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Effect of treatment with atypical drugs for 6 months on brain levels of N-acetyl aspartate or serum levels of brain-derived neurotrophic factor in early-stage first-episode schizophrenia – a preliminary study

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ABSTRACT

In the present study, we investigated the effects of atypical antipsychotic drugs on brain NAA and serum BDNF levels in early-stage first-episode schizophrenia patients. Sixteen (8 males, 8 females; mean age: 30 ±11 yr) of 18 patients were followed for 6 months. All patients were treated with atypical antipsychotic drugs. No changes in NAA concentrations in the three regions were observed from before treatment to 6 months after atypical psychotic treatment. In addition, serum BDNF levels also did not change from before to 6 months after treatment. These preliminary results suggest that relatively short-term treatment with atypical antipsychotic drugs may be unlikely to alter brain NAA concentrations and serum BDNF levels in early-stage first-episode schizophrenia.

Keywords: N-acetyl aspartate, brain-derived neurotrophic factor, magnetic resonance spectroscopy, schizophrenia, atypical antipsychotic drug

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INTRODUCTION

Proton magnetic resonance spectroscopy (1H-MRS) is a non-invasive functional neurological measurement. N-acetyl aspartate (NAA) might play a role in osmoregulation, myelination, glial cell signaling, and neuronal function, and is considered a sensitive marker of neuronal viability and function. The NAA signal is thought to indicate viable neurons. NAA is located almost exclusively in neurons, and reduced levels are considered a marker not only of neuronal loss but also of neuronal functioning, including mitochondrial activity [22]. Also, 1H-MRS studies have repeatedly found reduced concentrations of NAA in the prefrontal and temporal lobes, most consistently in chronic mediated schizophrenia patients [25]. Some investigators have found reduced NAA levels in the frontal lobes of antipsychotic drug-naïve patients [3,6,7], while others have found no differences between schizophrenia patients and controls [2,5,25]. An earlier meta-analysis by Steen et al. [26] of frontal and medial temporal lobe 1H-MRS findings in patients with schizophrenia and first-episode schizophrenia demonstrated that NAA levels were reduced in both regions but that there were no differences between first-episode schizophrenia and chronic schizophrenia. In short, the reduced levels seen in the brain regions in first-episode schizophrenia remain to be elucidated.

Brain-derived neurotrophic factor (BDNF) is a

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neurotrophic factor that plays a crucial role in the development, regeneration and maintenance of neural function in the central nervous system. A strong association has been demonstrated between BDNF signals and dopaminergic function in the brain [16]. BDNF is also involved in the neurodevelopment of dopaminergic–related systems [29], principally the mesolimbic dopaminergic systems [1]. Recent post-mortem studies have revealed reduced BDNF protein and BDNF mRNA levels in the hippocampus and prefrontal cortex of patients with schizophrenia [30,31], whereas other studies have found elevated BDNF levels in the anterior cingulate cortex and hippocampus [7,25]. In addition, there is disagreement regarding the significance of BDNF levels in schizophrenia patients and the extent to which they are affected by antipsychotic drugs [11].

We have previously reported that NAA levels in the left basal ganglia and parieto-occipital lobe were significantly reduced in untreated first-episode schizophrenia patients, and we have also reported that there were no differences in the serum BDNF levels between untreated first-episode schizophrenia patients and sex- and age-matched healthy controls [13]. These results indicate that the NAA levels in these regions more sensitively reflect early changes in the progression of schizophrenia than serum BDNF levels. Lang et al. [20] reported that BDNF serum concentrations reflect some aspects of neuronal plasticity, as indicated by the association between BDNF serum concentrations and NAA levels in the cerebral cortex. Recently, Lee et al. [21] reported that serum BDNF levels were increased by treatment with atypical or typical antipsychotic drugs. Taking these findings into account, it is possible that treatment with atypical antipsychotic drugs increases both brain levels of NAA and serum levels of BDNF. Thus, we hypothesized that treatment with atypical antipsychotic drugs alters brain NAA levels and serum BDNF levels in the patients and, to confirm our hypothesis, we conducted this study to investigate the effects of atypical antipsychotic drugs on brain NAA levels and serum BDNF levels.

