to oct-2018.

STUDY DESIGN:

A prospective cross-sectional study of MRI brain done in patients with headache who were referred to Radiology Department of Dr. Pinnamaneni Siddhartha institute of medical sciences & RF. The collected data was analysed by descriptive statistics. All statistical analysis was done through SPSS for Windows Version 16.0.

STUDY POPULATION:

A total of 34 patients both males & females who were referred to the department of radiology for MRI Brain study was the study population. Patients presented with cerebrovascular accidents were referred from regular OPD and inpatients of various departments of the institute were taken into the study. Informed consent was obtained from every patient after explaining them about the above procedure in their own language.

Inclusion criteria:
1. All patients with imaging evidence of hemispheric ischemic stroke will be subjected to Magnetic Resonance Spectroscopy.
2. Both sexes.
3. Patients of age between 20-80 years.

Exclusion criteria:
1. Patients with known cerebral tumours.
2. Patients with known metabolic encephalopathy.
3. Patients with known Infectious diseases.
4. Patients with claustrophobia.

EQUIPMENT :
MR scanner,1.5 Tesla Philips Achieva 16 channel.

MRI PROTOCOL:
Study was performed on all the subjects in the department of radiology referred from the department of medicine and neurology with CVA Less than 7 days at Dr. Pinnamaneni Siddhartha institute of medical sciences.All patients underwent routine MRI and 1H-MRS scans within 7 days after the onset of stroke. Routine MRI sequences included axial, sagittal T1-weighted imaging (T1WI), T2WI and diffusion-weighted imaging (DWI); layer thickness was 5 mm in order to determine the pathological conditions of cerebral tissue. The sequence of axial T2WI or DWI identified the infarct lesions and positions for 1H-MRS. The volume of interest will therefore be centred on image slice that is of most representative Multivoxel spectroscopy is obtained from ischemic area , assumed penumbra or adjacent to acute or sub acute infarct and it is compared with contra lateral normal side. The volume of a single voxel was 2x1x1 cm. Water signals were suppressed by the chemical shift saturation method. The sequence of S2DSI-144 was applied to collect spectrum, imaging parameters were as follows: repetition time (TR) was 2,000 msec, echo time (TE) was 144 msec and number of excitations (NEX) was 16 times. FuncTool Spectroscopy-2D Brain analysis software (Philips Signa Workstation 4.0, Philips, Asterdam, The Netherlands) was used to analyze and calculate the integral peak area of the corresponding chemical shift of NAA, total creatine (creatine + phosphocreatine) (Cr), choline compounds (Cho), and lactate (Lac) automatically, which provided a relative quantitative value of the concentration of these compounds. The values of the lactate, NAA, Cho, and NAA/ cho were calculated and analyzed.The volume of interest will therefore be centred on image slice that is of most representative.We compared it with the opposite side.

RESULTS:
In the present study all patients were evaluated for the lactate, NAA, choline and NAA/Choline metabolite abnormalities incomplete ischemia (infarct) region of brain and assumed penumbra(region adjacent to infarct) to determine preservation of N acetyl acetate (neural integrity) with elevated lactate (anaerobic glycolysis) which can act as potential marker of ischemic penumbra in the absence of perfusion studies.

Ischemia of the brain tissue is in a reversible within stage 6 h after stroke. Thrombolytic treatment can restore blood flow perfusion in this time, to reduce neurological damage and save the ischemic penumbra.

AGE INCIDENCE:
The youngest patient in this study was 41years old, the oldest being 79 years. The maximum number of patients were in the age group of 71-79 years.

SEX INCIDENCE:
In this study, males are more common than females accounting for 23 cases out of 34 and females accounting for 11 out of 34.

MR SPECTROSCOPY IN STROKE
Magnetic resonance spectroscopy (MRS) is a non-invasive *in vivo* method that allows the investigation of biochemical changes in both animals and humans.The application of MRS to the study of stroke has made possible dynamic studies of intracellular metabolism of cerebral ischemia. The majority of thestroke studies have been carried out using proton [1H]-MRS.

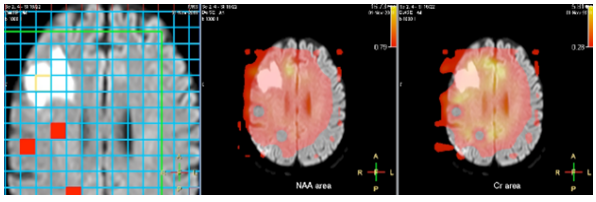
MRS changes in cerebral ischemia
MRS studies in humans demonstrate that after acute cerebral infarction lactate appears, while NAA and total Cr/PCr are reduced within the infarct compared to the contralateral hemisphere. Large variations in the initial concentrations of Cho have been observed in the region of infarction.

MR spectroscopic images in healthy volunteers have previously been characterized by a near-uniform distribution of NAA, with reductions only in the most caudal section and absence from the cerebrospinal fluid spaces, such as the lateral ventricles. With the method used in the current study, no lactate was detectedin contralateral normal areas, and choline was distributed fairly uniformly.

