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Role of Magnetic Resonance Spectroscopy in Early Detection of Alzheimer's Disease

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Abstract: *Aims and Objectives: To assess the role of magnetic resonance spectroscopy in diagnosing early manifestations of Alzheimer's disease and to improve its accuracy in diagnosis of neurodegenerative diseases.*
Materials and Methods: The study was conducted in a group of 60 patients, who underwent MRI, along with MR spectroscopy, at our hospital. The study group was divided into thirty cognitively impaired and thirty cognitively normal patients, based on their clinical symptoms. MR spectroscopy was performed in posterior cingulate gyrus region using single voxel technique and the metabolite ratios NAA/Cr, Cho/Cr, mI/Cr and NAA/mI were calculated. These ratios were correlated with imaging and clinical diagnosis. Receiver Operating Characteristics (ROC) analysis was performed to obtain cut off values with appropriate sensitivity and specificity.
Results: Among sixty patients, 38 (63.3%) male and 22 (36.7%) female subjects in the age group of 35 to 85 years were enrolled in this study. MRS showed that NAA/Cr and NAA/mIratios were significantly reduced (NAA/Cr: p value < 0.001, sensitivity 86.7%, specificity 70%; NAA/mI: p value < 0.001, sensitivity 83.3%, specificity 65.5%). The ROC analysis revealed estimated cut off values of NAA/Cr <1.635 and NAA/mI<3.720 and we proposed that these values have an acceptable sensitivity and specificity in predicting the natural outcome of the disease process.
Conclusion: Magnetic resonance spectroscopy can be used as a screening tool in neuroimaging of neurodegenerative diseases and can be considered as a possible adjunctive screening marker of preclinical Alzheimer's disease in clinical practice.
Keywords: *Magnetic resonance spectroscopy; dementia; mild cognitive impairment; Alzheimer's disease*

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I. Introduction

The term neurodegenerative disorders denotes an inhomogeneous group of neurological diseases which are mostly of unknown etiology. These diseases are genetically determined, and in few cases, either one group of nuclei or multiple neurofunctional systems may be involved [(1)]. Different neurodegenerative disorders can cause memory disturbances and cognitive impairment. An efficient approach has to be undertaken in the early detection and stratification of patients on the basis of the underlying cause[(2)]. With the increasing prevalence of neurodegenerative diseases with the aging society, neuroimaging of the diagnosis and therapy of these diseases has become quite important.

Magnetic resonance imaging (MRI) has become an important diagnostic tool in the evaluation and diagnosis of neurodegenerative diseases, due to its high tissue contrast, which is a major advantage as compared to other imaging modalities. Along with structural MRI, magnetic resonance spectroscopy (MRS) has become an invaluable tool and approach with which the metabolite levels can be assessed in a normal or a diseased individual [(3)]. MRS, along with MRI, provides greater information concerning tissue characterization and also helps in understanding the anatomical and physiological changes in metabolic and biochemical processes occurring within the brain.

Aging is one of the primary risk factors for dementia. Dementia has become a significant health problem with increasing life expectancy. The most common pathologies associated with dementia and mild cognitive impairment (MCI) are Alzheimer's disease (AD), cerebrovascular disease, dementia with Lewy bodies (DLB), vascular dementia (VaD) and frontotemporal lobar degeneration (FTLD) [(4)]. There are many ongoing researches to compose a stratification system to slow the process of AD, which is the commonest neurodegenerative form of dementia. Including structural and functional neuroimaging, assessment of neuronal biomarkers has been necessary to evaluate the cerebral pathology that can facilitate effective treatment in this condition. Proton MRS provides a measure of brain chemistry. MRS has become a unique tool that allows quantification of brain metabolites, including N-acetyl aspartate (NAA), myo-Inositol (mI), choline (Cho) and

creatine (Cr)[5]. Other metabolites that can be measured with MRS includes glutamine (Glu), glutathione, glutamate and gamma-aminobutyric acid (GABA).