To the best of our knowledge, few data exist about the effects of atypical antipsychotic drugs on brain NAA levels or serum BDNF levels in early-stage first-episode schizophrenia patients.

SUBJECTS AND MATERIALS

Subjects

A total of 23 patients who fulfilled the DSM-IV-TR criteria A, B, D, E, and F but who were within 6 months of disease onset were recruited for the study, and all underwent an MRS evaluation. After 6 months of follow-up, a diagnosis of schizophrenia was established in 20 of the 23 patients. Two patients were excluded from the study, one because of the difficulty of performing MRS given his mental state, and the other because image quality was impaired by severe artifacts from dental materials. Thus, 18 patients (9 males, 9 females; mean age: 31±12 yr) were ultimately enrolled in the study. All patients were screened using the Structured Clinical Interview for DSM-IV Disorders [9], and exclusion criteria for all groups included current or past serious medical or neurological illness or dependence on alcohol or illegal substances. The patients' psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) [19]. Sixteen (8 males, 8 females; mean age: 30±11 yr) of 18 patients were followed for 6 months. This study was approved by the Ethics Committee of the University of Occupational and Environmental Health. All participants gave written informed consent to participate in the study.

MRS methodology

All subjects were examined between 4:00 p.m. and 6:00 p.m. by 1H-MRS using a 3T MR system (Signa EXCITE 3T; GE Medical Systems) with a standard quadrature head coil (GE Medical Systems). The regions of interest (ROIs) for 1H-MRS were the frontal lobe, the left basal ganglia, and the parieto-occipital lobe (ROI size = 3.0 cm × 3.0 cm × 3.0 cm). Two oriented images (axial image and sagittal image) were used for each region because changes in NAA levels in those regions had been reported [4]. We put voxels in the frontal lobe, the left basal ganglia, and the parieto-occipital lobe (Figure 1). All of these ROIs were placed so as to avoid the lateral ventricle and skull.

We have previously obtained brain gamma-amino-butyric acid (GABA) measurements using a MEGA-PRESS sequence [23], and have reported that the reductions in the GABA concentrations were significantly greater in patients in the early stage of schizophrenia than in the controls [12]. By using a MEGA-PRESS sequence, as well as GABA, the spectroscopic measurements of other metabolites, including NAA, choline, creatine, glutamic acid, and glutamine (Gln) can also be obtained in the same voxel. Thus, in the present study, the NAA data were acquired with the MEGA-PRESS sequence using the following parameters: repetition time (TR) 3 sec, echo

time (TE) 68 msec, and 128 averages. The total acquisition time for each PRESS spectrum was approximately 6 min. All spectra were analyzed by an LC model [24] using phantom-generated basis functions for the MEGA-edited spectra. The line width, signal-to-noise ratio, and baseline of each spectrum were checked to ensure the robustness of the data. Eddy-current correction was applied by using an unsuppressed water spectrum at the appropriate echo time. The edited spectra were analyzed using LCM-basis functions that were generated from phantom measurements using the MEGA-PRESS sequence with the appropriate acquisition parameters. The NAA concentrations were evaluated as ratios to Cr.

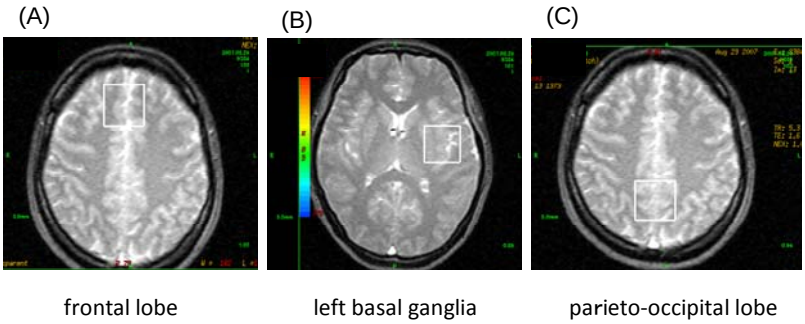

Fig. 1. Voxel positions for spectroscopic measurement in the frontal lobe (A), left basal ganglia (B), and parieto-occipital lobe (C). The white boxes represent the locations of the voxels (3.0 cm x 3.0 cm x 3.0 cm).

