Assessment of Neurochemical Alterations that Occur in Bipolar Patients Following Medication Using Proton Magnetic Resonance Spectroscopy.

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Abstract :

Several studies demonstrated the neurochmeical alterations in bipolar patients using proton magnetic resonance spectroscopy (MRS). Few studies compared between the changes that occur before treatment and that which occur after the patient achieved complete remission. Patients with bipolar disorder having manic episode were hypothesized to demonstrate metabolic abnormalities with in the anterior cingulate and that these abnormalities are altered with medication. Twenty patients with bipolar disorder (age 20-53 years, mean 29.5 ± 7.61) with a mean duration of (32.65 ± 12.93) to achieve complete remission were evaluated with proton MRS. The metabolic concentration of the anterior cingulate were calculated using a single voxel. The results of this study revealed that there is a significant decrease in the level of myo-inositol following treatment. In addition there is a trend towards increase in the level of N-acetyl aspartate following medication. However there was no significant difference in the level of choline and creatine. The results of this study suggest that there is abnormalities in the phosphoinositid cycle as evident by the significant changes that occur in the myo-inositol level. Changes that occur in N-acetyl aspartate level suggest that there is neuronal dysfunction in bipolar patients and that it may need more time to be more evident.

Introduction

Bipolar disorder is a common, life long illness that typically begins in late adolescence. The illness is implicated in functional impairment and represents an important risk factor for suicide ***(Oquendo and Mann, 2001***). However, the neurochemistry and pathogenesis of bipolar disorder remain poorly understood. Evidence implicating abnormal frontal circuitry in the pathophysiology of mood disorders is known ***(Soares and Mann, 1997).*** Morphometric measures of frontal (prefrontal and orbitofrontal) structures have demonstrated a trend for decreased volume particularly in gray matter ***(Lim et al, 1999; Sax et al, 1999)***. Cerebral blood flow and metabolism investigations suggest frontal hypometabolism in patients with mood disorders ***(Drevets et al. 1997)***. Consistent with these findings are histopathologic reports demonstrating marked reduction in density and size of cortical neurons and glial cells ***(Rajkowska, 1997; Ongur et al, 1998)***.

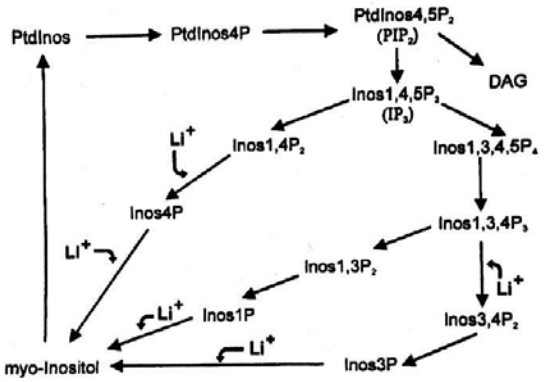
One strategy used to gain insight into the underlying pathophysiology of a disease/illness is to identify the mechanism(s) of action of medications which reduce symptom severity in the majority of patients afflicted with the disease/illness. There is mounting evidence suggesting that the phosphoinositide – protein kinase C (PI-PKC) signal transduction pathway is a common target of chronic mood stabilizer, atypical antipsychotic and antidepressant drugs ***(Calker and Belmarker, 2000)***.

Moreover, until very recently Lithium was the mainstay of long term treatment for

patients with bipolar disorder ***(Geddes et al, 2004)***. Lithium is an uncompetitive antagonist of inositol monophosphatase thus resulting in increased concentrations of the inositol monophosphates ***(Berridge and Irvine, 1989)***, and a corresponding decrease in myo-inositol concentration based upon these findings it was hypothesized that the clinical utility of lithium in bipolar disorder may be due to these actions on the PI cycle ***(Berridge et al, 1989)***.

Phosphotidylinositol (PI) is a major component of neuronal cell membranes. The phosphoinositide cycle (Fig 1) has been discovered as a major second messenger system ***(Berridge and Irvine, 1989)***. Receptor stimulation by neurotransmitters activates phospholipase C enzyme in a number of membrane receptor signaling pathways. Phospholipase C triggers the break-down of phosphatidylinositol-bis-phosphate (PIP2) to inositol 1,4,5 triphosphate (IP3), which releases calcium from internal stores. A series of phosphatases remove the phosphate groups from IP3 sequentially, releasing free inositol ***(Frey et al, 1998)***.

