

Proton Magnetic Resonance Spectroscopy of the Medial Prefrontal Cortex in Patients With Deficit Schizophrenia: Preliminary Report

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Objective: Proton magnetic resonance spectroscopy (^1H -MRS) was used to study medial prefrontal metabolic impairments in schizophrenic patients with the deficit syndrome. **Method:** The subjects were 22 schizophrenic patients categorized as deficit ($N=5$) or non-deficit ($N=17$) and 21 healthy subjects. ^1H -MRS was performed for the right and the left medial prefrontal cortex. **Results:** The patients with the deficit syndrome had significantly lower ratios of *N*-acetylaspartate to creatine plus phosphocreatine than did the healthy subjects or nondeficit patients. **Conclusions:** As *N*-acetylaspartate levels could reflect neuronal density and/or viability, this finding suggests a neuronal loss in the medial prefrontal cortex of deficit patients.

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Proton magnetic resonance spectroscopy (^1H -MRS) can measure levels of cerebral metabolites such as *N*-acetylaspartate, which has been described as a neuronal/axonal marker, choline, which is known to increase in myelin breakdown, and *myo*-inositol, a glial cell marker whose increase could reflect a gliosis. Studies with ^1H -MRS in schizophrenia have shown contradictory findings (1–3), which could be due to heterogeneous patient groups. Therefore, the aim of this study was to examine, with a single-voxel spectroscopy technique, whether a low ratio of *N*-acetylaspartate to creatine is associated with primary and enduring negative symptoms in schizophrenic patients with the deficit syndrome (4).

METHOD

The Schedule for the Deficit Syndrome (5) was used to evaluate 22 right-handed schizophrenic patients (DSM-IV) without history of

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head injury, past or present neurological disorders, alcoholism, or drug abuse. Five were categorized as having the deficit syndrome, and 17 were categorized as nondeficit. We matched 21 healthy subjects with the patients for age, educational level, sex, and handedness. None of the comparison subjects had any history of the lifetime psychiatric disorders evaluated with the National Institute of Mental Health Diagnostic Interview Schedule (6), organic illness, alcoholism, or drug abuse. After complete description of the study to the subjects, written informed consent was obtained.

^1H -MRS was performed on a General Electric Signa 1.5-T MRI system with a standard quadrature head coil. Proton spectra were obtained from an 8-cm³ voxel in the medial prefrontal cortex including the anterior cingulate region. The spectra were obtained by using a stimulated echo acquisition mode (STEAM) sequence (TE/TR=30 msec/1500 msec).

Repeated measures analysis of variance (ANOVA) was used to test the metabolite differences between groups (deficit versus nondeficit versus healthy). Post hoc pairwise comparisons with Bonferroni correction were used to identify which group differences accounted for the significant overall *F* value (Bonferroni/Dunn tests). A separate repeated measures ANOVA with the same factors was performed to compare untreated and treated patients. All of these tests were two tailed, and results were considered significant with probability levels of $p<0.05$. Correlations between metabolite ratios and length of illness (time between first episode and time of evaluation), dose of antipsychotic in chlorpromazine equivalents, and level of exposure to antipsychotic medications (chlorpromazine-equivalent dose times years of exposure) were performed by Spearman tests.

RESULTS

One patient was drug naive, and four had been free of medication for at least 6 months. Among the treated

TABLE 1. Ratios of Metabolites in the Medial Prefrontal Cortex of Healthy Subjects and Schizophrenic Patients With and Without the Deficit Syndrome

Metabolite Ratio and Brain Hemisphere	Healthy Subjects (N=21)		Schizophrenic Patients			
	Mean	SD	Nondeficit (N=17)		Deficit (N=5)	
Ratio of <i>N</i> -acetylaspartate to creatine plus phosphocreatine						
Left ^a	1.35	0.21	1.42	0.23	1.15	0.36
Right ^a	1.33	0.16	1.27	0.22	1.13	0.06
Ratio of choline to creatine plus phosphocreatine						
Left	0.88	0.13	0.97	0.17	0.86	0.17
Right	0.91	0.11	0.93	0.18	1.06	0.56
Ratio of <i>myo</i> -inositol to creatine plus phosphocreatine						
Left	0.66	0.13	0.69	0.26	0.70	0.18
Right	0.72	0.15	0.62	0.15	0.63	0.03

^a Significant group effect ($F=3.45$, $df=2$, 41, $p<0.04$; repeated measures ANOVA)

patients, two without and three with the deficit syndrome were receiving atypical neuroleptics. Each of the treated patients was in a stable phase, defined by no change in dose of antipsychotic medication for 2 months.

The deficit and nondeficit schizophrenic patients did not differ significantly in age, age at onset of illness, or duration of illness. ANOVA showed a significant difference in *N*-acetylaspartate/creatine among the healthy subjects, schizophrenic patients with the deficit syndrome, and nondeficit patients (table 1). Post hoc analyses showed that the deficit patients had significantly lower ratios of *N*-acetylaspartate/creatine than the healthy subjects ($p=0.01$) and the nondeficit patients ($p=0.009$). No difference in *myo*-inositol/creatine or choline/creatine was observed among the deficit patients, nondeficit patients, and healthy subjects. No difference in any metabolite ratio was noted between the untreated and treated patients. No significant correlation was found between any metabolite ratio and length of illness, dose of medication, or level of exposure to antipsychotics.

DISCUSSION

The major finding was a lower *N*-acetylaspartate/creatine ratio in the prefrontal cortex of the patients with the deficit syndrome than in the healthy subjects and nondeficit patients. As *N*-acetylaspartate could reflect neuronal density, this result suggests a neuronal loss in the prefrontal cortex of deficit patients, supporting previous results showing hypofrontality in deficit schizophrenia (7). This finding is also consistent with that of Shioiri et al. (8), who found, by using ³¹P-MRS, that abnormalities in phosphomonoesters and β -ATP were related to the severity of negative symptoms but not specifically to primary negative symptoms. A lower than normal *N*-acetylaspartate/creatine ratio was also observed by Bertolino et al. (1) in the dorsolateral prefrontal cortex of schizophrenic patients but was not particularly linked to negative symptoms. The absence of high ratios of choline/creatine and *myo*-inositol/creatine in our patients with the deficit syn-

drome is not consistent with gliosis and therefore does not support a neurodegenerative process in deficit schizophrenia.

As no correlation between *N*-acetylaspartate/creatine and length of illness in the deficit patients was observed, this result suggests that the low *N*-acetylaspartate/creatine ratio probably did not reflect an ongoing process. Antipsychotic treatment did not affect the *N*-acetylaspartate level, since there was no difference between the treated and untreated patients, and no relationship between *N*-acetylaspartate/creatine and the dose of antipsychotic or level of exposure to medication was noted. This is consistent with the result of Bertolino et al. (9), who found a low *N*-acetylaspartate/creatine ratio in the dorsolateral prefrontal cortex of unmedicated schizophrenic patients, suggesting that lower *N*-acetylaspartate/creatine ratios are independent of drug effects.

The absence of segmentation analyses is one major limit of the present study. The voxels contained various proportions of gray and white matter. Determining these proportions could be informative since some studies in schizophrenia have shown low levels of *N*-acetylaspartate in white but not gray matter (10). Thus, the lower *N*-acetylaspartate level observed in our study could be due to a larger prefrontal white matter volume in deficit patients, as has been suggested (11).

In conclusion, these preliminary results provide support for neuronal loss in the prefrontal cortex of deficit schizophrenic patients, but further studies with segmentation analyses are needed to determine the reason for these lower *N*-acetylaspartate levels.

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