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Original article

Dorsolateral prefrontal *N*-acetyl-aspartate concentration in male patients with chronic schizophrenia and with chronic bipolar disorder

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Abstract

Objectives. — A study of *N*-acetyl-aspartate (NAA) can provide data of interest about cortical alterations in psychotic illnesses. Although a decreased NAA level in the cerebral cortex is a replicated finding in chronic schizophrenia, the data are less consistent for bipolar disease. On the other hand, it is likely that NAA values in schizophrenia may differ in men and women.

Methods. — We used proton magnetic resonance spectroscopy (^{1}H MRS) to examine NAA levels in the prefrontal cortex in two groups of male patients, one with schizophrenia ($n = 11$) and the other with bipolar disorder ($n = 13$) of similar duration, and compared them to a sample of healthy control males ($n = 10$). Additionally, we compared the degree of structural deviations from normal volumes of gray matter (GM) and cerebrospinal fluid (CSF) in the dorsolateral prefrontal cortex.

Results. — Compared to controls, schizophrenia and bipolar patients presented decreased NAA to creatine ratios, while only the schizophrenia group showed an increase in CSF in the dorsolateral prefrontal region. There were no differences in choline to creatine ratios among the groups.

Conclusions. — These data suggest that the decrease in NAA in the prefrontal region may be similar in schizophrenia and bipolar disorder, at least in the chronic state. However, cortical CSF may be markedly increased in schizophrenia patients.

Keywords: Schizophrenia; Bipolar disorder; *N*-acetyl-aspartate; Spectroscopy; Prefrontal cortex

1. Introduction

N-Acetyl-aspartate (NAA) levels are dependent on the quantity of viable neuronal tissue [44]. Its concentration may be decreased in the cerebral cortex in schizophrenia, at least in chronic stages of the disease [24,30].

It would be of great interest to know whether there are similar decreases in NAA in the chronic stages of other psychotic disorders, such as bipolar disorder, which could help us understand its cerebral substrates and possible differences from schizophrenia. This is of special interest in the light of recent data that show both distinctive and similar patterns of brain abnormalities in schizophrenia and bipolar illness related to genetic risk [28]. Differences in NAA concentration between chronic bipolar disorder and chronic schizophrenia could reflect a difference in the outcome of brain alterations between these diagnoses.

Spectroscopic data for bipolar disease are less consistent than for schizophrenia. In the frontal region -the region most commonly studied in schizophrenia—one group described decreased NAA and choline levels, expressed as absolute data,

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in bipolar patients [14]. Another recent study of this disorder did not find decreased frontal NAA [17], nor did a postmortem study [37]. Studies in other regions in bipolar disorder reported decreased NAA in the hippocampus [8] and an increase in the thalamus [18]. In bipolar disorder, normal NAA/Cr ratios have been also found in the cingulate gyrus [1]. These results suggest the importance of studying bipolar and schizophrenia patients with the same methodology. To our knowledge, no study has yet compared the spectroscopic data for both diagnoses.

To achieve this, we studied patients with chronic bipolar disorder and schizophrenia, investigating differences in frontal NAA concentrations, as well as their relationship with the structural alterations described in each disease. Since there seem to be relevant differences between males and females in structural [36] and spectroscopic [12] characteristics, at least in schizophrenia, we limited our study to males.

Our hypothesis was that there would be greater alterations in patients with schizophrenia compared to controls. We expected a significant decrease in NAA concentration relative to controls in schizophrenia but not in bipolar patients. A simultaneous study of volumetric and spectroscopic data could improve our understanding of the pathological brain processes underlying each disorder.

