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Neurochemical alterations in anterior cingulate cortex in bipolar disorder: a proton magnetic resonance spectroscopy study (1H-MRS)

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Summary

Aim. The aim of this study was to determine neurochemical alterations in bipolar disorder using proton magnetic resonance spectroscopy (1H-MRS).

Method. We investigated a group of 27 patients diagnosed with bipolar disorder (with manic and mixed episodes, depression and after remission of symptoms) and 10 healthy subjects. MR imaging and 1H-MRS were performed on a 1.5 T scanner. Voxels of 8 cm^3 were positioned in the anterior cingulate, left frontal lobe and left temporal lobe. Spectral peaks of NAA (N-acetylaspartate), Glx (glutamate/glutamine/GABA complex), Cho (choline), Cr (creatine/phosphocreatine) and mI (myo-inositol) were analyzed and the ratios of these metabolites to creatine (Cr) and non-suppressed water signal were determined.

Results. In the anterior cingulate cortex of patients with bipolar disorder a significantly higher Cho/H_2O ratio ($p = 0.029$) and a trend toward higher Cho/Cr ratio values ($p = 0.096$) were observed as compared to healthy controls.

Conclusions. The findings of our study prove that neurochemical changes occurring in the anterior cingulate cortex of bipolar patients are related to altered choline levels.

Key words: bipolar disorder, cingulate gyrus, proton magnetic resonance spectroscopy

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Introduction

Magnetic Resonance Spectroscopy (MRS) is a modern neuroimaging technique that allows direct measurement of chemical compounds in vitro and in vivo, including chemicals produced in metabolic processes [1]. It is used to study metabolic changes of the central nervous system (CNS) in various psychiatric disorders, such as schizophrenia, Alzheimer's disease, affective disorders, eating disorders and autism [2–6]. In clinical practice, proton magnetic resonance spectroscopy (^{1}H-MRS) is most commonly used because hydrogen plays a key role in life processes. The ^{1}H-MRS measures signals derived from various metabolites, e.g., N-acetylaspartate (NAA) – the marker of neuron functions; creatine and phosphocreatine (Cr+PCr) – considered to determine the brain energetic state; choline-containing compounds (Cho) – known to be associated with cellular membrane turnover; glutamine and glutamate (Glx), gamma-aminobutyric acid (GABA); myo-inositol (mI) – involved in osmoregulatory functions; lipids (Lip), lactates (Lac) [1]. Neurochemical changes detected by MRS may help to examine the neurobiology underlying the symptoms of psychiatric disorders as well as track the course of these diseases and the patients' response to treatment.

Functional neuroimaging studies performed to date to investigate bipolar affective disorders allowed researchers to develop a model of "functional neuroanatomy", which assumes that in bipolar disorder there appear abnormalities in the structure and function of key emotional control networks in the human brain, i.e. decreased connectivity between ventral prefrontal networks and limbic brain structures including, most importantly, amygdala [7]. In their functional studies, Mayberg et al. indicated also the increased activity in subgenual cingulate region in the states of sadness, and the decreased activity in the same area during the remission of the symptoms of depression that followed the antidepressant treatment [8]. The above observations have been used to apply the deep brain stimulation method in subgenual cingulate gyrus for treatment-resistant depression: chronic stimulation of this area has been connected with the remission of the depression symptoms [9]. Moreover, a study of bipolar patients with the use of vMRI revealed regional deficits in the frontal lobe, particularly in the anterior cingulate gyrus and the orbitofrontal cortex [10].

Proton spectroscopy studies of the brain regions connected with pathophysiology of the bipolar disorder have confirmed the presence of a number of metabolic changes in those areas, which can be trait marker of bipolar disorder. The study of the patients with different stages of illness has described the decrease of NAA in hippocampus [11], the decrease of creatine and choline in dorsolateral prefrontal cortex [12], and the increase of choline in cingulate gyrus [13]. The decrease of levels of NAA, choline, creatine and Glx has been verified in basal ganglia, with the simultaneous increased levels of myo-inositol [14]. However, there are also reports that do not observe the altered levels of GABA, glutamate and glutamine in basal ganglia or the whole brain [15].

