PROTON MAGNETIC RESONANCE SPECTROSCOPY STUDY IN FRONTAL WHITE MATTER OF PATIENT WITH MAJOR DEPRESSIVE DISORDER

Hari Singh1, Vandana Verma2, Vineet Modi3, Sanjeev Kumar4, Abhay Kumar5, Neeraj Kumar6, Utkarsh Yadav7

1Assistant Professor, Department of Radio-diagnosis, Sarojini Naidu Medical College, Agra, Uttar Pradesh.
2Professor, Department of Radio-diagnosis, Sarojini Naidu Medical College, Agra, Uttar Pradesh.
3Third Year Junior Resident, Department of Radio-diagnosis, Sarojini Naidu Medical College, Agra, Uttar Pradesh.
4Senior Resident, Department of Radio-diagnosis, Sarojini Naidu Medical College, Agra, Uttar Pradesh.
5Second Year Junior Resident, Department of Radio-diagnosis, Sarojini Naidu Medical College, Agra, Uttar Pradesh.
6First Year Junior Resident, Department of Radio-diagnosis, Sarojini Naidu Medical College, Agra, Uttar Pradesh.
7First Year Junior Resident, Department of Radio-diagnosis, Sarojini Naidu Medical College, Agra, Uttar Pradesh.

ABSTRACT

BACKGROUND
Depression is one of the major problems of modern society and 350 million people worldwide are suffering from MDD. The purpose of this study was to examine the biochemical characteristics of the bilateral frontal white matter of first-episode, treatment-naive, non-late-life adult patients with MDD and healthy controls by using single-voxel 1H MRS.

METHODS
We included 45 MDD patients (24 male and 21 female), 20 healthy controls (12 males and 8 females). There were no significant differences in sex, age, and education status between the MDD group and the healthy control group. MRS scanning was performed on both the control and patient groups.

RESULTS
Study showed the means of the metabolite ratio in the bilateral frontal white matter in major depressive patients and healthy controls the NAA/Cr and Choline/Cr ratio was found to be significantly decreased in major depressive disorder patients compared with the healthy control subjects. Furthermore, there was no significant correlation between the metabolite ratio and HDRS score or the illness duration.

CONCLUSIONS
Findings suggest that the biochemical abnormalities in prefrontal white matter, especially in the left dorsolateral white matter, may occur early in the course of MDD and may be related to the neuropathology of depression.

KEYWORDS
Proton Magnetic Resonance Spectroscopy, Frontal White Matter, Major Depressive Disorder.

HOW TO CITE THIS ARTICLE: Singh H, Verma V, Modi V, et al. Proton magnetic resonance spectroscopy study in frontal white matter of patient with major depressive disorder. J. Evid. Based Med. Healthc. 2019; 6(30), 2009-2012. DOI: 10.18410/jebmh/2019/409

BACKGROUND
In its earliest days, psychiatry has sought to relate psychological processes to brain mechanisms. But development and research application of newer imaging modalities are now beginning to discover structural, functional, and neurochemical changes in the brain. Magnetic resonance spectroscopy (MRS) provides a non-invasive method for characterizing chemistry and cellular features.

Depression is one of the major problems of modern society and 350 million people worldwide are suffering from MDD. It adversely affects the socio-economic and personal life of affected individuals. There were no known biological markers that can with absolute certainty be used as diagnostic markers and prognostic indicators of this severe and debilitating disorder.

Until now, most studies have examined the alterations in frontal grey matter in MDD with fewer studies focusing on understanding white matter pathology in MDD. The purpose of this study was to examine the biochemical characteristics of the bilateral frontal white matter of first-episode, treatment-naive, non-late-life adult patients with MDD and healthy controls by using single-voxel 1H MRS.

METHODS
This cross-sectional study was conducted on the indoor and outdoor patients from the department of psychiatry referred for Magnetic resonance imaging to the Department of Radiodiagnosis, Sarojini Naidu Medical College, Agra from January 2017 to July 2018. MRS scanning was performed on both the control and patient groups.
Inclusion Criteria of Cases
All participants diagnosed as Major Depressive Disorder (MDD) according to the international classification of disease (ICD-10) categorized mild-moderate-severe depression and without psychotic symptoms were recruited for the study group.

Inclusion Criteria of Control
In addition, subjects referred for other illness for were carefully screened by a diagnostic interview, a Structured Clinical Interview for international classification of disease (ICD-10), to rule out the presence of current or past psychiatric illness were taken as control. “Informed Consent” was taken from all after briefing them a complete description of the study.

