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Biochemical changes in the frontal lobe of HIV-infected individuals detected by magnetic resonance spectroscopy

(AIDS dementia complex/brain cortex)

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ABSTRACT **We have developed a proton magnetic resonance spectroscopy method that selectively can sample cortical gray matter and adjacent white matter in the frontal lobe. We have used this approach to study a group of patients (n = 7) infected with HIV and clinical manifestations of the AIDS dementia complex (ADC), a group of patients (n = 8) infected with HIV without any indications of ADC, and seven controls. The patients without ADC had a statistically significant increase in the ratio of myo-inositol to creatine in white matter compared with normal controls. In contrast, the group of patients with ADC had almost normal levels of myo-inositol to creatine in both gray matter and white matter and showed a statistically significant decrease in the *N*-acetylaspartate to creatine ratio in gray matter compared with either the normal controls or the patients without ADC. Patterns of spectral abnormalities correlated with neuropsychological measures of frontal lobe dysfunction, suggesting that the evaluation of frontal lobe metabolism by magnetic resonance spectroscopy can play a role in the early detection of ADC, in determining its progression, and in assessing responses to therapeutic interventions.**

Infection with HIV type 1 (HIV-1), the causative agent of AIDS, frequently is complicated by the development of a slowly progressive dementing illness referred to as AIDS dementia complex (ADC), HIV-1 encephalopathy, and more recently as HIV-1-associated cognitive/motor complex (1). The incidence of this disorder in HIV-1-infected individuals remains uncertain. From a series of clinical studies it has been estimated that at the time of AIDS diagnosis one-third of patients exhibit overt symptoms of ADC and one-quarter exhibit subclinical ADC, progressing to an eventual preterminal prevalence in two-thirds of patients (2). Autopsy studies suggest that at death the brain has abnormalities in a majority of AIDS patients (3). Impaired memory and concentration with psychomotor slowing represent the most common early clinical presentations of ADC. In the most advanced stages of this disease, patients exhibit global cognitive impairment accompanied by slowed verbal and motor responses (4).

Several autopsy studies have been carried out on patients with HIV to establish the neuropathology of ADC (3, 5, 6). Abnormalities have been found predominantly in white matter and subcortical structures. Although ADC has been largely attributed to subcortical damage, increasing interest has focused on cortical changes. Significant loss of neurons in the frontal cortex (7, 8), loss of synaptic density, and loss or damage of dendritic processes (9, 10) have been described in the brains of patients with AIDS.

Interest has been focused on the early detection of central nervous system (CNS) involvement in HIV-1-infected patients with a view to assessing possible therapeutic interventions. Neuropsychological investigations have suggested that measures of frontal subcortical functions may be particularly sensitive measures of HIV-related cognitive decline (11–15). These studies have shown that neuropsychological testing can identify subtle cognitive dysfunction in early AIDS patients and perhaps even in asymptomatic HIV-positive individuals, although this last finding is somewhat controversial (16–18).

MRI typically shows brain atrophy and diffuse or localized white matter abnormalities in patients with ADC. However, mild brain abnormalities detected on MRI need not reflect the presence of underlying HIV encephalopathy (19) nor show progression over time (20), suggesting that MRI may not be sensitive enough for the early detection and evaluation of the progression of ADC.

Magnetic resonance spectroscopic (MRS) studies (20–27) on HIV-1-infected patients have proven to be more sensitive than MRI in detecting CNS involvement. A common finding in all of the MRS studies is the reduced level of the *N*-acetylaspartate (NAA)-to-creatine (Cr) ratio. Although the brain in ADC probably is diffusely involved, pathological and neuropsychological studies have pointed to the frontal lobe as a predominant area of cortical involvement. The frontal lobe has not been specifically assessed in previous MRS studies. In most MRS studies spectra have been obtained from voxels located predominantly in parietal regions. Because of the limited spatial resolution used, these voxels contain variable quantities of gray and white matter. Recently, two-dimensional MRS imaging has been used to evaluate patients with ADC with a spatial resolution of 0.8 cm^3 (27). The study described the largest reductions in NAA levels in the white matter of the frontal lobe, present in patients even with only mild neurocognitive symptoms. However, the study failed to find any statistically significant reductions of NAA in frontal gray matter. This may be a result of sampling regions that contained both gray and white matter.