Figure 1 : Phosphoinositide cycle



Phospholipase C triggers the breakdown of phospahatidylinositol-bis-phosphate (PIP2) to inositol 1,4,5-triphosphate (IP3), which has a function as a second messanger. Lithium reduces brain levels of myo-inositol by inhibition of inositol-phosphatase. Frey et al 1998.

Magnetic resonance spectroscopy (MRS) is a non-invasive computerized imaging technique that relies on the same nuclear magnetic resonance (NMR) principles that form the basis of magnetic resonance imaging (MRI) and functional MRI (fMRI). It is used in both clinical and research settings to study brain chemistry, as it enables the relative quantification of certain compounds and their constituents in specific brain regions ***(Chakos et al, 1998)***. In psychiatry, MRS is increasingly used to research the neurochemical changes that occur in psychiatric disorders such as schizophrenia, dementia and affective disorders ***(Malhi et al, 2002)***. Recently it has been used to identify the neurochemical effects and predictors of response to medication commonly used to treat bipolar disorder ***(DelBello et al, 2006)***.

Over the past decade a growing number of magnetic resonance spectroscopic studies investigating the neurochemical basis of bipolar disorder have been accumulated. However, there have been mixed results from these studies preventing a conclusion

on the direction of the alterations expected on individual neurochemcials ***(Brambilla et al, 2005a)***.

With these considerations in mind, the aim of this study was to identify the neurochemical effects of treatment in bipolar patients presenting with manic with psychotic features in the anterior cingulate. We hypothesized elevated myo-inositol (MI) would reflect impaired phosphoinositide metabolism and decreased N acetyl aspartate (NAA), choline (Cho)and Creatine (Cr) of the prefrontal cortex would reflect impairments in neural function and that these metabolites are altered with medications.

Methodology :

Subjects:

Patients hospitalized with bipolar disorder receiving the diagnosis manic with psychotic features were recruited from consecutive admissions to the inpatient psychiatric units at the Institute of Psychiatry Ain Shams University Faculty of Medicine. Twenty patients were between 20 ad 53 years with a mean age (29.5 ± 7.61).

Twelve patients were male (60%) and 8 patients were female (40%). The diagnosis were made according to ICD10 using the ICD10 symptoms check list. The mean duration of the illness was 7.15 ± 5.33, with a mean age of onset 22.35 ± 6.6 and a mean number of episode 5.2 ± 3.49. Ten patients (50%) had a positive family history of mood disorder as out lined in table 1 and 2.

Patients with history of ICD10 substance dependence excluding tobacco, any major medical or neurological disorder, a history of head trauma, any contraindication to receiving a magnetic resonance imaging (MRI), a diagnosis of mental retardation were excluded from the study.

The institutional review boards of research of Ain Shams University Institute of Psychiatry approved the study protocol. All participants provided an informed consent after complete description of the study protocol was provided to them.

Procedures:

Manic symptoms were assessed using the Young Mania Rating Scale Score (YMRS) ***(Young et al, 1978)***. The mean score before starting any medication was 47.65 ± 6.1. The patient before scanning did not receive any medication except for Midazolam intravenous between 15 to 20 mg to sedate the patients during scanning as any slight movement affect the scanning. Medications to which the patient responded include mood stabilizer, antipsychotic and ECT are summarized in table 3. The medication was adjusted according to the protocol of each unit and patients' past history of medication to which they responded. The mean duration to which the patients achieved complete remission was 32.65 ± 12.93 to which the mean score of YMRS was 4.8 ± 2.04.

Magnetic resonance imaging and spectroscopy:

Structural imaging and spectroscopy were performed using a 1.5 T Philips Intera scanner and a quadrate proton head coil. Following sagital image localization, a 3D coronal volume scan (SPGR; 124/60 slices; matrix: 256 x 192; 1 NEX; Flip angle = 45; SLT = 1.5/3mm; TE = 5 ms; TR = 35 ms) was acquired for image segmentation and T2 weighted axial images were used for spectral localization.

