Original Article

Proton Magnetic Resonance Spectroscopy of Brain to Study the Cerebral Metabolic Abnormalities in COPD Patients: A Case Control Study in North India

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ABSTRACT

Background. To investigate changes in the cerebral metabolism of nondiabetic and normolipidaemic patients with chronic obstructive pulmonary disease (COPD) using localised *in vivo* proton magnetic resonance spectroscopy (^{1}H MRS), and to correlate these with the severity of disease.

Methods. Twenty-eight symptomatic COPD patients and 19 healthy controls underwent ^{1}H MRS of brain, pulmonary function testing and respiratory muscle strength evaluation. The parieto-temporal and occipital regions were localised for ^{1}H MRS. The metabolic ratios of N-acetyl aspartate to cretinine (NAA/Cr) and choline containing compound to creatinine (Cho/Cr) were calculated by integrating area under the each peak.

Results. The mean value of NAA/Cr and Cho/Cr in parieto-temporal area in COPD patients were (1.86±0.54) and (0.77±0.23), respectively. The mean values of NAA/Cr and Cho/Cr in occipital area in COPD patients were (1.75±0.44) and (0.61±0.25), respectively. Compared with healthy control subjects, the mean values of Cho/Cr in COPD patients were lower, both in parieto-temporal (0.77±0.23 *vs* 0.89±0.35; p=0.17) and occipital (0.61±0.25±*vs*0.67±0.08; p = 0.36) areas of the brain.

Conclusions. The cerebral metabolism, pulmonary function testing and respiratory muscle strength altered in symptomatic COPD patients. The clinical significance of cerebral metabolic changes in COPD patients needs to be further investigated. **[Indian J Chest Dis Allied Sci 2009;51:15-19]**

Key words: Chronic obstructive pulmonary disease, Pulmonary function, Magnetic resonance spectroscopy, Cerebral metabolites.

INTRODUCTION

Neuropsychological deficit is a common problem in patients with chronic obstructive pulmonary disease (COPD). Many studies[1-5] have evaluated the correlation between neuropsychological dysfunction and pulmonary function in COPD patients. Decreased forced expired volume in the first second (FEV_1) is an independent predictor of neuropsychological dysfunction.[1] Cognitive disturbance is common in patients with hypoxemic COPD.[2] Oxygen therapy relieves neuropsychological deficits[3-5] in COPD and arterial hypercapnia characterises the severity of cognitive dysfunction.[6] However, very few studies have evaluated direct metabolic cahgnes in the brain, which might well have a direct relationship to the cognitive deficit in COPD patients. Proton magnetic resonance spectroscopy (^{1}H MRS) is a sensitive technique that detect metabolic changes of the brain *in vivo*. It has been convincingly used to assess metabolic changes of the brain in various clinical disorders.[7-11]

Magnetic resonance image guided *in vivo* magnetic resonance spectroscopy (MRS) is a technique that provided the *in vivo* neurochemistry non-invasively. It is the application of basic principles of nuclear magnetic resonance (NMR) and involves no ionizing radiation. It generally involves the same scanning equipment and environment as magnetic resonance imaging. Using ^{1}H MRS, different metabolites present in brain can be measured. They are: N-acetyl aspartate (NAA), total creatine (Cr+PCr), choline containing compound (Cho), glutatamate, glutamine, aspartate, alanine, myo-inositol, lactate and glucose.

In this study, our hypothesis was that cerebral metabolism would be disturbed in COPD patients due to chronic hypoxia/hypercapnia and this may affect the levels of cerebral metabolites. This may have some clinical significance. We therefore, investigated changes in the cerebral metabolism of non-diabetic

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and normolipidaemic COPD patients, using localised *in vivo* ^{1}H MRS and to correlate these findings with the severity of disease and degree of pulmonary results.