Measurement of serum BDNF levels

The serum BDNF levels were measured using a BDNF Emax Immunoassay Kit (Promega, Madison, WI, USA) according to the manufacturer's instructions. In short, 96-well microplates were coated with anti-BDNF monoclonal antibody and incubated at 4°C for 18 hours. The plates were incubated in a blocking buffer for 1 hour at room temperature. The samples were diluted 100 times with assay buffer, and the BDNF standards were kept at room temperature under horizontal shaking for 2 hours, followed by washing with an appropriate washing buffer. The plates were incubated with antihuman BDNF polyclonal antibody at room temperature for 2 hours and washed with the washing buffer. The plates were then incubated with anti-IgY antibody conjugated to horseradish peroxidase for 1 hour at room temperature, and incubated in peroxidase substrate and tetramethylbenzidine solution to induce a color reaction. The reaction was stopped with 1 mol/L hydrochloric acid. The absorbance at 450 nm was measured with an Emax automated microplate reader. The standard curve was linear from 5 pg/mL to 5000 pg/mL, and the detection limit was 5 pg/mL. The intra- and interassay coefficients of variation were 5% and 7%, respectively. The recovery rate of the exogenously added BDNF in the measured plasma samples exceeded 95%.

Statistical methods

Statistical analysis was performed using the paired t-test to investigate brain levels of NAA, serum BDNF levels, and PANSS scores. The Pearson correlation coefficient was used to examine the relationship between two variables. The level of significance was set at $p < 0.05$.

RESULTS

The administered atypical antipsychotic drugs and mean dosage are shown in Table 1. PANSS scores were lower after 6 months of treatment with atypical antipsychotic drugs (Table 2). However, the use of atypical antipsychotic drugs for 6 months did not change brain NAA/Cr levels in the three brain regions in early-stage first-episode schizophrenia patients (Figure 2). Serum BDNF levels were not altered after 6 months of treatment with atypical antipsychotic drugs (baseline: 15.2 ± 6.7 ng/mL; after 6 months: 16.4 ± 6.3 ng/mL). In addition, no correlation was found between serum BDNF levels and NAA/Cr levels in any of the three brain regions at baseline (Figure 3). There were no correlations between the PANSS total scores and the NAA/Cr levels in the three brain regions at baseline (Figure 4). Serum BDNF levels did not correlate to any PANSS scores (positive, negative, general pathology, and total) at baseline (Figure 5). Finally, no correlations were

observed between changes in NAA or serum BDNF from baseline to 6 months after treatment initiation and any of the PANSS scores.

Table 1. Atypical antipsychotic drugs and dosages

Atypical	Number of patients	Daily dose (mean ± S.D.) (mg)
Risperidone	5	2.9 ± 1.2
Olanzapine	5	10.1 ± 4.3
Aripiprazole	4	16.2 ± 5.8
Quetiapine	2	200; 300

Table 2. Changes in PANSS scores

	T0	T6	p-value	% improvement
PANSS-P	15.9 ± 4.2	12.2 ± 3.9	p < 0.001	33.3
PANSS-N	17.2 ± 5.3	13.4 ± 2.4	p < 0.001	26.3
PANSS-G	34.2 ± 10.1	26.5 ± 7.9	p < 0.001	31.4
PANSS-T	68.1 ± 17.0	53.2 ± 12.2	p < 0.001	25.3
GAF	34.3 ± 9.4	51.2 ± 11.9	p < 0.001	