We previously have described a high-resolution MRS approach, using a surface coil and one-dimensional (1D) phase encoding (28) that can yield high-quality spectra from voxels as small as 0.36 cm^3 at magnets operating at 1.5 T. This spatial resolution is sufficient to obtain spectra from voxels containing almost pure cortical gray matter. In the present study we have

Abbreviations: HIV-1, HIV type 1; ADC, AIDS dementia complex; CNS, central nervous system; MRS, magnetic resonance spectroscopy; NAA, *N*-acetylaspartate; TR, repetition time; TE, echo time; VOI, voxel of interest; Cr, creatine and phosphocreatine; Cho, choline-containing compounds; mI, myo-inositol; 1D, one-dimensional.

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used this approach to evaluate frontal lobe metabolism in a group of HIV-1-infected patients with and without cognitive impairment. Our purpose was to test whether the separate evaluation of frontal cortical gray and white matter can determine the degree of CNS involvement of HIV.

METHODS

Patients. All of the patients gave informed consent approved by the institutional review board at our institution. The study comprises a population of 15 HIV-1-infected patients (11 men and 4 women) recruited from the Immunodeficiency Program of the Hospital of the University of Pennsylvania. The mean age was 38.3 ± 7 (mean ± SD) years, ranging from 29 to 57. A standardized interview was administered, which included a medical history and sociodemographic data, and each patient underwent neurological, psychiatric, and neuropsychological examinations. The clinical assessment was performed blinded to the results of the MRI and MRS. Patients' charts were reviewed, and additional information not supplied by the patients was noted. The $CD4^+$ T-lymphocyte count from each patient was recorded. None of the patients had previous neurological disease, major psychiatric disorder, or head injury. Eleven patients were infected through homosexual practice, two through heterosexual transmission, and two had past history of intravenous drug use. All of the patients had $CD4^+$ T-lymphocyte counts less than 200 cells/ml at the time of evaluation. Using the Centers for Disease Control (CDC) classification (29), eight patients were in the asymptomatic stage of the disease, A3, and seven were symptomatic. Of the seven symptomatic patients, one patient was classified as CDC B3, and six patients were given a CDC classification of C3. Using the information obtained from the neurological and neuropsychological evaluations, each patient was given a grade of ADC using the clinical grading system described by Aronow *et al.* (30). On the basis of these criteria, eight patients were thought not to have ADC or have either minimal or equivocal symptoms of cognitive or motor dysfunction (ADC 0). Five patients presented with mild and two patients presented with moderate degrees of ADC (ADC ½). The mean age of the eight patients without cognitive impairment was 35.8 ± 3.9 years, with a range of 31 to 42, and an educational level of 12 ± 2.3 years, with a range of 9–15. The group of seven patients with cognitive impairment had a mean age of 41.3 ± 8.8 years, with a range of 29 to 57 and an educational level of 14.7 ± 3.7 years, with a range of 10 to 20. No statistically significant differences between the two groups were found in age and educational level ($P > 0.15$, two-tailed unpaired Student's t test). The mean $CD4^+$ T-lymphocyte count in the ADC 0 group was 107.3 ± 71.5, whereas in the ADC ½ group it was 49.9 ± 37.1 ($P = 0.08$, two-tailed unpaired Student's t test).

Neuropsychological Assessment. Several tests were selected from the full neuropsychological test battery for analysis. These were selected on the basis of reports in the literature, which indicate that these specific tests can detect cognitive impairment in this population (11–14, 16–18). These tests included measures of psychomotor speed, attention, and verbal memory such as the Trail-Making Test A and B (31), the Finger Tapping Test (31), the Grooved Pegboard Test (32), the Digit (33), and the Rey's Auditory Verbal Learning Test (34). The correlation between neuropsychological scoring and spectroscopic findings was evaluated.

Magnetic Resonance. All of the magnetic resonance studies were performed on a 1.5-T Signa system (General Electric Medical Systems, Milwaukee, WI). Conventional MRI was performed with a standard quadrature head coil. Patients were excluded from the study if any pathology seen on MRI could not be directly attributed to HIV infection of the brain.

