Basal Ganglia Metabolite Abnormalities in Minor Motor Disorders Associated With Human Immunodeficiency Virus Type 1

Hans-Jürgen von Giesen, MD; Hans-Jörg Wittsack, PhD; Frank Wenserski, MD; Hubertus Köller, MD; Harald Hefter, MD, PhD; Gabriele Arendt, MD

Background: Minor motor disorders (MMDs) associated with human immunodeficiency virus type 1 (HIV-1) predict HIV-1 dementia and death. Little is known about the time course and neuropathologic mechanisms of HIV-1 MMDs.

Objective: To investigate the relationship between HIV-1 MMDs, as assessed by psychomotor speed, and metabolic alterations in the basal ganglia, as detected by proton magnetic resonance spectroscopy.

Patients and Methods: A total of 32 HIV-1–seropositive patients (10 with no MMD, 8 with incipient MMD, and 14 with sustained MMD, assessed through electrophysiologic testing of psychomotor speed including contraction times; 29 treated with highly active antiretroviral therapy) and 14 HIV-1–seronegative control subjects were examined for cerebral metabolite abnormalities in the basal ganglia by means of magnetic resonance spectroscopy.

Results: The 3 patient groups showed significantly different ratios of myoinositol/creatine ($P = .02$) in the basal ganglia. Whereas patients with no MMD or incipient MMD showed normal ratios, patients with sustained MMD showed higher values for myoinositol/creatine as a sign of glial proliferation. No differences in N-acetyl compounds, indicative of neuronal loss, were found.

Conclusion: Whereas metabolic alterations in the basal ganglia were not detected in patients with incipient HIV-1 MMD, patients with sustained HIV-1 MMD did have significantly altered metabolic spectra indicative of glial proliferation.

Arch Neurol. 2001;58:1281-1286
SUBJECTS AND METHODS

PATIENTS AND CONTROL SUBJECTS

Fourteen HIV-1–seronegative healthy volunteers (all white men; mean ± SD age, 33.6 ± 6.5 years) served as controls. Thirty-three HIV-1–seropositive subjects (all white homosexual men with no history of substance abuse) were recruited from the Neuro-AIDS outpatient clinic. Written informed consent was obtained in accordance with guidelines of the Declaration of Human Rights, Helsinki 1975. The study was approved by the local ethics committee. Demographic data for all subjects are shown in Table 1. None of the patients had evidence of HIV-1–associated myelopathy or HIV-1–associated peripheral polyneuropathy, none had ever had cerebral lymphoma or cerebral opportunistic infection, and none showed clinical signs of basal ganglia dysfunction. None fulfilled the clinical criteria for HIV-1–associated dementia1 at the time of MRS, and none subsequently developed HIV-1–associated dementia as of June 30, 2000.

All patients underwent regular electrophysiologic motor testing every 3 months before and after MRS. Evaluation further included the motor scores of the Unified Parkinson’s Disease Rating Scale16 and the HIV Dementia Scale.17

MAGNETIC RESONANCE IMAGING

Both magnetic resonance (MR) imaging and MRS were performed on a 1.5-T whole-body MR scanner (Siemens Magnetom Vision; Siemens, Erlangen, Germany) between May 25, 1999, and January 18, 2000. The following sequences were performed in all patients and controls: axial, coronal, and sagittal T1-weighted fast-low angle shot sequence (repetition time [TR], 300 milliseconds; echo time [TE], 6 milliseconds; 20 slices, 6 mm; matrix, 144 × 256; field of view [FOV], 230 mm), axial T2-weighted turbogradient spin echo sequence (TR, 7040 milliseconds; TE, 115 milliseconds; 20 slices, 6 mm; matrix, 345 × 312; FOV, 230 mm), axial fluid-attenuated inversion recovery sequence (TR, 9000 milliseconds; TE, 105 milliseconds; inversion time, 2200 milliseconds; 18 slices, 6 mm; matrix, 144 × 256; FOV, 230 mm), and coronal T1-weighted spin echo sequence after application of intravenous gadopentetate dimeglumine (TR, 560 milliseconds; TE, 17 milliseconds; 20 slices, 6 mm; matrix, 144 × 256; FOV, 230 mm). Structural abnormalities led to exclusion. All MR images were evaluated qualitatively by an experienced neuroradiologist (F.W.) who was blind to the clinical status of patients and controls.