The purpose of this study is to identify metabolite changes in suspected cases of dementia and MCI and correlate with normal subjects and also, validate the utility of conventional MRS as screening method for preclinical Alzheimer's disease.

II. Materials and Methods

2.1. Study population

The study was conducted over a period of 2 years from September 2016 to September 2018. Sixty patients, in the age group of 35 to 85 years, referred to the Department of Radiodiagnosis, who were clinically suspected cases of neurodegenerative pathologies were selected and subjected to MR imaging of brain after taking an informed consent.

Based on the clinical diagnosis, the demented and cognitively impaired individuals were considered as case subjects and the cognitively normal patients who were referred for neuroimaging for other indications and showed normal imaging of brain were considered as control subjects. Studies that lacked confident clinical or pathological diagnosis were excluded. Patients with evidence of cerebral illness that affects the brain function (brain infection, seizure, cerebrovascular disease, head trauma, substance abuse or psychiatric disorders) were excluded from the study.

2.2. MRI protocol

MRI study was performed using SIEMENS MAGNETOM AVANTO MR Machine with a 1.5 Tesla scanner. Reference T2 weighted fast spin-echo images of the brain (TR/TE 4220/117 with slice thickness of 5mm) was acquired in three planes (coronal, sagittal and axial to brain). These MR images were used as a guide to select a volume of tissue from which the MR spectrum was acquired. MRS was performed using a single voxel technique with short TE of 30ms and TR of 1500ms. This technique was done using point resolved spectroscopy (PRESS) sequence. The voxel size measured 20x20x20mm and the voxel was placed on a mid-sagittal, coronal and axial slice images covering the posterior cingulateregion. Six saturation bands were placed to exclude the area outside the volume of interest. Spectra was then generated and the acquisition time for generation of MR spectra was 3 to 4 minutes. Peak assignment of the MRS spectra is as follows: NAA at 2.0ppm, Cho at 3.2ppm, Cr at 3.02ppm and mI at 3.5ppm. The software also helped determine the area under each of these peaks by fitting them to standard curves. The metabolite quantification was assessed and the metabolite ratios such as NAA/Cr, Cho/Cr, mI/Cr and NAA/mI are calculated.

2.3. Image analysis

The MR images of the brain were analyzed. T2 weighted images were evaluated to assess the degree of atrophy and other sequences were used to check for associated findings such as infarcts or hemorrhage. The MRS spectra was analyzed after its acquisition. The metabolites NAA, Cr, mI and Cho were quantified and the metabolite ratios NAA/Cr, Cho/Cr, mI/Cr and NAA/mI were calculated for cases and control subjects.

2.4. Statistical analysis

For each case, the patient identification details, age, gender, clinical symptoms, imaging and clinical diagnosis, MRS ratios were recorded and data was collected on Microsoft Excel spreadsheet. The metabolite ratios of case subjects were compared to those of control subjects and their clinical diagnosis. Collected data was analyzed using SPSS software according to frequency, percentage, mean, standard deviation, descriptive statistics and confidence intervals. Chi square test, T test and Receiver Operating Curve (ROC) analysis was performed to obtain cut off values with appropriate sensitivity and specificity.

III. Results

3.1. Qualitative analysis

In this study, a total of 60 patients were taken, out of which 38 (63.3%) were male patients and 22 (36.7%) were female patients (Table 1). Our youngest patient was 36 years old and oldest 81 years. Out of 60 patients, 5 patients (8%) were below the age of 40, 16 (27%) between 41-50 years, 15 (25%) between 51-60 years, 17 (28%) between 61-70 years and 7 (12%) above 71 years of age (Table 2).

The 60 cases included in this study consisted of 30 case and 30 control subjects based on the imaging and clinical diagnosis. Based on the clinical symptoms, 60 patients presented with dementia (n = 24, 40%), MCI (n = 18, 30%), generalised weakness (n = 34, 56.7%), Gait imbalance (n = 10, 16.7%), seizures (n = 6, 10%), resting tremors (n = 10, 16.7%), giddiness (n =14, 23.3%) and headache (n = 16, 26.7%). Dementia and generalised weakness were the most common symptoms found in case subjects. Most of the control subjects presented with either headache or giddiness (Table 3).