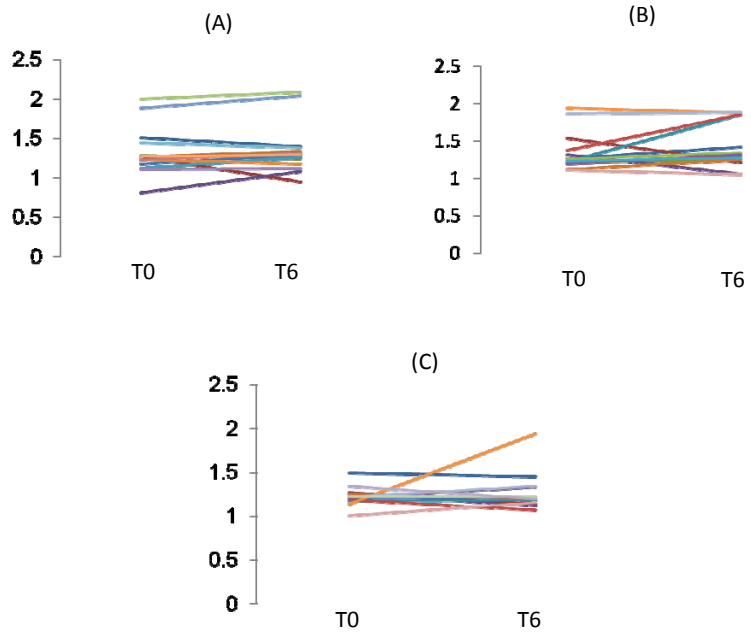

Fig. 2. The NAA/Cr concentrations before and 6 months after treatment with atypical antipsychotic drugs.
T0: before treatment; T6: 6 months after treatment
F: frontal lobe; LtBgg: left basal ganglia; PO: parieto-occipital lobe

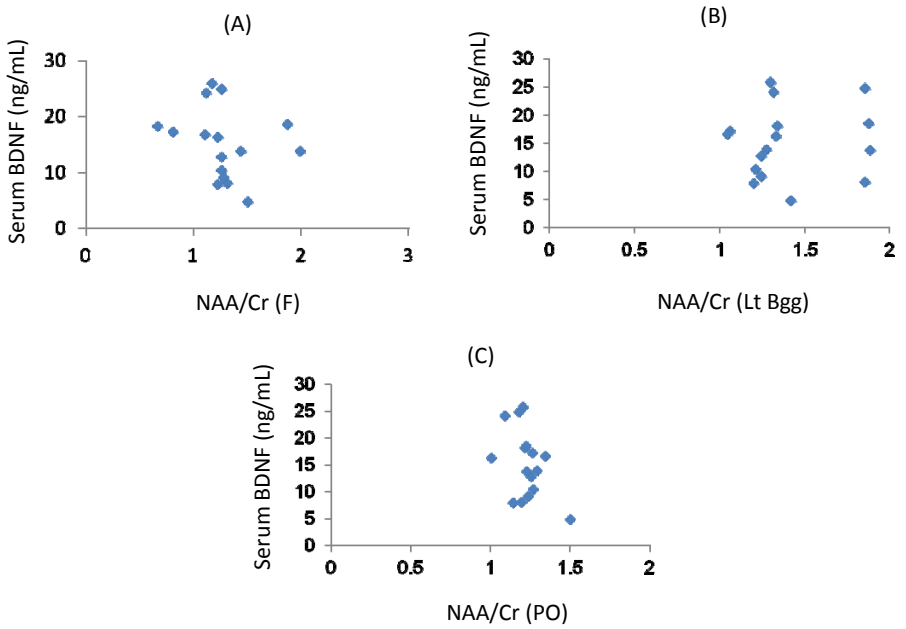

Fig. 3. No association between NAA/Cr in brain regions and serum BDNF levels at baseline.
F: frontal lobe; LtBgg: left basal ganglia; PO: parieto-occipital lobe