Exclusion Criteria
1. Presence of other acute psychiatric illness except for anxiety disorder,
2. History of treatment with any acute psychotropic medication within the last 12 weeks,
3. History of neurological or organic brain disorder,
4. Substance dependence except for nicotine.
5. Any physical illness demonstrated by personal history or clinical or laboratory exam.
6. First-degree relatives showing a history of neurological or mental illness in controls.
7. All Contraindications to MRI scanning.
8. Refusal to give consent

MRS studies were performed on a 1.5 T MR system. A standard eight-channel head coil was used for radio frequency transmission and reception of the MR signal. Magnetic resonance imaging examination protocol included three dimensional fast spoiled gradient-echo (3D-FSPGR) sequence (repetition time (TR)/echo-time (TE) = 6/2.5 ms, slice thickness: 1 mm, number of slices: 160, interslice gap: 0 mm, field of view (FOV): 220 × 220, number of excitation (NEX) = 1) that was obtained to confirm the absence of any structural and signal abnormality of the brain. The analysis of the spectral data was performed with the MRI manufacturer-supplied software (Achieva: Philips). The values of the NAA/Cr, Cho/Cr ratios were automatically analysed by the MR system.

RESULTS
Table 1, 2, 3, 4, 5, 6, 7 shows the demographic and clinical data of all study participants of we included 45 MDD patients (24 male and 21 female), with mean age of 30.21±9.1 (range 18 to 58) years and 20 healthy controls (12 males and 8 females) with a mean age of 30±9 (range 18 to 58) years. The mean number of marital status 50±10.1 (married 16, non-married 27 and widow 2). The mean number of patients for MDD was found to be more in urban as compare to rural habitats distribution (rural 14, (male 6 female 8); urban 31, (male 18 and female 13). The mean number of education years was 10±3 (class 5-16) years for patients and control. The mean number of professional status among patients were 7±2 (skilled-5, unskilled-5, unemployed-28, professional-7). The mean socioeconomic status of the MDD patients were 600±2000 Rs. among patients, the mean duration of illness was 9.20±6.02 (30 to 24) months and the mean HDRS score was 30±7.01 (18 to 41). There were no significant differences in sex, age, and education status 0 between the MDD group and the healthy control group.

Table 8 shows the means of the metabolite ratio in the left and right frontal white matter in major depressive disorder patients and healthy controls. In left frontal white matter, the NAA/Cr and Choline/ Cr ratio found to be significantly decreased in major depressive disorder patients compared with the healthy control subjects. Similarly, significantly lower NAA/Cr, Choline/ Cr ratio. Ratios were observed in the right frontal white matter of major depressive patients as compared to healthy controls. Furthermore, there was no significant correlation between the metabolite ration and HDRS score or the illness duration.
DISCUSSION

To our knowledge, this is the first study using a single voxel in Indian subcontinent 1H MRS to demonstrate biochemical changes of the bilateral prefrontal white matter in first-episode treatment naive non-late-life adult patients with MDD. In this study, MDD patients showed significantly lower NAA/Cr ratios in the bilateral dorsolateral white matter and lower Cho/Cr ratios in the bilateral dorsolateral white matter compared with the control subjects. These data suggest that biochemical abnormalities in the white matter may provide an important neurobiological substrate to MDD, especially in the early stage of the disease without the interference of medication.

Many factors, including the mean age of subjects, age at onset of depression, illness duration, depression severity, drug administration, and methods of imaging data processing and analysis, could result in these inconsistencies. In general, most MRS studies have tended to focus on gray matter and have not investigated the white matter to the same extent.