The MR images were used to assess the presence and localization of brain atrophy. Out of 60 cases, 30 patients were found to have cerebral atrophy. In these 30 patients, 7 (24%) were found to have mild cerebral atrophy, 12 (40%) had diffuse cerebral atrophy, 9 (30%) had diffuse cerebral atrophy with predominantly temporal lobe atrophy and 2 (6%) had diffuse cerebral atrophy with temporal and frontal lobe atrophy predominantly (Table 4). The cognitively impaired patients were diagnosed as Alzheimer's disease based on clinical and imaging diagnosis.

3.2. Quantitative analysis

After assessing the degree of atrophy on MR imaging, the metabolite ratios in posterior cingulate region were analysed. The NAA/Cr, Cho/Cr, mI/Cr and NAA/mI ratios were analysed on the basis on mean, standard deviation, confidence interval, p value and receiver operating characteristic curve. Based on the mean and standard deviation, reduced NAA/Cr, increased Cho/Cr, increased mI/Cr and reduced NAA/mI ratios were found in case subjects as compared to control subjects. On the basis of statistical analysis, of these four ratios, NAA/Cr was found to be significantly reduced in the case subjects as compared to control subjects (p value < 0.001, sensitivity – 86.7%, specificity – 70%). NAA/mI was also found to be significantly reduced in case subjects (p value < 0.001, sensitivity – 83.3%, specificity – 65.5%). Cho/Cr and mI/Cr were not found to be significant in our study (Cho/Cr p value = 0.456, mI/Cr p value = 0.989) (Table 5).

Receiver operating characteristics (ROC) analysis was performed to determine the accuracy of these metabolite ratios. Area under the curve for NAA/Cr and NAA/mI in posterior cingulate gyrus were 0.862 and 0.813 respectively. From ROC curve analysis, NAA/Cr and NAA/mI ratios were found to be most sensitive in both posterior cingulate region. NAA/Cr and NAA/mI ratios were significantly lower in subjects with dementia and mild cognitive impairment compared to subjects who were cognitively normal. Based on the coordinate assessment of the curve, we have proposed cut off values of 1.635 and 3.720 for NAA/Cr and NAA/mI ratios in posterior cingulate with a sensitivity of 86.7% and 83.3% and specificity of 70% and 65.5%respectively (Table 6).

IV. Discussion

Alzheimer's disease is the most common neurodegenerative form of dementia and there has been in-depth research projects taking place to devise treatment plans to slow the progression of disease. Establishing a system for identifying subjects at risk of prodromal Alzheimer's disease could play a valuable role in enabling preventive therapy at preclinical stages of Alzheimer's disease. Magnetic resonance spectroscopy has been found and proven to be effective in non-invasive and repeated quantification of brain metabolites. Along with conventional MR imaging, MRS can be used as a tool in capturing early brain biochemical abnormalities for early diagnosis and tracking subjects with dementia caused by Alzheimer's disease. One of the main objectives of this study was to validate the utility of conventional magnetic resonance spectroscopy as a screening method for preclinical Alzheimer's disease. Our study showed that certain metabolite ratios such as NAA/Cr and NAA/mI ratios can be used as standard reference values to suggest that the patient is at risk of developing Alzheimer's disease in future.

In the present study, a total of 60 patients were evaluated, out of which 30 cognitively impaired patients were considered as case subjects and 30 cognitively normal patients were considered as control subjects. The mean age of these 30 patients were in the age group of 61-70 years, which was in agreement with the study conducted by Katz et al[(6)], where it was shown that the incidence of dementia increased exponentially with age, and the highest incidence was between 60 and 80 years. Regarding sex prevalence, a study conducted by Peterson et al[(7)] showed that incidence of dementia and mild cognitive impairment was higher in males than females, which was also found in our study.

