CAN METABOLITE LEVELS QUANTIFIED WITH ^{1}H-MRS IN THE HIPPOCAMPUS PREDICT RECURRENCE OF MOOD EPISODES IN FIRST EPISODE MANIA PATIENTS? A 5-YEAR FOLLOW-UP STUDY.

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INTRODUCTION:

- First episode mania (FEM) marks the onset of BD.
- Studies suggest that recurrence rates are common and occur in 58% of patients within 1 year and 74% of patients within 4 years of FEM despite clinical care[1].
- While numerous clinical factors have been reported to be associated with recurrence, none lend themselves to accurate prediction of recurrence.
- Studies using proton Magnetic Resonance Spectroscopy (^{1}H-MRS) have found differences in markers of neuron oligodendrocyte coupling – N-acetyl aspartate (NAA), as well as the excitatory neurotransmitter, Glutamate (Glu)[2].

OBJECTIVE:

- To examine if the baseline metabolite levels, NAA & Glu measured using ^{1}H-MRS predict recurrences over 5 years follow-up of patients with FEM.

METHODOLOGY:

- FEM (DSM-IV criteria) patients, with/without psychotic symptoms, with/without comorbidities within 3 months of FEM were recruited from Vancouver Hospital Health Sciences Center (VHHSC) and affiliated sites from 2009-2015.
- Patients were excluded based on the standard criteria for exclusion for Magnetic Resonance Imaging (MRI) and a previous manic episode diagnosed retrospectively.
- Age and sex matched healthy controls with no history of psychiatric disorder and no family history of any major psychiatric disorder in the first- or second-degree relatives were recruited.
- It was a naturalistic follow-up study for 5 years and treatment was given as per clinical need.
- The baseline assessment included a structured clinical interview using the Mini International Neuropsychiatric Interview (MINI) to confirm the diagnosis of FEM/BD by an academic research psychiatrist.
- The clinical rating scales were Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HAM-D).

Baseline MR Data Collection:

- 3T Philips Achieva (Best, The Netherlands).

MRI:

- T1 & T2 weighted images were obtained first.

MRS localized with PRESS:

- 30*15*15 mm^3 hippocampus in right and left hemisphere.
- TE / TR = 35/2000 ms.
- Chemical shift selective (CHESS) pulses were used to suppress the water signal, and water-unsuppressed signals were also obtained for eddy current correction and to reference metabolite signals.
- In total, 128 water-suppressed and 16 non-water-suppressed transients were acquired from each voxel.

MRS Data Processing:

- FSL-FAST segmentation of the 3DT1 images into grey matter, white matter, and cerebrospinal fluid with the single voxel location mapped to the segmentation maps. Figure 1 gives the Voxel location.
- The metabolite basis set for the FSL-MRS fitting routine was simulated with actual radiofrequency pulse shapes.
- Residual water peak removal and phase correction was done as a part of processing.
- Metabolite concentrations with absolute errors higher than 30% of median were considered poorly fit and rejected. Figure 2 gives one of the best spectroscopy fits.

RESULTS:

- We had collected baseline MRS for 65 patients and 35 controls. But, there were 17 patients and 17 controls with baseline MRS with better fit and had completed 5 years of follow-up.
- There were no recurrences in 3 (17.6%) patients. 9 (52.9%) patients had depressive episode, 4 (23.5%) had manic and 1 (5.9%) had hypomanic episode as the first recurrence after FEM.
- Baseline NAA was significantly higher in the patients and controls (Figure 4, patients mean rank = 20.71; controls mean rank = 14.29, p = 0.04).
- However, Glu levels at baseline were trending towards significance and were lower in the patients than controls (Fig 3, patients mean rank = 13.82; controls mean rank = 20.38, p = 0.056).
- Cox regression analysis done to see if NAA/Glu predict the time to first recurrence of any mood episode was not significant (NAA mean – 17.09, Hazard ratio – 0.88 [95% C.I – 0.77,1.09] p = 0.34; Glu mean -17.5, Hazard ratio – 2.0 [95% C.I – 0.79, 1.03] p = 0.15).