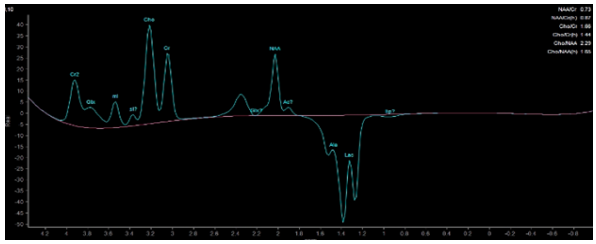
Detection of various metabolites in the Infarct and assumed penumbra region.

LACTATE :
The peak of Lac is not seen or is hardly visualized in the normal brain. The peak of Lac is a doublet at 1.33 ppm which inverts below the baseline at TE of 135-144 msec. A small peak of Lac can be visible in some physiological states such as newborn brains during the first hours of life.Lac is a product of anaerobic glycolysis, so its concentration increases under anaerobic metabolisms such as cerebral hypoxia, ischemia, seizures and metabolic disorders (especially mitochondrial ones). Increased Lac signals also occur with macrophage accumulation (e.g. acute inflammation).The rise in brain lactate that results from the mismatch between glycolysis and oxygen supply has been demonstrated by numerous [1H]-MRS experiments making it a hallmark for the detection of cerebral ischemia. The persistence of lactate weeks or months following stroke onset has been observed. The appearance of Lac is considered to be a sensitive marker in the early stage of infarction, and it appears before the routine MRI examination shows abnormal changes.In this study, elevated lactate was observed in all 34 patients (100%) in the infarct region who were scanned successfully. Lactate, therefore is an indicator of acute cerebral ischemia. Lactate was present in 26 cases in the penumbra region and normal in 8 cases out of 34 cases in the present study.However lactate can be considered as a sensitive indicator of early ischemia, but it is not a specific indicator because it elevated in many other conditions.

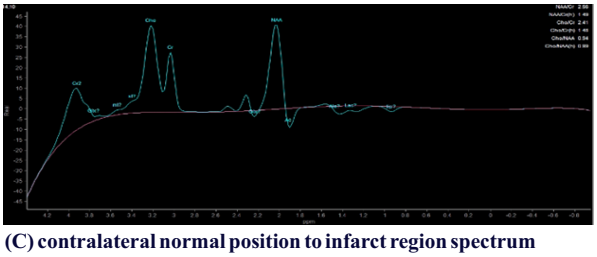
FIGURE 1:
(A) MR spectroscopy voxel position in acute right MCA infarct.
(B) Infarct region spectrum
(C) contralateral normal position to infarct region spectrum
(D) Assumed penumbra region spectrum
(E) Contralateral normal position to assumed penumbra region spectrum



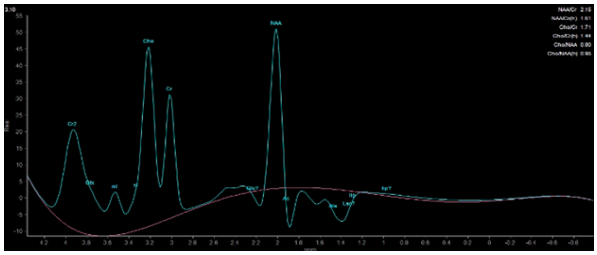
(A) MR spectroscopy voxel position in acute right MCA- ACA j/n zone infarct.



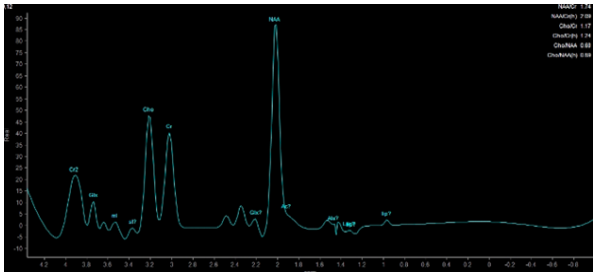
(B) Infarct region spectrum



(C) contralateral normal position to infarct region spectrum



(D) Assumed penumbra region spectrum



(E) Contralateral normal position to assumed penumbra region spectrum.

Findings of NAA in the infarct and assumed penumbra region :
NAA has been shown to be predominantly localized to neurons, axons, and dendrites within the CNS. The NAA resonance is absent or depleted from lesions known to involve neuronal/axonal loss such as brain tumours, infarcts, multiple sclerosis or seizure foci. For this reason, NAA isbelieved to be a specific marker of viable neurons,axons and dendrites.

In the present study, NAA was decreased in 32 (94%) out of 34 cases in the infarct region and 24 (76.5%) out of 34 in assumed penumbra region. Both the regions show a P value of < 0.05 which indicates NAA was significantly reduced compared to the contralateral normal parenchyma.

From the above data, NAA was higher in the penumbra region than infarct region which indicates that both the regions show a decrease in NAA values but the range of decrease in values was significantly more in infarct region than assumed penumbra.