MATERIAL AND METHODS

Twenty-eight symptomatic COPD patients who were under 70 years of age and 19 healthy control subjects participated in this study. All subjects underwent ^{1}H MRS of brain, pulmonary function testing, respiratory muscle strength testing, blood sugar and lipid profile estimation. The study was carried out at the Departments of Medicine and Nuclear Magnetic Resonance, All India Institute of Medical Sciences, New Delhi. Patients were enrolled from out-patient service of the Department of Medicine, between January 2002 to October 2003. The approval from the institutional ethics committee was obtained. Informed written consent was taken from all the subjects. Chronic obstructive pulmonary disease was defined according to the American Thoracic Society (ATS) criteria.[12] All patients were in a clinically stable condition without oxygen supplementation for at least one week before their participation in this study. Patients who had a history of or current chronic alcoholism, renal failure, chronic liver disease, hyperlipidaemia, diabetes mellitus, cerebrovascular disease, or other diseases that might affect neuropsychological function were excluded.

Biochemical Investigations

Blood samples were taken after 12-hour overnight fast for the estimation of blood glucose, total cholesterol (TC), serum triglycerides (TG), and high-denstiy lipoprotein cholesterol (HDL-C). An oral glucose tolerance test was performed according to the criteria enuniciated by World Health Organization.[13] Total cholesterol, TG and HDL-C were measured using commercially available kits (Randox Laboratory, San Francisco, CA, USA) on a semi-automated analyser (Micro Semi-Autoanalyser 2000, C.L. Micromed, Italy). Value of low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald's formula; LDL-C = TC – (HDL-C + TG/5).[14] Non-HDL cholesterol was calculated by deducting the value of HDL-C from total cholesterol.[15] Diabetes mellitus was diagnosed according to the World Health Organization criteria.[13] Normolipidaemia has been defined by the standard criteria used by National Cholestrol Educational Program.[16]

^{1}H Magnetic Resonance Spectroscopy (MRS) of Brain

The ^{1}H MRS was carried out using a 1.5 Telsa MRI/MRS scanner (Siemens, Germany). After scout images in three orthogonal planes, multi-slice T_2-weighted axial images of the whole brain was acquired. Thereafter, T_1-weighted multi-slice images in coronal and sagittal sections were also be obtained. Using these images well-defined regions of brain namely, parieto-temporal and occipital regions were localised for ^{1}H MRS. Single voxel volume localisation RF pulse sequence STEAM or PRESS at echotim (TE) of 30 or 135 and with a repetition time (TR) of 2 seconds was used for ^{1}HMRS; 256 scans were acquired for obtaining good signal-to-noise ratio in an MR spectrum. The metabolic ratios NAA/Cr and Cho/Cr were calculated by integrating area under the each peak.

Pulmonary Function Test and Respiratory Muscle Strength (MIP/MEP)

Pulmonary functions including forced vital capacity (FVC), forced expired volume in the first second (FEV_1) and peak expiratory flow rate (PEFR) were measured by spirometer (Morgan PK, UK) according to the ATS criteria.[17] Maximal static inspiratory (MIP) and maximal expiratory pressure (MEP) were measured in the sitting position. The MIP was measured near residual volume and MEP was measured near total lung capacity. Best of three satisfactory readings was taken for analysis. This technique has been validated in our laboratory and the prediction equations for normal north Indian subjects have been derived and reported by us previously.[18,19]

Statistical Analysis

The data were recorded in Microsoft Excel worksheet. All the entries were carefully checked for any error. After confirming the approximate normality, descriptive statistics for biochemical, brain metabolites and lung function parameters were computed by arithmetic mean and standard deviation. Pearson correlation coefficient was used to quantify the extent of relationship between brain metabolites and other quantitative variables. STATA 9.0 intercooled version software (STATA Corp., Houston, Texas, USA) was used for statistical analysis. In this study, p-value less than 0.05 was considered as statistically significant.

RESULTS

The data obtained from 47 subjects (39 males) were analysed. Of these, 28 patients had COPD and 19 were healthy control subjects (25 COPD patients had history of smoking). No patient had cerebrovascular disease, hyperlipidaemia, diabetes mellitus and hypertension. All healthy control subjets were non-smokers.