Immediately after high-resolution MRI, 1D-proton spectra were obtained with the stimulated-echo acquisition mode for localization. Water suppression was achieved by using three chemical shift-selective radio-frequency pulses followed by a dephasing gradient applied on each of the three axes. The sequence parameters included the following: 19-cm field of view, spectral bandwidth 2,500 Hz, 32 phase-encoding steps, repetition time (TR) 2,000 ms, echo time (TE) 31 ms, mixing time 10.6 ms, 2,048 complex points, eight-step phase cycling, and 16 acquisitions. We selected a voxel of interest (VOI) of 30 to 40×6×10 mm, including cortical gray and white matter. Spectra from contiguous 6×6×10-mm voxels were obtained from the VOI by 1D phase-encoding. Cortical sulci were included in the VOI in all cases. Because the thickness of cortical gray matter is about 3 mm (35), the inclusion of cortical sulci in the VOI guarantee about 6-mm thickness of gray matter. To avoid partial volume effects, the spatial distribution of gray and white matter included in the VOI has been checked to be relatively invariant in at least six of the MRI (1.5-mm contiguous slices) that contributed to the MRS slice (10-mm thickness). Scalp and marrow were excluded from the VOI to prevent contamination from lipids. Gradient shimming on the VOI and optimization of solvent suppression were performed before the start of the acquisition. The spectral acquisition time was 17 min, and the total examination time, including MRI and MRS studies, was about 55 min. The MRI procedure was well tolerated by all of the patients.

The spectral processing was performed with ProNMR (Softpulse Software, Guelph, Ontario, Canada) using zero filling to 4K data points, 1.5-Hz line broadening applied in the time domain, two-dimensional Fourier transformation, and zero-order phase correction. Areas under the peaks were determined using a Marquardt fitting routine to Lorentzian line shapes in the frequency domain, and peak area ratios were calculated. MRI and MRS were evaluated blind to the neurological status of the patients.

A control group of seven volunteers (five men and two women; mean age = 33.7 ± 7.1 years, with a range of 24–44), with no known neurologic and psychiatric diseases and no identified risk factors for HIV infection, underwent MRS. There were no statistically significant differences in the age between patients or subgroups of patients and controls ($P > 0.1$ from two-tailed unpaired Student's t test). Mean metabolite ratios for gray and white matter were calculated using the mean values determined from each patient, because more than one spectrum from gray and white matter was obtained in most of the cases. Statistical comparisons between metabolite ratios from patients and controls were made using a two-tailed unpaired Student's t test corrected for multiple measures from the same patient. Values of $P < 0.05$ were considered significant. Pearson product-moment correlations were used to analyze the relationship between clinical and neuropsychological parameters and spectral findings.

RESULTS

The MRI scans of these patients were judged abnormal if there were any hyperintense regions in white matter on the long TR/long TE images and/or the presence of gray matter atrophy on short TR/short TE images. Based on these criteria four patients (26.7%) presented with mild to moderate atrophy and six patients (40%) presented with white matter abnormalities, which in most of the cases consisted of minimal foci of high signal intensity (four patients) and more diffuse areas of abnormal white matter signal in two patients. Using the presence of atrophy and/or white matter abnormalities as criteria for the presence of disease, seven patients (46.7%) presented with "abnormal" MRI. The MRI in the subgroup of patients with ADC was "abnormal" in five patients (71.4%) and in only two patients (25%) without ADC.

A representative study from an HIV-1-infected patient showing the VOI prescription in the left prefrontal lobe along

with the stack-plot of proton spectra from adjacent voxels obtained by 1D phase-encoding is shown in Fig. 1. The signal-to-noise ratio from spectra coming from the margins of the VOI was lower compared with intermediate voxels probably due to partial volume effects. Typical spectra from frontal gray matter and white matter with the principal metabolites identified are shown in Fig. 2 for a normal control (*A*), a patient at ADC stage 0 (*B*), and a patient at ADC stage 2 (*C*). The peak assignments were made based on the published literature, and the chemical shifts were determined using NAA as a chemical shift standard. The peaks at 2.01 ppm and 3.0 ppm were used for the quantification of NAA and Cr, respectively.

The results of an analysis of peak area ratios for gray and white matter are summarized in Table 1 for normal controls and for the two patient groups. *P* values are shown for those comparisons that were at ($P < 0.05$), or near (P values between 0.05 and 0.1) statistical significance.