The clinical presentation of these subjects varied in different patients. Most of the case subjects presented with generalised weakness (56.7%) and dementia (40%) whereas giddiness and headache were the commonest complaints among the control subjects, however they were found to be cognitively normal. The cognitively impaired patients were diagnosed as Alzheimer's disease based on clinical and imaging diagnosis.

In our present study, we found that NAA/Cr was found to be significantly reduced in posterior cingulate gyrus of the case subjects as compared to cognitively normal subjects (p value < 0.001, sensitivity 86.7% and specificity 70%). Similarly, NAA/mI in posterior cingulate gyrus (p value < 0.001, sensitivity 83.3% and specificity 65.5%) was found to be significantly reduced in case subjects. Cho/Cr and mI/Cr were not found to be statistically significant in posterior cingulate gyrus, hence has been excluded (Cho/Cr in posterior cingulate gyrus: p value 0.456, mI/Cr in posterior cingulate gyrus: p value 0.989). Of the two significant ratios, NAA/Cr in posterior cingulate gyrus was found to be most sensitive (86.7%) and was more accurate to suggest that a cognitively normal patient with low NAA/Cr ratio in posterior cingulate gyrus might be at a risk of progression to clinical Alzheimer's disease.

Kantarci et al [8), (9)]performed two consecutive studies and showed that NAA/Cr is decreased in the posterior cingulate region in cases of Alzheimer's disease. However, NAA/Cr ratio is also found to be reduced in other forms of dementia such as vascular and frontotemporal dementia. Along with conventional magnetic resonance imaging, it is important to differentiate between common dementias and bring out a probable diagnosis. In our study, we have shown reduced levels of NAA/Cr ratios in posterior cingulate gyrus in case subjects and therefore, we can only imply that patients are at a risk of developing neurodegenerative disease in future and further investigations have to be undertaken to determine the same.

One of the other positive findings in our study was significant reduction in NAA/mI in posterior cingulate gyrus, which was consistent with studies performed by Waragai et al[(10)] and Schott et al[(5)]. Both the studies showed that NAA/mI ratio was the best means of discriminating patients from controls and since it is regarded as the best predictor of the pathological likelihood of Alzheimer's disease, it is a good marker in suggesting that the patient is at risk of progression of clinical Alzheimer's disease. Few studies showed raised Cho/Cr and mI/Cr ratios in posterior cingulate gyrus, which was also seen in our case. However, the statistical analysis did not reveal any significance, hence the sensitivity and specificity could not be determined.

Based on our assessment, we have concluded that magnetic resonance spectroscopy can be used as a screening tool in neuroimaging of neurodegenerative diseases. However, the role of magnetic resonance spectroscopy in differentiating different types of dementia is yet to be assessed. NAA/Cr and NAA/mI ratios in posterior cingulate gyrus measured using magnetic resonance spectroscopy should be reconsidered as possible adjunctive screening marker of preclinical Alzheimer's disease in clinical practice.

There were a few limitations to our study. Technical aspects such as motion and susceptibility artifacts caused hindrance to the present study. Since most patients in our study group were among the elderly age group and the case subjects were cognitively impaired, hence the MR spectra could not be obtained due to motion artifacts[(11)]. Lower SNR was also produced due to poor field homogeneity, which resulted in broadening of peaks. While acquiring single voxel data from several locations in the brain would have been useful, such an approach would require an excessively long acquisition protocol that would result in longer scan time. Another major limitation of the current study was lack of neuropathological confirmation of diagnosis in patients. It is quite difficult to differentiate common dementias on the basis of clinical findings alone.