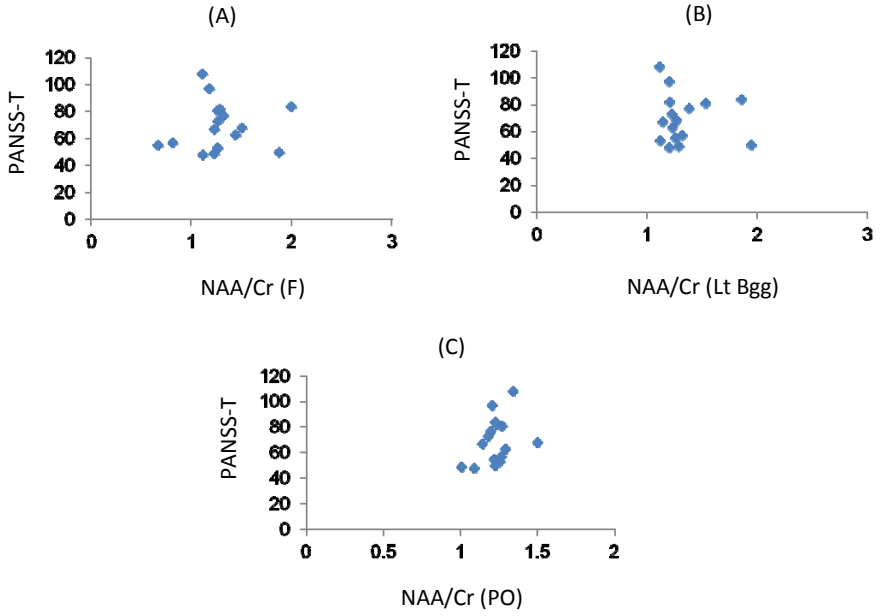

Fig. 4. No association between NAA/Cr in brain regions and PANSS-T at baseline.
F: frontal lobe; LtBgg: left basal ganglia; PO: parieto-occipital lobe
PANSS-T: total scores in PANSS

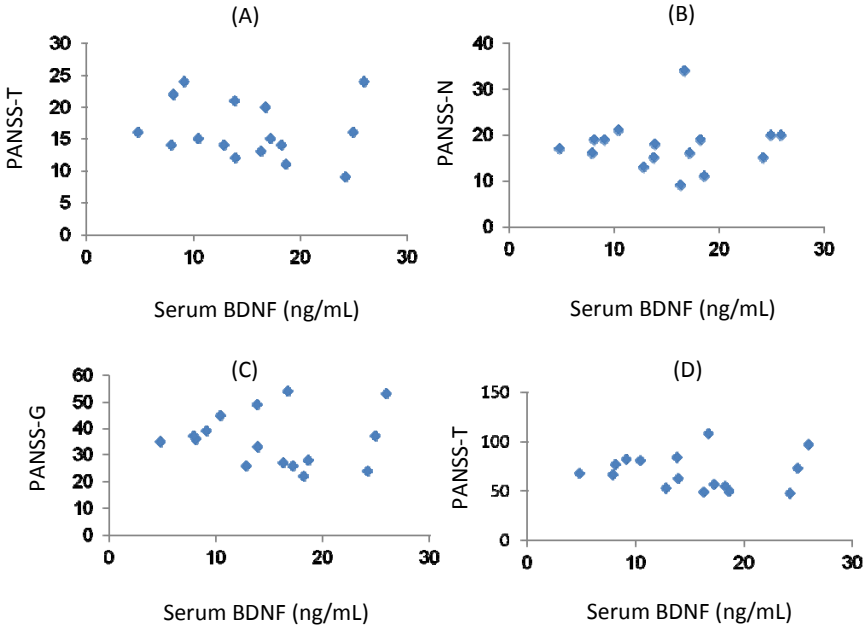

Fig. 5. Serum BDNF levels and individual PANSS item scores at baseline.
PANSS-: positive; PANSS-N: negative; PANSS-G: general psychopathology