Aim

Taking into consideration the above mentioned reports, the aim of our study was to determine the neurochemical changes in patients with bipolar disorder with the use of proton MR spectroscopy.

Material and methods

The examined group consisted of 27 patients suffering from bipolar I disorder diagnosed according to ICD-10 and DSM-IV criteria. The group included 19 women (70%) and 8 men (30%); the mean age was 43 years (from 23 to 59 years, SD – 11.27). The Montgomery-Asberg Rating Scale (MADRS) [16] and Young Mania Rating Scale (YMRS) [17] were used to assess the mental condition of bipolar patients. Among the participants of this study, there were 11 patients with manic (n = 7) and mixed episodes (n = 4), 10 with a depressive episode and 6 during remission of the symptoms. The participants were either hospitalized in the psychiatric hospital in Choroszcz (Department of Psychiatry, Medical University of Białystok) (n = 16) or were ambulatory patients (Outpatient Department/Outpatient Mental health Clinic) (n = 11). All patients, except one man who achieved remission, were on psychotropic drugs. Specifically, 26 patients were taking mood stabilizers; 7, 13, 7 and 2 were taking lithium, valproic acid, carbamazepine and lamotrigine, respectively. In addition, 15 patients were on antipsychotic medications whereas 11 were on antidepressants. The control group comprised 10 healthy individuals: 6 women (60%) and 4 men (40%). The mean age was 40.2 years (from 24 to 56 years, SD – 11.99). The following exclusion criteria were used: organic damage of the CNS upon the medical history and routine neurological examination (a history of head trauma, epilepsy, serious neurological disorders); active alcohol or psychoactive substance abuse, contraindications for magnetic resonance (MR) scanning. All participants provided written consent to the study, according to the protocol approved by the Medical University of Bialystok Bioethics Committee.

MR imaging and ^{1}H-MRS examinations were performed using a 1.5 T scanner in the Department of Radiology, Medical University of Bialystok. Voxels (volumes of

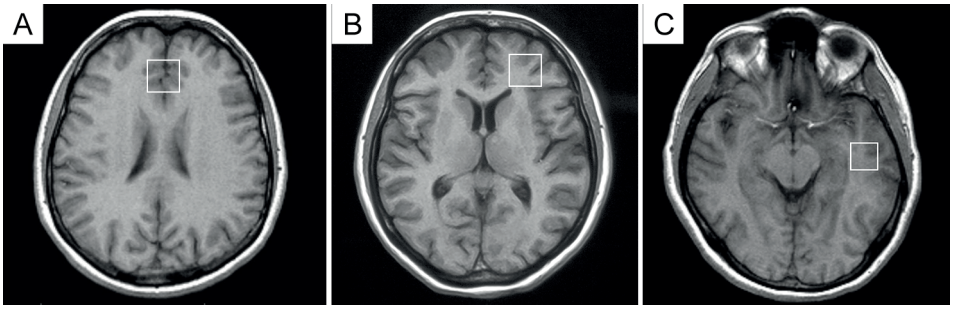

Figure 1. **Voxel placement: anterior cingulate gyrus (A), left frontal lobe (B), left temporal lobe (C)**

interest) of 2 x 2 x 2 cm were positioned in the anterior cingulate gyrus, left frontal lobe and left temporal lobe (Figure 1.).