Water suppressed localized spectra were acquired using a 16 x 16 MRS I grid [field of view : 16 x 16 cm; voxel size : 1 x 1 x 2 cm; in plan (axial) thickness : 2 cm] and the PRESS pulse sequence (echo time = 6000 ms; repetition time = 31 ms and 144 ms). A single voxel was centered on the anterior cingulate cortex and midline with sufficient tissue surrounding it being no closer than 1 cm from the skull.

Data were processed and pertinent metabolic ratios were obtained via intensity values generated by the machine. The spectral peak areas for Myo-inositol (MI), N-acetyl aspartate (NAA), choline (Cho) and creatine (Cr) were expressed as peak intensity curves in both short Fig (2,4) and long sequences (Fig 3,5).

Table (1): Descriptive analysis of the sample

	Minimum	Maximum	Mean ± Sd
Age	20	53	29.5 ± 7.61
Age of onset	16	43	22.35 ± 6.6
No. of episode	2	13	5.2 ± 3.49
Duration of illness	1	21	7.15 ±5.33
YMRS before treatment	30	54	47.65 ± 6.1
YMRS after treatment	2	8	4.8 ± 2.04
Time to B.L	15	55	32.65 ± 12.93

Table 2: Gender and Family history

Sex	Male	12	60%
	Female	8	40%
Family history	Positive	10	50%
	negative	10	50%

Patient	Age	Sex	Age of onset	No. of episode	Family history	Duration of illness	YMRS before treatment	YMRS after treatment	Time to return to baseline	Medications
1	30	M	17	12	Negative	13	52	6	55	Carbamazpine, Risperdone, ECT
2	23	F	21	2	Positive	2	50	7	35	Lithium, Haloperidol, ECT
3	30	M	25	5	Negative	5	52	4	34	Carbamazpine, Haloperidol, ECT
4	28	M	20	6	Positive	8	50	6	40	Lithium, Trifluperazine, ECT
5	25	M	20	5	Positive	5	54	8	28	Lithium, Olanzapine ECT
6	26	F	20	6	Negative	6	39	2	20	Carbamazpine, Haloperidol ECT
7	30	F	28	3	Negative	2	40	2	19	Lithium, Risperdone, ECT
8	20	M	16	4	Positive	4	49	8	53	Divaloprate. Clozapine ECT
9	28	F	16	12	Negative	12	50	4	25	Carbamazpine, Triflueperazine ECT
10	33	F	16	8	Positive	17	50	8	20	Lithium, Haloperidol, ECT
11	28	M	22	2	Negative	6	50	5	28	Lithium, Divaloprate, Aripiprazole ECT
12	26	F	16	4	Positive	10	43	5	20	Lithium, Risperdone, ECT
13	28	M	27	2	Positive	1	52	7	52	Lithium,Carbamazepine Risperdone, ECT
14	53	F	43	5	Negative	10	30	4	15	Carbamazpine,Chloropromazine
15	35	M	28	2	Negative	7	50	4	33	Lithium, Haloperidol, ECT
16	20	M	18	3	Negative	2	42	3	54	Lithium, Haloperidol, ECT
17	42	M	21	13	Negative	21	54	6	37	Lithium, Haloperidol, ECT
18	26	M	20	5	Positive	6	53	4	35	Lithium, Clozapine ECT
19	24	M	22	2	Positive	2	45	5	25	Lithium,Risperdone, ECT
20	35	F	31	3	Positive	4	48	2	20	Lithium, Haloperidol, ECT

Statistics: Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 10. Wilcoxon Signed Ranks test was used to detect the difference between metabolites before and after medications

Results:

The result of our study reveal that there is significant decrease in myoinositol level (Z = 2.9, P<0.01), in the post medicated patients. However, although the increase in N-acetyl aspartate is non significant, there is a trend towards increase of NAA in most patients (Z=0.3, P>0.05). Moreover there is no statistical difference in Choline (Z=0.73, P>0.05). and creatine level (Z = 0.21, P>0.05). in patients following medication (table 4).