Comparison of the Patient Group at ADC Stage 0 with Normal Controls. Most of the metabolite ratios in this group of patients were similar to those found for normal controls. The only statistically significant finding was that the myo-inositol (mI)/Cr ratio in white matter was found to be higher in this group than in normal controls. The mI/Cr ratio also was higher in gray matter in this group, but this elevation was below our criterion for statistical significance.

Comparison of the Patient Group at ADC Stage ½ with Normal Controls. The most striking difference was the finding of reduced NAA/Cr in gray matter compared with normal controls. There was a trend for the NAA/Cr in white matter to be lower than in controls; however, this difference was below our criterion for statistical significance.

Comparison of the Patient Group at ADC Stage 0 with the Patient Group at ADC Stage ½. The patients at ADC stage ½ had a significantly lower NAA/Cr ratio in gray matter as compared with the other patient group. The ratio of NAA/Cr in white matter was also lower in the patient group with more advanced disease. There was a trend for the mI/Cr ratio to be higher in the group with ADC stage 0, although this difference was slightly below our criterion for statistical significance.

Correlations Between Spectral Ratios, Clinical Status, and Performance on Neuropsychological Tests. We found a high negative correlation between the degree of ADC determined clinically and the levels of NAA/Cr in gray matter ($P = 0.005$), and the mI/Cr in gray matter ($P = 0.05$). The $CD4^+$ T-lymphocyte count correlated significantly with the level of NAA/Cr in white matter ($r = 0.59, P = 0.02$). Increasing levels of mI/Cr in white matter seem to correspond with higher $CD4^+$ T-lymphocyte counts, although this trend was not statistically significant ($r = 0.43$, $P = 0.11$).

Poorer performance on the neuropsychological tests tended to correlate with decreasing levels of NAA/Cr in gray and white matter, with increases in mI/Cr in gray matter and increasing levels of mI/Cr in white matter. Because the ratios of NAA/Cr in gray matter and mI/Cr in white matter were most commonly abnormal and seemed to be independent variables ($r = 0.19, P = 0.5$), we computed an aggregate score, consisting of the sum of mI/Cr in white matter and the inverse of NAA/Cr in gray matter. The correlations between this aggregate score and the neuropsychological test scores are presented in Table 2. The aggregate score showed a statistically significant tendency to increase with worsening performance of the following tests: the Grooved Pegboard Dominant and Nondominant Hand, the Finger Tapping Nondominant Hand, the Trail Making-A, and the Digit Symbol. As illustrated in Fig. 3, the use of this aggregate score increased the significance of the correlations compared with single metabolite ratios.

DISCUSSION

Previous MRS studies (20–27, 36), which have sampled regions containing both gray matter and white matter, have shown reductions in NAA/Cr in patients with ADC. Using a high spatial resolution approach (0.36 cm^3 nominal voxel size) we have found decreased NAA/Cr ratios predominantly in the gray matter in the frontal cortex of HIV-1-infected patients. Because NAA is largely confined to neurons (37) and has been recognized as a marker of neuronal-axonal loss or dysfunction, these results suggest the presence of damage or loss of neurons