The voxels have been located based on previous MRS studies of patients with bipolar disorder [18]. Positioning of the voxels has been conducted by an experienced radiologist in three anatomical terms of location: plane sagittal, plane coronal and plane axial, with simultaneous minimizing the content of the cerebrospinal fluid. The anterior cingulate gyrus voxel has been placed in centre line, in front of the corpus callosum. The left frontal lobe voxel has been placed above the anterior horn of the left lateral ventricle, and it is mainly comprised of the white matter and the cortex of the superior frontal gyrus and middle frontal gyrus. The left temporal lobe voxel has been placed in inferior-lateral temporal lobe area, and it is comprised of the white matter and the cortex of the inferior temporal gyrus and middle temporal gyrus. A point-resolved single voxel localized spectroscopy (PRESS) sequence was used with the following parameters: TE = 35 ms, TR = 1500 ms, NEX = 192. The multiply optimized insensitive suppression train (MOIST) method was used for suppressing the signal from water. Spectroscopic data were analyzed using the software package provided by Picker. The levels of chemical compounds in MR spectra were evaluated in relation to Cr and nonsupressed water signal. Relative concentrations of the following chemicals were calculated: NAA (N-acetylaspartate) – detected at 2.01-ppm chemical shift, Glx (glutamate/glutamine/GABA complex) in the area from 2.11 to 2.45 ppm, Cho – at 3.22 ppm, Cr+PCr – at 3.03 ppm, and mI – at 3.56 ppm.

Statistical analysis was performed using Statistica 10 software. Non-parametric tests were applied due to a small sample size. Mann-Whitney U test and chi-square test were used to compare demographic data (the latter to compare sex distribution). The comparison of ^{1}H-MRS results of both patient group and control group was done with the Mann-Whitney U test. Spearman's rank correlation coefficient was used to measure the correlation between metabolite levels and symptom severities. P-values < 0.05 were considered statistically significant.

Results

The examined patients with bipolar disorder did not differ significantly in age, sex and education from healthy individuals (Table 1).

Table.1 Clinical **and demographical data for patients with bipolar disorder and controls**

	Patients N = 27	Controls N = 10	p
Age (years)	43 ± 11.27 (23–59)	40.2 ± 11.99 (24–56)	0.516
Females/males	19/8	6/4	0.549
Education (years)	14.93 ± 2.51 (11–18)	14.9 ± 2.85 (10–18)	0.986
Age of illness onset (years)	34.15 ±10.65 (14–55)	–	
Disease duration (years)	8.79 ± 7.21 (0.5–28)	–	
Number of hospitalizations	4.41 ± 3.88 (0–15)	–	

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MADRS (score)	12.59 ± 12.05 (0–41)	–	
– depressive episode (n = 10)	20.9 ± 9.89 (9–41)	–	
– manic episode (n = 7)	3.28± 3.45 (0–9)	–	
– mixed episode (n = 4)	24.25 ± 9.54 (16–38)	–	
– remission (n = 6)	1.83 ± 1.83 (0–4)	–	
YMRS (score)	7.19 ± 7.87 (0–23)	–	
– depressive episode (n = 10)	1.1 ± 1.66 (0–5)	–	
– manic episode (n = 7)	15.71 ± 5.15 (9–23)	–	
– mixed episode (n = 4)	16.00 ± 2.94 (13–19)	–	
– remission (n = 6)	1.5 ± 1.87 (0–5)	–	

Mean ± SD; Mann-Whitney U test and chi-square test (sex distribution). MADRS – Montgomery-Asberg Rating Scale; YMRS – Young Mania Rating Scale

The average ratios of chemical compounds in select brain regions analyzed by ^{1}H-MRS in both examined groups are presented in Table 2.

Table 2. **Mean ratios of chemical compounds in studied regions for patients with bipolar disorder and controls**