V. Conclusion

Magnetic resonance spectroscopy is one of the recent techniques that provides further information regarding the metabolites in brain. This study has shown that metabolite changes can be demonstrated and quantified using proton magnetic resonance spectroscopy in patients suspected of a neurodegenerative disease. MRS helps to measure metabolites and their ratios and will be able to predict the natural course of the disease process. Hence, magnetic resonance spectroscopy may have a role in early diagnosis and progression monitoring of the disease. NAA/mI and NAA/Cr ratios in posterior cingulate gyrus were found to be significantly reduced. Future technical advances to improve the stability of acquisition, and serial MRS may yet prove to be a useful biomarker for therapeutic studies.

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Table 1: Gender wise distribution of patients studied

Gender	Frequency	Percent
Male	38	63.3
Female	22	36.7
Total	60	100.0

Table 2: Age wise distribution of patients studied

Age	Frequency	Percent
30-40	5	8
41-50	16	27
51-60	15	25
61-70	17	28
Above 70	7	12
Total	60	100

Table 3: Distribution of subjects according to clinical symptoms

Clinical symptoms	Frequency	Percent
Dementia	24	40
MCI	18	30
Generalised weakness	34	56.7
Gait imbalance	10	16.7
Seizures	6	10
Resting tremors	10	16.7
Giddiness	14	23.3
Headache	16	26.7

Table 4: Distribution of case subjects according to brain atrophy

Atrophy	Frequency	Percent
Mild cerebral atrophy	7	24
Diffuse cerebral atrophy	12	40
Predominantly temporal lobe atrophy	9	30
Predominantly temporal and frontal lobe atrophy	2	6

Table 5: Mean values of metabolite ratios in posterior cingulate gyrus

Metabolite Ratios		N	Mean	p value	Significance
NAA/Cr	Cases	30	1.569	0.000	SIG
	Controls	30	1.679		
Cho/Cr	Cases	30	0.698	0.456	NOT SIG
	Controls	30	0.652		
mI/Cr	Cases	30	0.744	0.989	NOT SIG
	Controls	30	0.744		
NAA/mI	Cases	30	3.387	0.000	SIG
	Controls	30	3.849		

Table 6: Estimated cut off values of significant ratios

Metabolite ratios	Positive if less than or equal to	Sensitivity	Specificity
NAA/Cr in posterior cingulate gyrus	1.635	86.7%	70%
NAA/mI in posterior cingulate gyrus	3.720	83.3%	65.5%