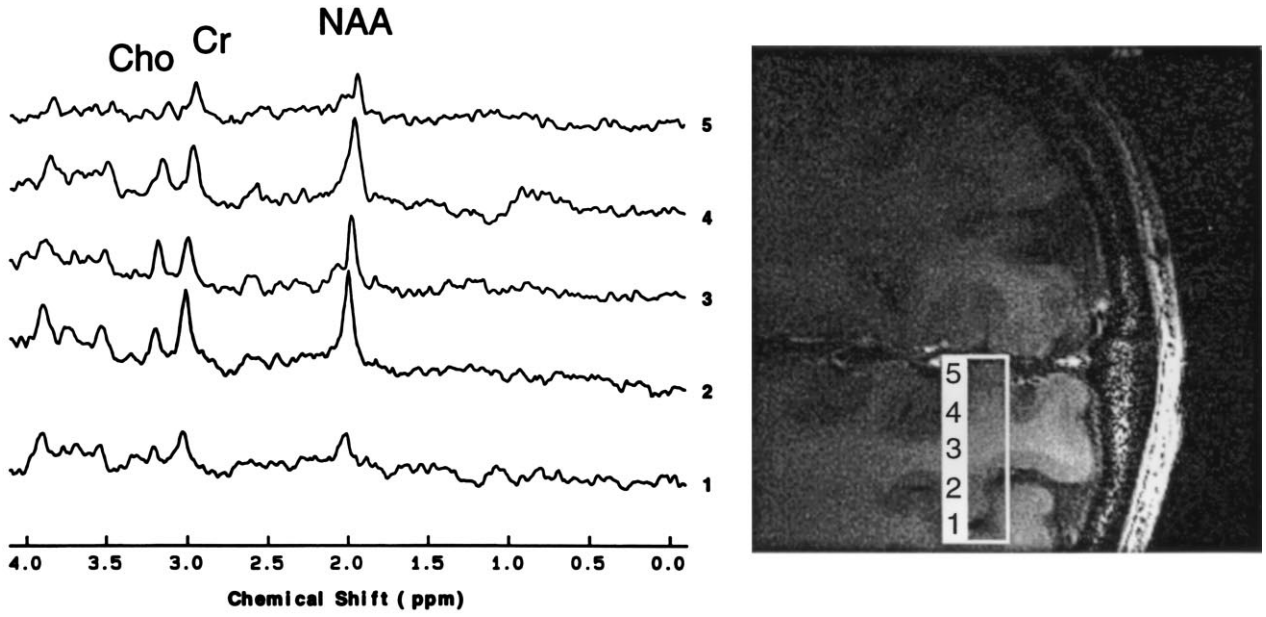

FIG. 1. A three-dimensional spoiled gradient echo MRI of the prefrontal lobe obtained in an HIV-1-infected patient showing the VOI and the corresponding 1D-stimulated-echo acquisition mode-localized proton spectra obtained from the selected VOI. Acquisition parameters include: TR 2,000 ms, TE 31 ms, mixing time 10.6 ms, and 0.36 cm^3 nominal voxel size. Spectra numbers 6 and 8 present low signal to noise because these regions contain cerebrospinal fluid. Spectrum number 7 corresponds to the interhemispheric fissure. The assignments of the resonances are indicated on the spectra.