Region	Ratios of Chemical compounds	Patients N = 27	Controls N = 10	p
Left frontal lobe	NAA/Cr	1.81 ± 0.36	1.66 ± 0.28	0.375
	Glx/Cr	2.00 ± 0.69	1.97 ± 0.61	0.951
	Cho/Cr	1.00 ± 0.20	0.93 ± 0.36	0.282
	mI/Cr	0.77 ± 0.19	0.68 ± 0.33	0.133
	NAA/H_2O	0.46 ± 0.08	0.43 ± 0.09	0.375
	Glx/H_2O	0.49 ± 0.13	0.51 ± 0.16	0.855
	Cho/H_2O	0.26 ± 0.06	0.23 ± 0.06	0.299
	Cr/H_2O	0.26 ± 0.04	0.27 ± 0.02	0.361
	mI/H_2O	0.19 ± 0.05	0.18 ± 0.09	0.145
Left temporal lobe	NAA/Cr	1.70 ± 0.35	1.90 ± 0.45	0.209
	Glx/Cr	2.07 ± 0.60	2.46 ± 0.97	0.441
	Cho/Cr	0.93 ± 0.21	0.92 ± 0.17	0.959
	mI/Cr	0.68 ± 0.26	0.73 ± 0.23	0.596
	NAA/H_2O	0.42 ± 0.10	0.41 ± 0.08	0.291
	Glx/H_2O	0.51 ± 0.15	0.55 ± 0.25	0.692
	Cho/H_2O	0.23 ± 0.07	0.20 ± 0.05	0.199
	Cr/H_2O	0.25 ± 0.04	0.23 ± 0.06	0.573
	mI/H_2O	0.17 ± 0.06	0.16 ± 0.06	0.797

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Anterior cingulate gyrus	NAA/Cr	1.64 ± 0.20	1.71 ± 0.44	0.737
	Glx/Cr	2.13 ± 0.52	2.03 ± 0.61	0.633
	Cho/Cr	0.81 ± 0.11	0.69 ± 0.19	0.097
	mI/Cr	0.67 ± 0.18	0.81 ± 0.21	0.116
	NAA/H_2O	0.47 ± 0.04	0.46 ± 0.06	0.818
	Glx/H_2O	0.59 ± 0.15	0.54 ± 0.11	0.153
	Cho/H_2O	0.23 ± 0.04	0.19 ± 0.05	0.029*
	Cr/H_2O	0.29 ± 0.03	0.28 ± 0.05	0.737
	mI/H_2O	0.19 ± 0.05	0.22 ± 0.05	0.427

Mean ± SD; *$p < 0.05$ Mann-Whitney U test

In the anterior cingulate gyrus of patients with bipolar disorder a significantly higher Cho/H_2O ratio ($p = 0.029$) and a trend toward higher Cho/Cr ratio values ($p = 0.096$) were observed as compared to healthy controls. Between the groups there were no statistically significant differences in concentration of other examined chemical compounds.

In the case of patients with bipolar disorder, worsening of manic symptoms measured by the YMRS score inversely correlated with the mI/H_2O ratio in their anterior cingulate gyrus ($R_s = – 0.43$; $p = 0.029$).There was no significant correlation between the patients' clinical condition evaluated using the MADRS and the content of the analyzed chemical compounds.

Discussion

In this study, a higher concentration of choline measured as the Cho/H_2O ratio was observed in the anterior cingulate gyrus of patients with bipolar disorder compared to healthy controls. As the anterior cingulate gyrus is mainly responsible for generating emotions, in patients with bipolar disorder this structure, with amygdala, plays a key role in cognition and emotion processing mainly in depressive states [19].

So far the reports concerning the levels of choline in studied brain areas in patients with bipolar disorder are inconclusive. In studies on untreated patients with different stages of illness a decrease in levels of choline in right caudate nucleus [14] and in left dorsolateral prefrontal cortex area has been observed [12]. In other reports the altered levels of choline have not been observed in the studied areas (i.a. anterior cingulate gyrus) in the group of patients with different stages of the illness (depression, hypomania, mania, euthymia) [11], or in the group of untreated patients, categorized mainly as depressive state and mixed state [20].

Our results are consistent with the findings by Moore et al. [13], who reported the elevated choline levels in the right anterior cingulate cortex of bipolar patients compared with control subjects. Signals derived from choline-containing compounds are related with concentration of phosphocholine and glycerophosphocholine, and reflect intensified metabolism in cellular membranes [21]. The elevated choline in patients

may indicate increased membrane breakdown and changes in signal conduction between cells in the anterior cingulate gyrus. Altered brain choline levels are associated with the clinical condition and the course of the disease; they correlate positively with depression severity [13] and mania severity [22], and negatively with a number of affective episodes [23].