Although the time course (and blood flow dependence) of the changes in NAA during cerebral ischemia have yet to be examined in detail, it has been reported that the signal from *N*-acetyl groups decreases rapidly by 10% within 1 hour after induction of global cerebral ischemia and that during focal ischemia NAA decreases more slowly, with a half-life of several hours . However further workup with diffusion-perfusion mismatch is required to establish the relationship between NAA levels and preservation of neuronal function and to ascertain its value as a quantitative index in assumed penumbra region.

Findings of choline in the infarct region:
Cho includes glycerol phosphate, choline, phosphorylcholine and phosphatidylcholine. Cho is an indicator of the cell membrane integrityIts peak is determined by the concentration of choline existing in membrane phospholipids and of acetylcholine used.as a neurotransmitter. Pathophysiological processes cause the decomposition of sphingomyelin and an increase in the number of cells may lead Cho levels to increase.

Changes in the choline peak have been shown to increase, decrease and stay the same following infarction. Cho is a marker of cellular membrane turnover (phospholipids synthesis and degradation)reflectingcellular proliferation. In tumours, Cho levels correlate with the degree of malignancy reflecting cellularity. Increased Cho may be seen in infarction (from gliosis or ischemic damage to myelin) or inflammation (glial proliferation) where as decrease is the result of edema, necrosis or cell loss. For this reason, Cho is considered to be nonspecific.

Cho was reduced in the infarct region in 18 (53%) of 34 cases and increased in 16 out of 34 cases as compared with the Cho signal in similarly positioned contralateral normal area (*P value <0.62*). This study shows no significant increase or decrease in the choline levels in the infarct region.

Findings of choline in the penumbra region
In this study, choline was decreased in 14 (41%) and increased in 20 (59%) patients.

P value between the increase and decrease of choline was 0.14 which is insignificant.

Comparision of ratios of NAA/Cho in infarct region to contralateral normal region
In the present study, the mean ratios of NAA/Cho in the infarct region compared to contra lateral normal region was 1.04 and 1.62 which showed a P value of < 0.001.This study shows a significant difference beteen infarct and contralateral normal region.

DISCUSSSION:
MRS as a predictor of outcome
Major advances in the treatment of acute stroke require the accurate prediction of the mortality of stroke patients and, therefore, the identification of patients likely to benefit from drug treatment. Multivoxel spectroscopic studies of stroke have attempted to provide information about the possible outcome of stroke. Infarct volume determined by DWI imaging has been shown to be a good predictor of outcome. Large cerebral infarcts have been shown to be associated with reduced NAA concentration and raised lactate as well as reduced blood velocity. The best predictor of outcome was infarct volume and not metabolite concentration alone. The addition of NAA concentration to infarct volume allows a better prediction of patients morbidity than either the NAA concentration or infarct volume alone.

Application of [1H]-MRS to the clinical study of cerebral ischemia
MR spectroscopy and multivoxel MR spectroscopic imaging have proven to be valuable tools in the study of cerebral vascular disease. Their role in the detection of potentially salvageable ischemic tissue suitable for treatment with thrombolytic and neuroprotective agents have been proved useful. The combined use of diffusion-weighted and perfusion imaging with ['H]-MRS may prove more valuable. The ability of multivoxel chemical shift imaging to detect changes throughout the brain makes it the most suited spectroscopy technique for the study of cerebral ischemia.

LIMITATIONS OF THE STUDY
- Comparison of MR spectroscopic images and MR images is complicated by the different spatial resolution of the two techniques. It is important to recognize the limited spatial resolution of the MR spectroscopic data sets and to appreciate that intervoxel signal contamination can occur between adjacent voxels. Therefore, a voxel of a normal brain that lies immediately adjacent to a lactate-containing infarct could easily be mistaken for penumbra, since it will have a normal MR appearance but may seem to contain some lactate signal, which actually originates from the adjacent voxel.
- Contamination may occur from pericranial lipid signals when head motion occurs, and it has also been suggested that ischemic brain tissue itself may exhibit an increase in free lipid signals, It is well known that lipid signals can mistakenly be assigned as lactate since they both resonate in similar regions of the proton spectrum.
- Susceptible to potential errors introduced by magnetic field inhomogeneities.

CONCLUSION:
This study has concluded that lactate was present in both the infarct and penumbra region. NAA was significantly reduced in the infarct region and there was a mild decrease in NAA concentration in the assumed penumbra compared to the infarct region. Choline was decreased and increased in both the infarct region and penumbra region with no significant difference. NAA/Cho was decreased in the infarct region compared to the contra lateral normal region.

NAA is a marker of neuronal density and activity. Also, NAA is a specific marker that may reflect infarction-related injury. Lac is a product of anaerobic glycolysis. The increase in the size of the Lac peak reflects the lack of oxygen supply and indicates the presence of infarction, but not necessarily the development of irreversible cerebral infarction. More studies with diffusion perfusion mismatch comparison should be proved with MR Spectroscopy.

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