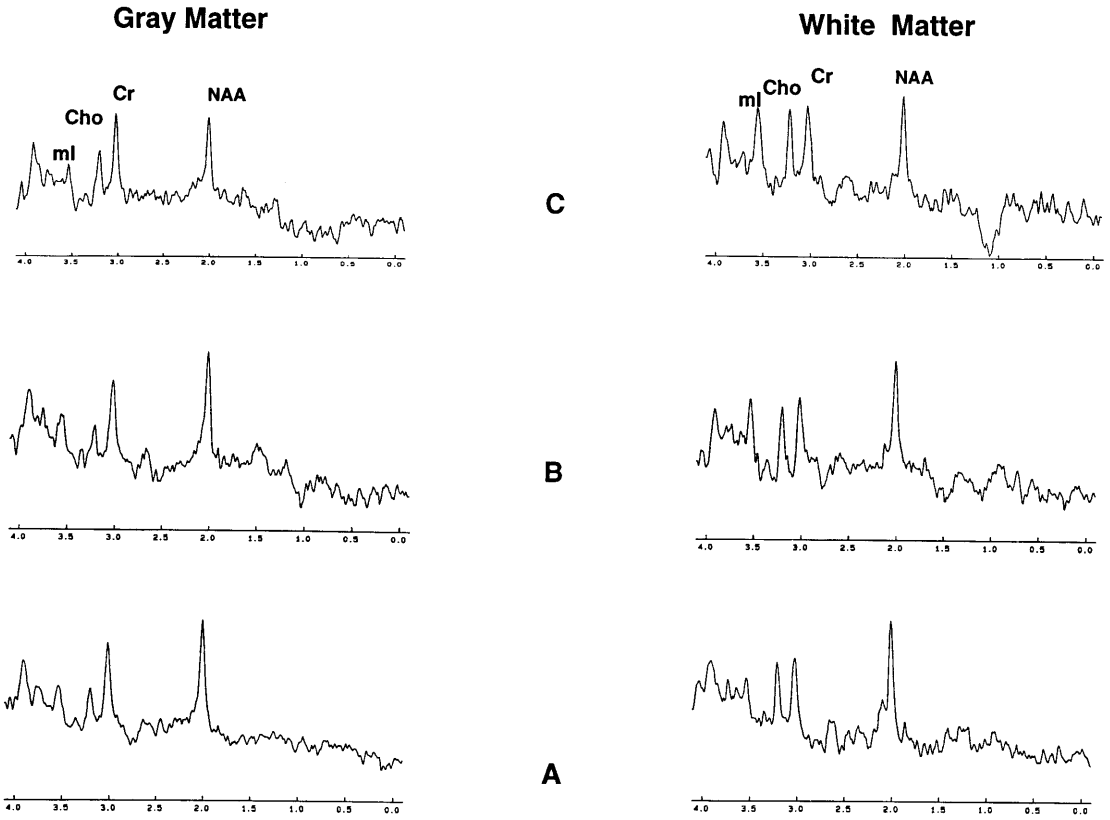

FIG. 2. Typical proton MRS spectra from 0.36 cm^3 frontal gray matter and white matter voxels obtained by 1D phase-encoding in (*A*) a healthy patient, (*B*) an HIV-1-infected patient without ADC, and (*C*) an HIV-1-infected patient with ADC stage 2. Acquisition parameters include: TR 2,000 ms, TE 31 ms, and mixing time 10.6 ms. Note the characteristic lower Cho peak in gray matter in comparison with white matter in all three patients. The NAA peak is decreased in gray and white matter in the patient with ADC. The mI peak is increased in white matter in the two HIV-1-infected patients.

in the frontal cortex of these patients, in agreement with previous pathologic studies (7, 8).

MRS studies on patients with HIV carried out with larger voxels in different regions of the brain have shown a correlation between the reduction in NAA and the severity of cognitive impairment (20, 22, 23, 26, 27). Our study shows that the decrease of NAA/Cr in the frontal lobe correlates both with the degree of ADC and with neuropsychological measures of frontal lobe dysfunction, suggesting that ADC may be directly related to the degree of neuronal loss or dysfunction in the frontal cortex. Pathological, neuropsychological, and recent spectroscopic data suggest that the frontal lobe may be preferentially affected in ADC. Preferential neuronal loss in the frontal cortex also has been implicated as wider range of neurological and psychiatric disorders (38).

We found no significant differences in choline-containing compound (Cho)/Cr levels between patients and controls, an observation in agreement with a previous report (20). However, other studies have shown increased Cho as a common finding in HIV-1-infected patients (22, 24, 25, 27, 36, 39). Further investigations are needed to clarify these different observations.

We have found a significant increase in the mI/Cr ratio of HIV-1-infected patients without clinical evidence of ADC or clinically evident cognitive impairment. Several recent reports (40, 41) also have shown an increase of brain mI in HIV-1-infected patients. The mI peak consists mainly of mI (70%) but also contains contributions from mI-monophosphate (15%) and glycine (15%) (42). Although, the role of mI in the CNS is still not completely understood, the level of mI has been found to be increased in other CNS diseases (43–45) and decreased in patients with chronic hepatic encephalopathy (46). In the brain, mI has been suggested as a glia-specific marker for *in vivo* NMR studies (47) because it is located

Table 1. Metabolite ratio analysis

		Patients, $n = 15$	
Area studied	Controls, $n = 7$	ADC 0, $n = 8$	ADC 1/2, $n = 7$
NAA/Cr GM	1.20 ± 0.12	1.28 ± 0.16	1.01 ± 0.12 (0.01)* (0.003)†
NAA/Cr WM	1.42 ± 0.25	1.44 ± 0.24	1.20 ± 0.19 (0.09)* (0.05)†
Cho/Cr GM	0.46 ± 0.08	0.42 ± 0.12	0.40 ± 0.14
Cho/Cr WM	0.74 ± 0.09	0.71 ± 0.08	0.67 ± 0.13
mI/Cr GM	0.44 ± 0.16	0.59 ± 0.13 (0.07)*	0.46 ± 0.11 (0.07)†
mI/Cr WM	0.51 ± 0.20	0.71 ± 0.12 (0.03)*	0.65 ± 0.13

Values given are mean ± SD. GM, gray matter. WM, white matter.
*P value in the comparison with the control group.
†P value in the comparison between ADC 0 and ADC 1/2. P values are reported for those comparisons that are at, or near, statistical significance.