Table. Concentration of brain metabolites measured by ^{1}H MRS

Brain Area	Brain Metabolites Ratios	Healthy Subjects (n = 19)	COPD Patients (n = 28)	p Value
Parieto-temporal	NAA/Cr	1.78±0.40	1.86±0.54	0.55
Parieto-temporal	Cho/Cr	0.89±0.35	0.77±0.23	0.17
Occipital regions	NAA/Cr	1.83±0.22	1.75±0.44	0.47
Occipital regions	Cho/Cr	0.67±0.08	0.61±0.25	0.36

Data are presented as mean ± SD.
NAA = N-acetyl aspartate; Cr = Creatine; Cho = Choline containing compound.

Biochemical Profile

The mean values of TC, TG, LDL-C, non-HDL cholesterol, fasting blood glucose, and post-oral glucose load blood glucose in the two groups were comparable.

Pulmonary Function Test and Respiratory Muscle Strength of Healthy Controls and COPD Patients

In COPD patients, the mean±SD value of FEV_1 was 57.0±9.0 predicted. The mean values of MIP (4.2±0.7 *vs* 7.4±1.6; p=0.001) and MEP (4.6±0.56 *vs* 7.5±1.7; p=0.0001) in COPD patients were lower compared to healthy controls. Only MEP has statistical correlation (p=0.05) with the levels of cerebral metabolites.

^{1}H MR spectroscopy and concentration of brain metabolites or healthy controls and COPD patients are shown in the table, figures 1 and 2.

The mean value of NAA/Cr and Cho/Cr in parieto-temporal area in COPD patients were (1.86±0.54) and (0.77±0.23), respectively. The mean values of NAA/Cr and Cho/Cr in occipital area in COPD patients were (1.75±0.44) and (0.61±0.25), respectively. Compared with healthy control subjects, the mean values of Cho/Cr in COPD patients were lower, both in parieto-temporal (0.77±1.23 *vs* 0.89±0.35; p=0.17) and occipital areas (0.61±0.25 *vs* 0.67±0.08; p=0.36) of the brain. However, this difference did not attain statistical significance.

Correlation Between Concentration of Brain Metabolites and Clinical Variables in Patients with COPD

In COPD patients, significant positive correlations were observed between respiratory muscle strength (MEP) and NAA/Cr in parieto-temporal area of brain (r=0.38, p<0.05). Other parameters did not correlate significantly in both the groups.

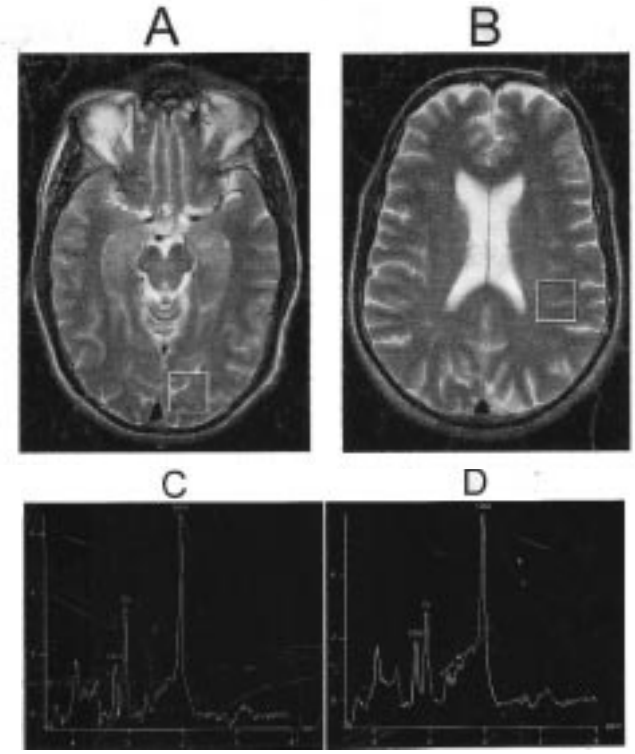

Figure 1. MRI of brain in transverse plane in a patient with COPD showing localisation of voxel in (A) left occipital and (B) left parieto-temporal region while (C) and (D) shows the respective MR spectrum acquired at TE = 30 ms and TR = 2000 ms.
NAA = N-acetyl aspartate; Cr = Creatine; Cho = Choline containing compound.