FIGURE 1: VOXEL LOCATION

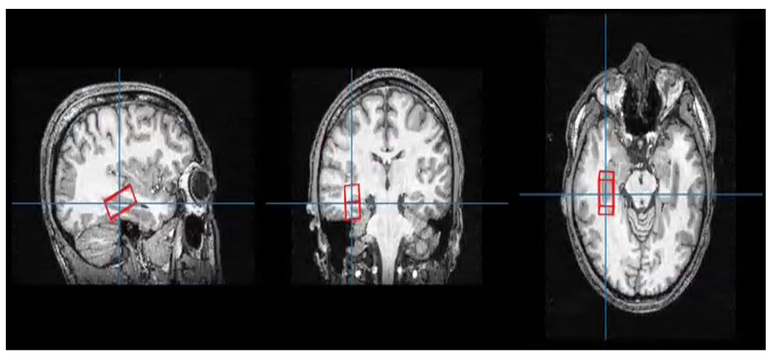


FIGURE 2: SPECTROSCOPY FIT

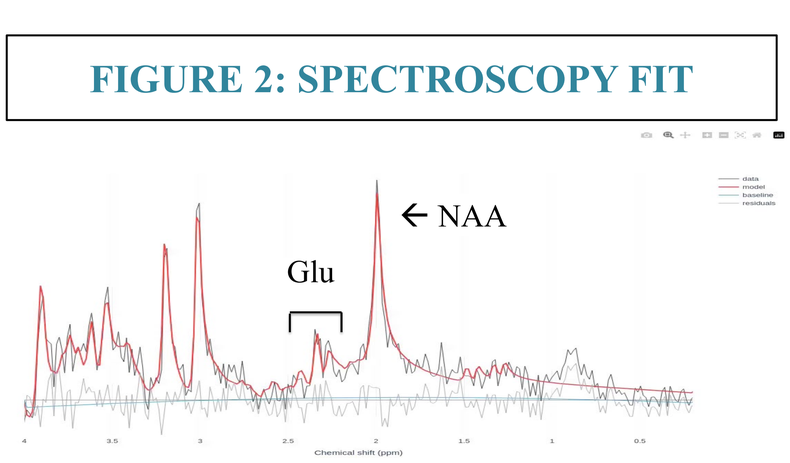


TABLE 1: SOCIO-DEMOGRAPHIC & CLINICAL DETAILS

Group	N	Age (years)	Sex (M:F)	Psychosis in FEM	Substance use	Anxiety disorder
Patients	17	22 ± 2.98	7:10	14 (82.3)	4 (23.5)	5 (29.4)
Controls	17	22 ± 3.4	7:10			

FIGURE 3: COMPARISON OF Glu LEVELS AT BASELINE

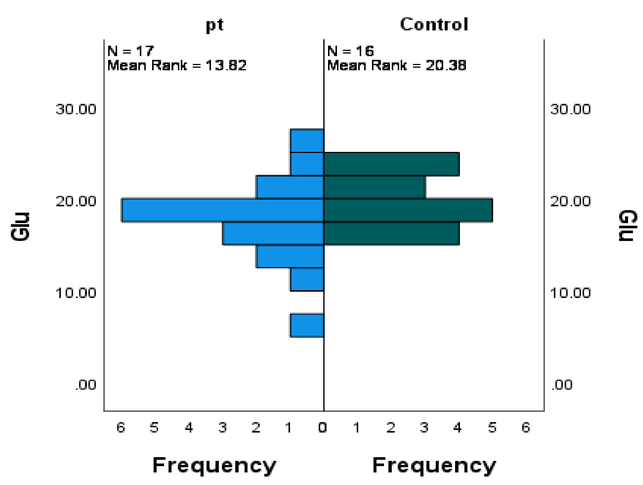
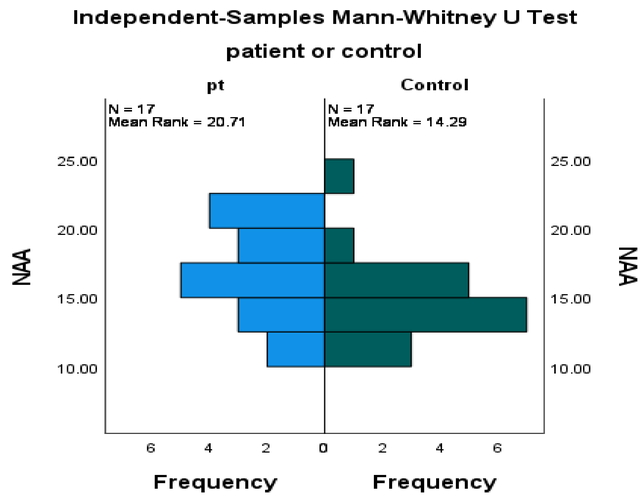


FIGURE 4: COMPARISON OF NAA LEVELS AT BASELINE



DISCUSSION & CONCLUSION:

- The levels of NAA were significantly higher in patients with BD when compared to controls which shows there are changes in NAA in patients with BD.
- However, early in the course of illness, NAA/Glu levels don't predict the time to first recurrence.
- Limitations: Poor quality of the MRS data leading to lesser sample size.

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2. Chabert J, Allauze E, Pereira B, Chassain C, De Chazeron I, Rotge JY, et al. Glutamatergic and N-Acetylaspartate Metabolites in Bipolar Disorder: A Systematic Review and Meta-Analysis of Proton Magnetic Resonance Spectroscopy Studies. Int J Mol Sci. 2022;23(16).

ACKNOWLEDGEMENT: We thank the staff and other Clinicians at UBC that supported the recruitment for this study including Nazlin Walji, Jayasree Basavireddy, Shannon Reid, Taj Dhanoa, Dr. Edwin Tam, Dr. David Bond, Dr. Astrid Vik, Dr. Manjunath, Dr. Kamyar Keramatian.