Table 2. Correlations between neuropsychological tests and the aggregate metabolite ratio (Cr/NAA GM + mI/Cr WM)

Test	*r*	*P*
Time Gait, sec	0.40	0.16
Grooved Pegboard, sec		
Dominant	0.58	**0.02**
Nondominant	0.61	**0.02**
Finger Tapping, no. taps		
Dominant	−0.43	0.11
Nondominant	−0.61	**0.02**
RAVLT, no. words		
First trial	−0.48	0.07
30-min recall	−0.25	0.37
Trail Making, sec		
Form A	0.75	**0.001**
Form B	0.19	0.52
Digit Symbol, raw score	−0.51	**0.05**

r is the production moment correlation coefficient, and *P* is the correlation coefficient in the population sampled. Statistically significant correlations are shown in bold.
GM, gray matter.
WM, white matter.
RAVLT, Rey's Auditory Verbal Learning Test.

primarily in glial cells and not in neurons. Because gliosis and reactive astrocytosis are common features in the pathology of ADC (3, 5, 6), our finding of elevated mI/Cr in the white matter of the group of patients without ADC may reflect an increase in the number of glia and/or alterations in their metabolism in white matter (45). A histopathological study of AIDS (10) reported that gliosis was preferentially present in cortical white matter compared with cortical gray matter, supporting the hypothesis that the increase of mI/Cr in white matter may be an indicator of reactive gliosis as a result of HIV infection.

In many of our cases mI/Cr is increased in white matter at a time when NAA/Cr is normal, suggesting that this can be an early metabolic event in the development of ADC. Whether mI accumulation in these patients precedes the fall in NAA and development of dementia is at present speculative, and further longitudinal studies are required to test this hypothesis. The fact that increased mI/Cr in white matter also may be detected in patients with ADC and that the level of this metabolite ratio in white matter seems to correlate with poorer performance on neuropsychological testing supports the hypothesis that increases in mI/Cr and decreases in NAA/Cr accompany the development of ADC. The possibility that the elevation of mI may precede the loss of NAA previously has been suggested for patients with Down syndrome (48), although the interpretation of the increased mI in this pathology may be different. The interpretation of these increases in the mI/Cr ratio is at present speculative but may reflect a decrease in the inflammatory reaction that accompanies neuronal loss. This fact may be related to the hypometabolism that accompanies ADC progression (49).

The group of patients with cognitive impairment was composed only of patients in the early stages of ADC. However, despite the mild degree of clinical symptomatology, spectral abnormalities were observed in 86% of the patients with ADC, whereas MRI was abnormal in 71% of the patients. More important is the fact that 63% of the patients without cognitive impairment demonstrated abnormal spectra, whereas MRI was abnormal in only 25%. Previous MRS studies have failed to find significant spectral abnormalities in patients without cognitive impairment (22, 23, 26). Therefore, our results suggest that the evaluation of the metabolism of the frontal lobe by MRS may be a sensitive method for the detection of early pathological events related to ADC. In our study only three patients (20%) did not present any definitive clinical, radiological, or spectral evidence of CNS involvement. All or some of these patients may represent the group of patients present in all clinical and pathological series that will never develop HIV encephalopathy.

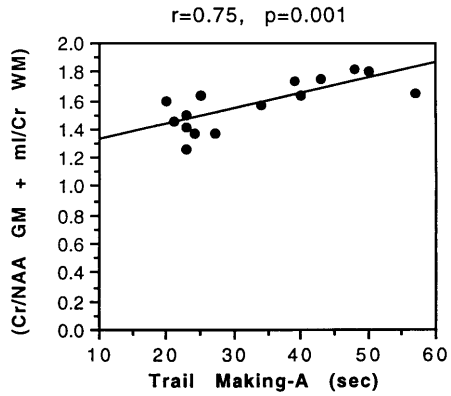

FIG. 3. The relationship between the time of performance of the Trail Making Test-A and the aggregate metabolite ratio (Cr/NAA in gray matter + mI/Cr in white matter). The regression line is given in the plot. GM, gray matter; WM, white matter.

The results presented in this study suggest that the evaluation of frontal lobe metabolism by high-resolution MRS may help in identifying early changes in brain metabolism that probably precede the damage of neurons, helping to select patients for possible therapies before irreversible damage has occurred. Additionally, this MRS approach may be a good method to evaluate objectively the degree and progression of ADC and to monitor the effect of therapy. Finally, this and other high-resolution MRS approaches provide noninvasive methods with which to monitor alterations in gray and white matter metabolism. This information may contribute to the understanding of the pathophysiology of ADC.

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