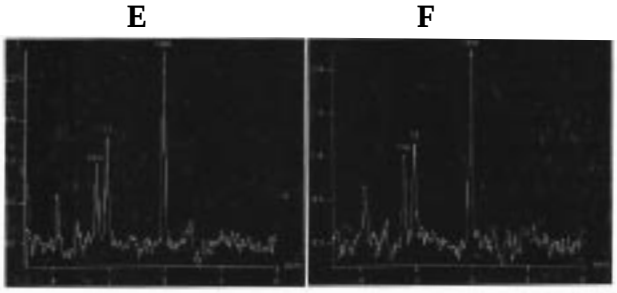

Figure 2. The spectrum obtained from healthy volunteer from the occipital (E) and parieto-temporal region (F) acquired at TE = 135 ms and TR = 2000 ms.
NAA – N-acetyl aspartate; Cr = Creatine; Cho = Choline containing compound.

DISCUSSION

To the best of our knowledge, this is the first study from India where cerebral metabolism was studied

using ^{1}H MRS in symptomatic COPD patients. These findings provide a neurochemical basis for the cerebral dysfunction in COPD patients. The total creatine gives an idea of the energy metabolism in the brain and is composed of resonance from creatine and phospocreatine. Choline containing compounds are an integral part of the neuronal membranes. Their signal strength on ^{1}H MRS is an indicator of the phospolipid metabolism in the brain. In our study, metabolite ratios were calculated for NAA/Cr and Cho/Cr as computing the absolute values of these metabolites was difficult.

A general decrease of the Cho/Cr cerebral metabolite was observed in parieto-temporal and occipital areas of the COPD patients as compared to healthy controls even though the difference was not statistically significant. The normal range of Cho/Cr ratio in healthy controls varies from region to region in human brain.[20-22] The range of Cho/Cr ratio values in normal healthy controls in parieto-temporal region is 0.80-0.90 and in occipital region it is 0.65-0.72.[20,21] These findings may be attributed to the regional differences in the specific changes that occurred in COPD patients. These cerebral metabolic changes are different from those in other diseases such as congestive heart failure (CHF)[9], diabetes mellitus[7], or hepatic encephlaopathy.[8] In contrast to patients with COPD, who showed more dramatic decreases in cerebral metabolites, patients with CHF showed a more prominent decrease of brain metabolites.[9]

In another study,[23] of 17 symptomatic COPD patients and 21 healthy volunteers, all subjects underwent ^{1}H MRS. The authors[23] reported that cerebral metabolism was significantly altered in symptomatic COPD patients. However, there was no statistically significant correlation in COPD patients between FEV_1,$PaCO_2$ and PaO_2 and the levels of cerebral metabolites. Our observations have been similar.

Most previous observations[24,25] with ^{1}H MRS strongly support the fact that NAA is a neuronal marker. The reduction of NAA generally has been reported in patients who have prominent neuronal losses, for example, glioma, stroke, dementias, and hypoxic encephalopathy. However, the NAA level of the control subjects and COPD groups did not show a significant correlation with age in our study. Neuronal cell death is generally considered to be an irreversible process accompanying ageing, and decreased levels of NAA are reported[24,25] frequently in healthy aged persons. The possibility of cerebral NAA restoration might be expected using long-term oxygen therapy for these COPD patients, as in the case with heart-transplanted CHF patients.[9] Further studies are needed to confirm whether these increases represent actual neuronal regeneration.

Mathur *et al*[26] studied the changes in cerebral ^{31}P magnetic resonance spectra (^{31}P MRS) in patients with stable COPD, and compared the results with MR spectra from similar areas of the brain in control subjects. It was interesting to speculate that as hypoxia increases, the ability of the neuron to buffer lactate, pump out protons, and retain bicarbonate might fail, resulting in intracellular acidosis. They concluded that this may be the mechanism underlying the decompensation in cerebral function with agitation, confusion, and ultimate unconsciousness that is characteristic of respiratory failure.

In conclusion, the results of our study demonstrate that the cerebral metabolism, pulmonary functions and respiratory muscle strength are altered in symptomatic COPD patients. The clinical significance of cerebral metabolic changes need to be further studied.

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