Structural MRI studies in MDD patients have found that increased white matter hyperintensities were common and severe in deep white matter and frontal-subcortical regions, especially at the level of the DLPFC and reduced white matter volume have also been revealed in the frontal lobe. Additionally, recent studies used diffusion tensor imaging (DTI) to report disruptions of white matter integrity and cortical-subcortical circuitry in MDD. Thus, our results together with these findings support the notion that structural and have found that increased white matter hyperintensities were common and severe in deep white matter and frontal-subcortical regions, especially at the level of the DLPFC and reduced white matter volume have also been revealed in the frontal lobe. In this study, lower NAA/Cr ratios in MDD patients were observed in the bilateral dorsolateral white matter compared to healthy subjects. NAA is thought to be present almost exclusively in neurons and their dendritic and axonal extensions but not in glia. The NAA signal provides a marker of neuronal and axonal integrity. For this reason, diminished NAA levels represent a reduction of neuronal and/or axonal population within this area or, at least, neuronal and/or axonal dysfunction. However, more recent studies have demonstrated that NAA levels can be expressed in mature oligodendrocytes. Oligodendroglia is known to serve as neuronal satellites in gray matter and form myelin sheaths in white matter. Therefore, decreased NAA levels in this study suggest oligodendrocyte and myelin abnormalities in the bilateral dorsolateral white matter. We also found decreased Cho/Cr in the left dorsolateral white matter of MDD patients compared to controls. Cho is an essential precursor of the neurotransmitter acetylcholine and the membrane lipids, phosphatidylcholine and sphingomyelin. Reduction of Cho levels is shown to associate with decreased membrane turnover and/or impaired intracellular signal transduction systems. Alternatively, as Cho is hugely present in oligodendrocytes, this finding, in conjunction with the NAA finding, suggests abnormalities in oligodendrocyte and myelinization in the bilateral dorsolateral white matter of MDD patients. On the other hand, we used the single voxel spectroscopy technique to assess ratios of NAA/Cr and Cho/Cr because multi voxel has some potential limitations should be taken into consideration. First, the relatively small sample size may have reduced the statistical power of our analyses, and small changes in the metabolite concentrations may not have been detected.
Especially in the left dorsolateral white matter, may occur early in the course of MDD and may be related to the neuropathology of depression. The lower ratios of NAA/Cr and Cho/Cr indicate perturbations of neuronal and/or axonal integrity, possible oligodendrocyte and myelin abnormalities in frontal white matter. Future studies can use 1H MRS absolute quantification to explore whether such biochemical abnormalities are progressive over the course of MDD as well as the relationship between these abnormalities and depression severity, response to treatment, and risk of relapse.

CONCLUSIONS
We used the single voxel spectroscopy technique to assess ratios of NAA/Cr and Cho/Cr. The single voxel technique has the advantage of acquiring chemical information from a single brain area, typically of large volume in order to obtain sufficient SNR, and with variable voxel placement. The biochemical abnormalities in prefrontal white matter, especially in the left dorsolateral white matter, may occur early in the course of MDD and may be related to the neuropathology of depression. The lower ratios of NAA/Cr and Cho/Cr indicate perturbations of neuronal and/or axonal integrity, possible oligodendrocyte and myelin abnormalities in frontal white matter. Future studies can use 1H MRS absolute quantification to explore whether such biochemical abnormalities are progressive over the course of MDD as well as the relationship between these abnormalities and depression severity, response to treatment, and risk of relapse.

REFERENCES
[1] DEPRESSION: a global crisis World Mental Health Day, October 10, 2012.
[2] Heiden A, Kettenbach JO, Fischer P, et al. White matter hyperintensities and chronicity of depression. Journal of Psychiatric Research 2005;39(3):285-293.
[3] Iosifescu DV, Papakostas GI, Lyoo IK, et al. Brain MRI white matter hyperintensities and one-carbon cycle metabolism in non-geriatric outpatients with major depressive disorder (part I). Psychiatry Res 2005;140(3):291-299.
[4] Steingard RJ, Yurgeln-Todd DA, Hennen J, et al. Increased orbitofrontal cortex levels of choline in depressed adolescents as detected by in vivo proton magnetic resonance spectroscopy. Biological Psychiatry 2000;48(11):1053-1061.
[5] Bae JN, MacFall JR, Krishnan KR, et al. Dorsolateral prefrontal cortex and anterior cingulate cortex white matter alterations in late-life depression. Biol Psychiatry 2006;60(12):1356-1363.
[6] Thomas AJ, O’Brien JT, Davis S, et al. Ischemic basis for deep white matter hyperintensities in major depression: a neuropathological study. Arch Gen Psychiatry 2002;59(9):785-792.
[7] Meyerhoff DJ, MacKay S, Bachman L, et al. Reduced brain N-acetylaspartate suggests neuronal loss in cognitively impaired human immunodeficiency virus-seropositive individuals: in vivo 1H magnetic resonance spectroscopic imaging. Neurology 1993;43(3 Pt 1):509-515.
[8] Urenjak J, Williams SR, Gadian DG, et al. Proton nuclear magnetic resonance spectroscopy unambiguously identifies different neural cell types. J Neuroscience 1993;13(3):981-989.
[9] Bhakoo KK, Pearce D. In vitro expression of N-acetyl aspartate by oligodendrocytes: implications for proton magnetic resonance spectroscopy signal in vivo. J Neurochem 2000;74(1):254-262.
[10] Uranova NA, Vostrikov VM, Orlovskaya DD, et al. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. Schizophrenia Research 2004;67(2-3):269-275.
[11] Kusumakar V, MacMaster FP, Gates L, et al. Left medial temporal cytosolic choline in early onset depression. Can J Psychiatry 2001;46(10):959-964.