Figure 2: Premedication short

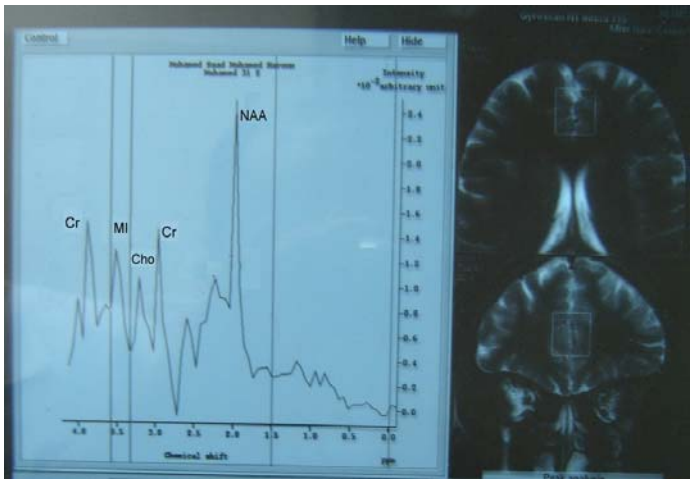


Figure (3): Pre-medication long

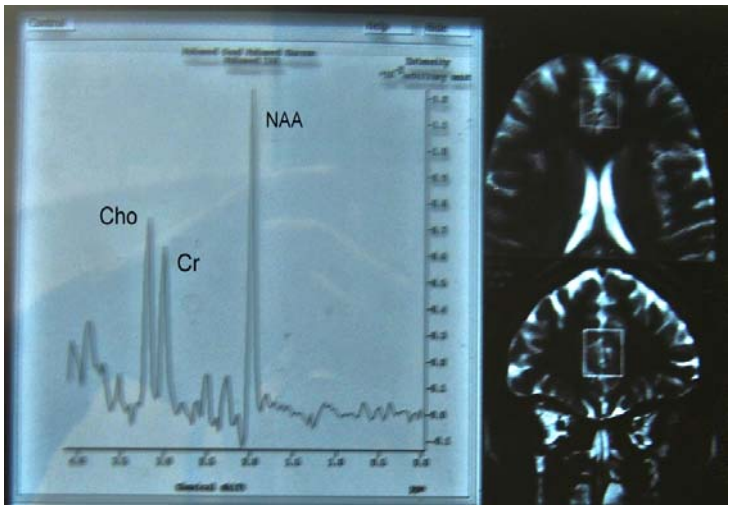


Figure 4: Post medication short

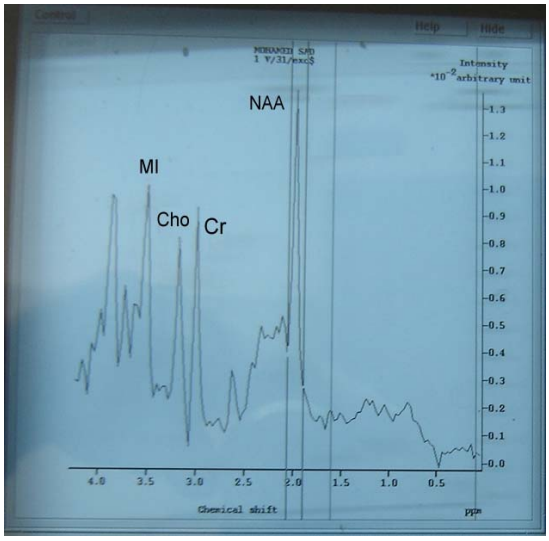


Figure 5: Post medication long

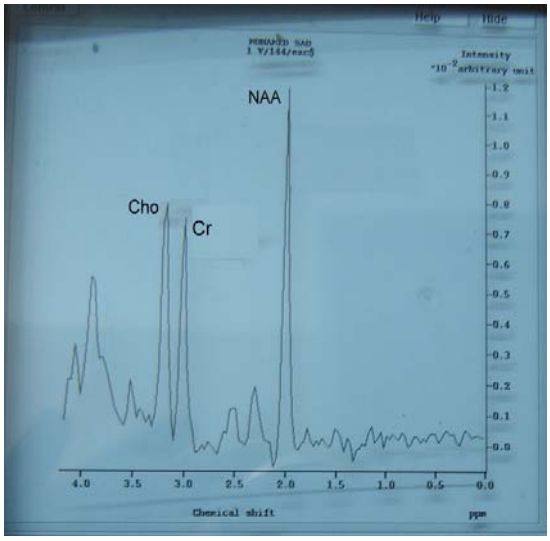


Table (4): Comparison between metabolites pre and post medication

	Pre medications			Post medications			Z value	Sign.
	Min	Max	Mean	Min	Max	Mean		
MI	53	515	162.6±125.9	36	150	75.7±29.6	2.9	<0.01
NAA	63	232	130±54.5	68	302	170±70.1	0.3	>0.05*
Cho	24	175	68.5±44.9	34	190	87.8±56.4	0.73	>0.05
Cr	8	224	99.4±56.1	20	176	98.5±48.9	0.21	>0.05

*although the p value of NAA is not significant, yet there is a trend towards increase.

Discussion:

Magnetic resonance spectroscopy (MRS) is a non-invasive approach that allows in vivo investigation of brain chemistry. The most commonly used spectroscopic approach is proton MRS (^{1} HMRS) which can detect myo-inositol (MI) N-acetyl aspartate (NAA), choline containing compounds (Cho) and creatine (Cr) which is composed of phosphocreatinine and creatinine which are high energy phosophate metabolites ***(Brambilla et al, 2004)***.

Anterior cingulate was chosen in this study since the prefrontal cortex has been linked to the regulation of the expression of emotional state. ***(Sax et al, 1999)***. Within the prefrontal cortex the anterior cingulate has extensive connections with other brain areas involved in emotional processing ***(Bush et al, 2002)***, such as amygdale, insula, thalamus and preiaqueductal gray matter, and orbital cortex ***(Lane et al, 1998; Barbas, 2000)***. Therefore it has been implicated in the pathophysiology of

bipolar disorder because it participates in modulating decision making, planning and mood regulation ***(Drevets et al, 1998, Vogt et al, 2003)***.

Myo-inositol (MI):

Myo-inositol plays a crucial role in the transduction of signals in the brain acting as a second messenger and being the key intermediate of the phosphinositol pathway and the substrate for recycling of inositol phospholipid ***(Stanley, 2002)***