IMAGE GALLERY

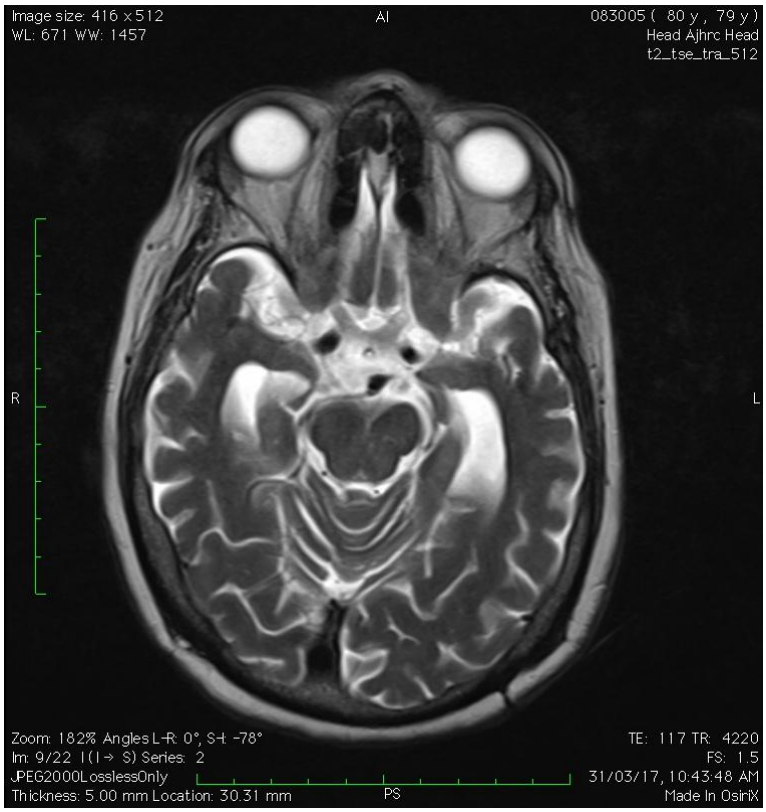
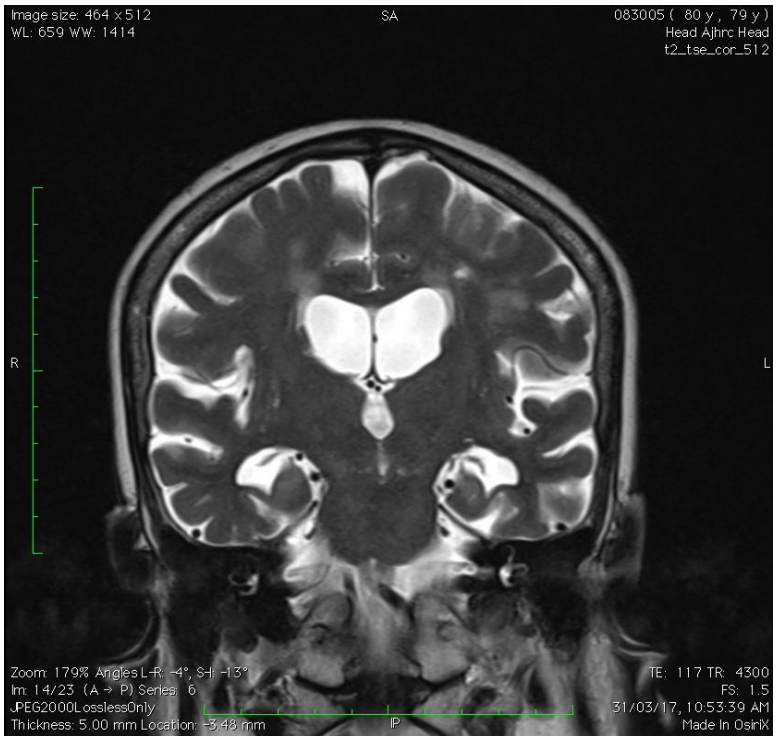


Figure 1: A, B –

T2 weighted axial and coronal images of brain depicting bilateral symmetrical temporal and hippocampal atrophy in a suspected case of Alzheimer's disease.