In the present study, the severity of manic symptoms negatively correlated with the level of myo-inositol in the anterior cingulate cortex. Inositol is located within astrocytes, is responsible for the regulation of osmosis and maintaining proper cell volume [1], and may play a role in pathophysiology of bipolar disorders [21]. Also Dager et al. [20] reported an inverse correlation between myo-inositol levels in the grey and white matter and worsening of mania in untreated bipolar patients, predominantly in a depressed or mixed-mood state. However, positive correlations were found between worsening of manic state in bipolar patients having a manic or mixed episode and the content of myo-inositol within the frontal white matter [22].

In the conducted study we have compared the group of patients with different stages of the illness to the group of healthy people, thus, the observed differences in the levels of choline might be the trait marker of the bipolar disorder. The survey results implicate that the decrease of NAA and increase of choline levels have been verified in euthymia [18] and the changes in levels of myo-inositol can be observed in states of depression or mania [24]. Yüksel and Öngür [25] in their review of findings of glutamatergic metabolites in mood disorders, find Glx level reductions in major depressive disorder and elevations in bipolar disorder regardless of the disease state. In addition, reduced glutamine/glutamate ratio is observed in depression and elevated in mania. These patterns suggest that modulation of the glutamine/glutamate ratio in opposite directions may be related to clinical state [25]. However, due to Frye et al. [26] it is unclear whether anterior cingulate glutamate is related to the different disease state (increased level of glutamate in bipolar disorder and decreased level of glutamate depressive disorders) or to the current phenomenologic presentation (increased glutamate in non-melancholic depressed bipolar versus decreased glutamate in melancholic bipolar depressed subjects).

The determination whether the differences in the levels of the chemical compound are correlated with the psychopathological state is possible by longitudinal study, which compares the same patients being in different illness episodes with the healthy people. Examining patients – in the state of depression and after mania/hypomania episodes, did not acknowledge the changes in levels of NAA and choline in the studied brain regions [11]. The double assessment of the patients – in the state of hypomania and euthymia has indicated the decrease of NAA, myo-inositol and choline levels in anterior cingulate gyrus and frontal cortex only in the state of hypomania [27]. Nevertheless, the longitudinal study of the patients suffering from bipolar II rapid cycling disorder has indicated the increased levels of NAA, choline, creatine and Glx in the every episode of the illness, which suggests that the increased neuronal activity might be significant biological feature of bipolar II disorder [28].

The limitation of our study is the fact that the studied patients have been treated. It is known from the research papers that mood stabilizers, such as lithium, carba-

mazepine and valproic acid exert their therapeutic effects through regulation of the phosphatidylinositol system [29]. The lithium treatment causes the lowering of the Glx levels and the raise of myo-inositol in the grey matter [30], but also results in normalization of the NAA, which is an indirect proof of neuroprotective effect of lithium [31]. Moreover, the antipsychotic medications increase the levels of NAA [32, 33]. It might affect the observable lack of differences in the range of NAA, mI, and Glx. The registered increase in choline levels can be connected with the impact of olanzapine [33]; nonetheless, the antidepressants may decrease the levels of choline [13].

The next limitation is the number of the studied groups: the patient group and the control group, which might be too small to detect the significant differences in the levels of the chemical compounds between the two groups [18]. Furthermore, the limitations of our study may also result from the technical aspects of ^{1}H-MRS method. We have analyzed the proportions of the chemical compounds concerning the creatine (Cr) and the unsuppressed water signal, and not their concentration. We have not performed the segmentation within the voxels as this procedure was not available in our study, therefore, our results can be influenced by the different content of the white and grey matter in the voxels. Nonetheless, the voxel positioning has been performed in a specific manner to minimize the content of the cerebrospinal fluid and obtain the maximal content of the grey matter.

Conclusions

The results of our study confirm that neurochemical changes occurring in the anterior cingulate gyrus of patients with bipolar disorder are related to altered choline levels.

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