The results of our study indicate that there is significant reduction of the myo-inoistol level following complete remission. This is in agreement with previous reports ***Davanzo and colleagues 2001***, who found increased myo-inositol level in the anterior cingulate cortex of children with bipolar disorder during the manic phase and subsequent decease following 7 days of lithium intake. Also ***Cecil et al, 2003***, reported 16% elevation in the myo-inositol concentration in the frontal cortex in bipolar patients in the manic phase. Moreover other studies investigating the euthymic state found no difference in the level myo-inositol between patient and healthy control ***(Winsberg et al, 2000; Silverstone et al 2002; chang et al, 2003)***. The results of our study support the hypothesis of previous studies that in bipolar patients who are acutely ill, there is abnormal PI cycle activity. In euthymic patients any abnormalities in PI cycle functioning are normalized possibly secondary to the effect of medications.

N-acetyl aspartate (NAA) :

N-acetyl aspartate is the second abundant aminoacid after glutamate, in the human brain and is the most prominent peak in the proton spectrum after water. NAA is found only in the mature neurons and is thought to be a marker of neuronal integrity, viability and activity ***(Urenjak et al, 1993)***. Our results reported a trend towards an increase in NAA concentration following medications. This is in agreement with ***Moore et al 2000*** who reported an increase in NAA concentration with in the frontal lobe following 4 weeks of lithium therapy in adult patient. Consistent with these finding ***DelBello et al 2006*** who reported olanzapine remitters patients exhibited a greater increase in medial ventral prefrontal NAA level compared with non-remitter. Also **Cecil et al 2003** reported 8% lower for NAA level in children with a mood disorder with in the cerebellar vermis compared with healthy children. Furthermore increased bilateral thalamic NAA levels have been shown in euthymic male patients with bipolar 1 disorder compared with healthy control ***(Deicken et al, 2001)***. ***Brambilla et al 2005a*** concluded that this increase in NAA level may reflect neuronal hypertrophy, reduced glial density or abnormal synaptic or dendritic pruning. The result of our study though revealed only a trend towards increase in NAA level yet it is preliminary and needs replication with assessment of the effect of medication on the long term basis and its effect on the structure changes that occur due to medications.