2. Patients and methods

Eleven males with schizophrenia (10 paranoid, 1 undifferentiated), 13 with type I bipolar disorder, and 10 healthy controls were enrolled. The diagnosis was made according to DSM-IV criteria. The patients (bipolar and schizophrenic) were clinically stable in a euthymic state, with no changes in medication in the past 3 months. Disease duration was similar in bipolar and schizophrenia patients (Table 1). Of the schizophrenia patients, 3 were treated with clozapine, 2 with haloperidol, and 6 with olanzapine, all with monotherapy. Those treated with haloperidol were treatment resistant and were enrolled just prior to conversion to clozapine. Of the bipolar patients,10 were receiving lithium, 3 valproate, 2 carbamazepine, 1 lamotrigine, 1 quetiapine, and 1 risperidone. Seven bipolar patients had a past history of episodes with psychotic symptoms. There was a significant age difference among groups (Kruskal–Wallis test, $\chi^2 = 10.9$, $df = 2$, $P = 0.004$), since the controls were younger, but there were no differences between the bipolar disorder and schizophrenia groups.

Structural and metabolic data on the schizophrenia patients and controls were used in previous reports using samples that partially overlapped with the present one [30,31,33].

Diagnosis was confirmed using a semi-structured clinical interview (SCID, patient version) and information provided by relatives and clinical staff. We evaluated parental socioeconomic level using the Hollingshead Index [22].

After providing written information, we obtained the written informed consent of the patients and their relatives. The ethics committees of the participating centers endorsed the study.

The 10 healthy controls had a below college educational level and no significant differences from patients with respect to parental education or socioeconomic level. Exclusion criteria for patients and controls were: residual schizophrenia, neurological disease, MRI findings deemed clinically relevant from a neurological perspective by a radiologist blind to diagnosis, history of cranial trauma with loss of consciousness, substance abuse during the past 3 years (other than caffeine or nicotine), history of axis I psychiatric disorders or treatment (other than schizophrenia or bipolar disorder in patients), or current treatment with a known CNS depressant or stimulant (in controls).

3. Imaging methods

3.1. Spectroscopy

3.1.1. Spectral acquisition

Proton spectra were acquired using a Philips 1.5 T Gyroscan ACS scanner, with a localized single voxel PRESS (point resolved spectroscopy) sequence [9] (TE = 136 ms;

Table 1
Mean (SD) volumetric and spectroscopic values for each group

	Schizophrenia ($n = 11$)		Bipolar ($n = 13$)		Controls ($n = 10$)	
Age (years)	36.7 (5.8)		37.8 (6.7)		27.2 (4.9)	
Illness duration (years)	9.1 (3.9)		10.2 (7.3)		2.45 (0.54)	
Right NAA/Cr	1.84 (0.53)*		1.82 (0.48)		1.89 (0.46)	
Left NAA/Cr	1.53 (0.30)*		1.68 (0.58)**		1.13 (0.48)	
Right Cho/Cr	1.36 (0.55)		1.04 (0.31)		1.07 (0.30)	
Left Cho/Cr	1.15 (0.42)		1.01 (0.56)			
Right DLPF CSF	6.29 (6.05)**	16.92 (5.34)	−1.26 (4.00)	17.30 (5.14)	−0.60 (3.14)	14.28 (3.59)
Left DLPF CSF	5.69 (6.49)**	16.14 (5.24)	−1.06 (4.54)	16.97 (6.12)	0.30 (2.83)	14.81 (4.33)
Right DLPF GM	−4.09 (3.91)	30.88 (5.00)	−2.01 (3.38)	36.23 (5.65)	−1.16 (2.59)	35.52 (4.74)
Left DLPF GM	−3.05 (3.71)	28.74 (4.04)	−0.94 (3.35)	33.48 (5.49)	−0.85 (2.08)	34.54 (4.20)
Intracranial volume	1384.20 (105.11)		1395.12 (176.99)		1431.68 (45.43)	

NAA/CR, *N*-acetyl-aspartate–creatine ratio; Cho/Cr, choline–creatine ratio; DLPF, dorsolateral prefrontal cortex; CSF, cerebrospinal fluid; GM, grey matter. For volume measurements, two data are shown: age corrected residuals used for statistical analysis (left column, see Section 2) and raw values in cc (right column), to help appraisal of group differences.

Significant differences in the patient groups with respect to controls are shown at $^*P < 0.05$, $^{**}P < 0.01$ levels, Mann–Whitney U-test.