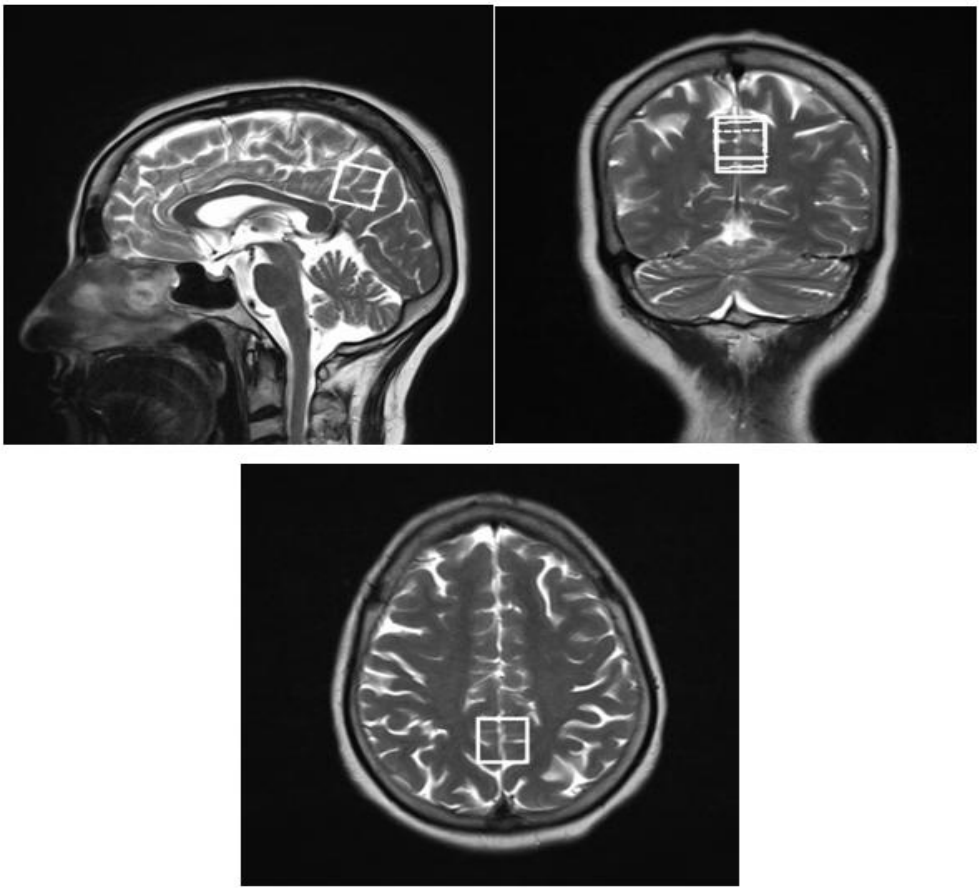


Figure 2. T2 weighted images in sagittal, coronal and axial sections showing voxel placement in posterior cingulate gyrus

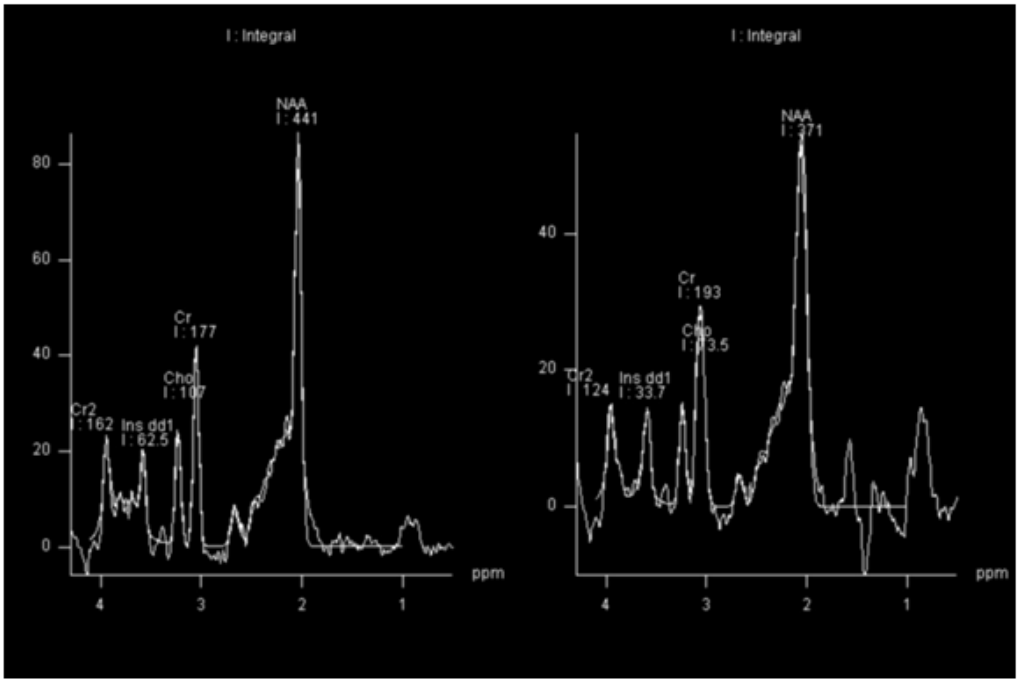


Figure 3: A, B – MR spectra obtained from a cognitively normal (A) and suspected Alzheimer (B) subjects in the region of posterior cingulate gyrus