Choline (Cho):

Choline (Cho) resonance is predominantly composed of phosphorylcholine (PC) and glycerophosphoryl choline. Therefore, the Cho Peak is considered as a potential biomarker for the status of membrane phospholipids metabolism ***(Moore and Galleway 2002)***. The results of our study find no significant difference between choline level before and after medication. This is consistent with other studies where

subjects were mostly on lithium which couldnot detect any significant difference in choline levels between patients and controls in different brain regions ***(Stoll et al, 1992; Bruhn et al, 1993; Kato et al, 1994; ohara et al, 1998; Amaral et al, 2002; Brambilla, 2005b)***. However other studies reported increased choline in the basal ganglia of euthymic bipolar patients compared with healthy subjects, a findings not attributable to lithium since most of the subjects on these studies were not taking lithium ***(Sharma et al, 1992; Lafer et al, 1994; Kato et al, 1996; Hamakawa et al, 1998)***. Another study by ***Moore et al 2000*** reported increase choline in the right cingulate cortex compared with control subjects. From the previous studies ***Bramella et al 2005a*** concluded that elevated choline levels in bipolar disorder if present may be specific for basal ganglia and may be independent of lithium treatment suggesting alterations in membrane metabolism.

Creatine (Cr)

Creatine peak reflects the presence of both creatine and phosphocreatine. The equilibrium between creatine and phosphocreatine is determined by the cellular demand for high energy phosphate stored as creatine phosphate ***(Moore and Galloway, 2002)***. The results of our study revealed that there is no statistical difference between creatine level before and after medication. This is consistent with other studies which investigated the level of creatine during the manic phase in the dorsolateral prefrontal cortex, medial orbital cortex and prefrontal cortex and find no significant difference between patients and control ***(Cecil et al, 2002; Micheal et al, 2003)***. Other studies as ***Hamakawa et al 1998, 1999 and Brambella et al 2005b*** also reported no significant difference between euthymic bipolar patients and normal cortrol in the basal ganglia, frontal cortex and dorsolateral prefrontal cortex. Moreover studies investigated the depressive phase ***Friedman et al 2004 and Dager et al 2004*** reported the same result in cingulate, thalamus, parietal and occipital lobe. Therefore it seems that the level of creatine is relatively constant through out the phases of the illness.

Limitation of the study:

It should be pointed out that the present study has a number of limitations. We only investigated metabolism in the anterior cingulate cortex using a single voxel technique with inability to compare between the right and left cingulate as this would need more time with equivalent increase in sedation doses. Also the small number of the subjects with heterogeneity regarding the duration of the illness, family history and medication used.

In conclusion we have noted alterations in the myo-inositol level and N-acetyl aspartate in the anterior cingulate before and after treatment. However, the results of this study is very preliminary and need further replication taking in consideration larger samples, other phases of the illness as depressive and mixed phases, first episode patients with longitudinal studies, using same treatment and further detailed analysis of the aminoacid moieties

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تغيير التغييرات الايميائية التى تحدث فى مرضى الاضطراب الوجدانى الثنائى القطب باستخدام التحليل الطيفى للرنين المغناطيسى

تناولت العديد من الدراسات الخاصة التغييرات الكيميائية التى تحدث فى مرضى الاضطراب الوجدانى باستخدام التحليل الطيفى للرنين المغناطيسى. ولكن القليل من هذه الدراسات قارن بين هذه التغييرات قبل بداية العلاج وبعد اكتمال الشفاء. فى هذا البحث تم اختيار عشرين من مرضى الاضطراب الوجدانى ثنائى القطب نوبة هوس، والذين تـم تشخيصـهم باستخدام التقسيم العالمى للأمراض (ICD 10)، كما تم تقييم المرضى قبل العلاج وبعد اكتمال الشفاء باستخدام مقياس YMRS. وقد أظهرت الدراسة أن مستوى مادة الـ MI ينخفض بشكل كبير بعد العلاج، كما يوجد ميل الـى زيـادة مستوى مادة NAA، ولكن لا يوجد تأثير على مادة الـ Cho والـ Cr. وبذلك تشير هذه الدراسة الى احتمال تـأثير العلاج على الـ phosphoinositide cycle.