The reduced levels of NAA in schizophrenia, in particular in the frontal lobe, is a consistent finding [26]. The results of Jessen et al. [18] suggest that reduced NAA levels are already present at the prodromal stage before full disease manifestation. Support for the finding that reduced NAA levels occur early on is provided by Cecil et al. [6], who found a reduced levels of NAA/Cr in first-episode schizophrenia patients. In a study we recently conducted [13], reduced NAA/Cr levels were observed only in the left basal ganglia and parieto-occipital lobe, but not the frontal lobe, in untreated first-episode schizophrenia. Fujimoto et al. [9] have also shown that there is a reduced bilateral NAA/choline (Cho) ratio in basal ganglia in chronic medicated schizophrenia patients. In view of this, reduced NAA levels might be a consistent finding in early- and chronic-stage schizophrenia. According to the meta-analysis by Brugger et al. [4], little difference in NAA levels was found between first-episode schizophrenia patients and chronic schizophrenia patients. Reduced NAA levels were observed in the frontal lobe, temporal lobe, and thalamus in both groups compared with control subjects. In addition, no significant difference was found between first-episode and chronically-ill schizophrenia patients, indicating a lack of progression of the disorder.

In the present study, treatment with atypical antipsychotic drugs for 6 months did not alter NAA/Cr levels, even though the PANSS scores were improved. Furthermore, no correlations were observed between NAA/Cr levels and serum BDNF levels or PANSS-T scores. We hypothesized that treatment with atypical antipsychotic drugs increases brain NAA levels, but this hypothesis was not supported. One possible reason for our failure to obtain data supporting our hypothesis is that clinical improvement may not necessarily depend on the brain changes. Whitford et al. [32] have reported evidence of progressive white matter atrophy over the first 2 to 3 years of illness in patients with first-episode schizophrenia, even though the psychotic symptoms (positive and negative PANSS) in these patients improved over this interval. Moreover, Choe's follow-up study did not find any changes in NAA with treatment [7], either. These results from previous studies may support our findings and suggest that there are ongoing changes in the brains of first-episode schizophrenic patients during the initial few years after diagnosis despite ongoing antipsychotic drug treatment. Another reason for our findings may be that the changes in the clinical data may precede the changes in the brain. Some cross-sectional studies have shown that patients who use atypical antipsychotic drugs have higher NAA levels in the prefrontal cortex than those who use typical antipsychotics [5,27], but there have been few longitudinal follow-up studies. Bertolino et al. [3]

have reported that patients treated with antipsychotic drugs exhibited increased NAA selectivity in the dorsolateral prefrontal cortex. Therefore, our study, with short follow-up periods (an average of 6 months), may not be sufficient to observe progressive changes.

Recently, Green et al. [14] performed a meta-analysis and found that blood BDNF levels were lower in schizophrenia patients than in healthy controls. We, however, observed no difference in serum BDNF between untreated first-episode schizophrenia and healthy controls [13]. In addition, we demonstrated that serum BDNF levels were unchanged after 6 months of treatment with atypical antipsychotic drugs, and that there were no associations between serum BDNF levels and any of the PANSS items. It is therefore possible that the reduction in serum BDNF levels occurred with the progression of the disease, and that treatment with atypical antipsychotic drugs did not alter, or at least did not promote, further reductions in serum BDNF levels in the patients. A recent paper by Lee et al. [21], however, reported a significant increase in serum BDNF levels in 4 weeks of treatment with antipsychotics, both typical and atypical, that paralleled the improvement in PANSS and was affected by the medication used. In any case, it remains unknown whether atypical antipsychotic drugs increase serum BDNF levels or not in any stages of the disease in schizophrenic patients.

Our study has some limitations. First, the sample size was very small and was also lacking in statistical power. Second, our patients received various kinds of atypical antipsychotic medications, which exhibited different pharmacological profiles at MRI examinations, and this may have affected the MRI data and serum BDNF measurements. The heterogeneity of our sample population may be due to our inclusion of patients over a wide age range. Further research to compare NAA and BDNF levels before and after treatment with all types of antipsychotic medications in a large number of patients should be performed, in order to obtain more robust results, and to compare the extent of the changes in NAA and BDNF levels among atypical agents. Third, we cannot rule out the possibility that other factors, such as the natural course of the disease, affected our results.

In conclusion, our results suggest that it is not very likely that 6 months of treatment with atypical antipsychotic drugs alters brain NAA levels and serum BDNF levels in early-stage first-episode schizophrenia. In any case, further study in a large sample size should be performed to reconfirm these preliminary results.

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CONFLICTS OF INTEREST

None.

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