MAGNETIC RESONANCE SPECTROSCOPY

On the basis of the 3 orthogonal T1-weighted MR images, the target volumes for 1H-MRS were planned for the region of basal ganglia. The size of volumes was 2 × 2 × 2 cm3 (Figure), leading to a sufficient signal-to-noise ratio within a reasonable measurement time. Volumes were placed as demonstrated in the Figure, including the striatum and parts of the thalamus. This placement includes regions of less interest than the striatum; however, another placement would necessarily have included parts of the ventricle system, leading to systematic difficulties in the interpretation of data because of an inhomogeneous sampling volume including not only gray and white matter but also cerebrospinal fluid. Spectroscopic data were acquired by a stimulated echo acquisition mode18 sequence using a TE of 20 milliseconds, a TR of 1500 milliseconds, and 256 acquisitions. The spectral line widths were 8 to 9 Hz for the water resonance resulting from the preceding shimming procedure. Water suppression was performed with a frequency-
Electrophysiologic Motor Testing

Electrophysiologic assessment of psychomotor speed included the analysis of most rapid voluntary isometric index finger extensions. The variables measured in this context were simple reaction time, ie, the time span between a short “go” signal and the onset of contraction, and contraction time (CT), ie, the time span between the onset and peak force of the contraction (for methodologic details see Arendt et al). Normal values for 98 HIV-1-seronegative controls have been published. The CTs were rated “pathologic” if at least the value of one hand fell outside the mean ± 2 SDs. Patients were separated into 3 groups. Group 1 consisted of patients who had never shown pathologic CT values. Mean ± SD duration of asymptomatic follow-up before MRS was 49.3 ± 34.6 months. These patients were thus completely asymptomatic. Group 2 consisted of patients who showed pathologic CTs for the first time during their individual follow-up. These patients were considered to have incipient HIV-1 MMDs. Group 3 included patients who showed repeated and thus sustained pathologic prolongations of CTs for a mean period of 28.4 ± 24.2 months (significantly longer than groups 1 and 2; Fisher protected least significant difference [PLSD], P < .01). These patients would fulfill the criteria for HIV-1 MMD. If CT was pathologic for both hands, we chose the more marked prolongation and performed MRS for the contralateral basal ganglia. There was no difference in the distribution between right and left basal ganglia sampled between the groups (group 1: right, n = 5; left, n = 5; group 2: right, n = 5; left, n = 3; group 3: right, n = 8; left, n = 6).

Statistics

Statistical analysis was performed with the commercially available software package Statview (Version 5.0.1.; SAS Institute Inc, Cary, NC, 1998). Analysis of variance (ANOVA) was performed to evaluate differences in basal ganglia metabolite concentrations and metabolite ratios between the different groups. Post hoc analyses with Fisher PLSD were used to determine the significance of differences between any 2 groups. To investigate possible relationships between variables, we performed regression analyses using the metabolite ratios and differences in CD4 cell counts, log plasma viral load, and CT values for 6-month periods: (1) the 6 months before MRS, (2) from 3 months before to 3 months after MRS, and (3) from MRS to 6 months thereafter.

COMMENT

The present study was designed to answer the question of whether (and, if so, at what time) MRS can detect metabolic abnormalities constituting a possible pathophysiologic and functional correlate of HIV-1-associated MMDs. So far, most studies have applied MRS to the examination of HIV-1-seropositive patients with manifest dementia. The MRS spectra in demented patients were characterized by reduced levels of NAA and increased levels of choline in white matter regions. Metabolic abnormalities were more marked in more advanced stages of dementia. A Cho increase appeared before the NAA decrease. According to these findings, the NAA/Cr and Cho/Cr ratios have been found to be decreased and increased, respectively, in demented patients. Whereas NAA/Cr and NAA/Cho ratios were reduced in cognitively impaired patients in the centrum semiovale and mesial cortex, no significant NAA differences could be detected in the basal ganglia. Since NAA is a marker for mature neurons, a decrease in NAA in demented patients has been interpreted as a sign of neuronal loss or damage in relatively late stages of HIV-1-associated brain damage. However, focusing on earlier and subclinical stages of the disease may help to better treat or prevent HIV-1 cognitive-motor complex rather than focusing on manifest disease stages when neuronal death is already present and possibly extensive. One study that included both demented and asymptomatic patients found
NAA/Cr decreases and both mI/Cr and Cho/Cr increases in both white and gray matter in demented patients, but only slight changes in the NAA/Cr and mI/Cr peaks in asymptomatic patients. We therefore defined the groups in this study according to the very first, subtle, but electrophysiologically detectable manifestation of psychomotor slowing, which is highly predictive of the later development of HIV-1–associated dementia. The psychomotor test allows us to distinguish between patients who are functionally completely normal and those who show either incipient or sustained functional damage. Naturally, the approach bears the risk that patients are examined at such an early point during the course of the disease that minor metabolic abnormalities may escape detection. To further improve the chances of detecting very early signs of HIV-1–associated central nervous system dysfunction, we chose the basal ganglia as the region of interest. We recently showed that psychomotor slowing in HIV-1–seropositive patients is associated with metabolic disturbances in the basal ganglia. There is unequivocal evidence that the basal ganglia play a pivotal role in HIV-1 infection of the brain. Because we selected our patients for this study according to strict criteria, they did not, as a whole, show any notable metabolic abnormalities as detected by MRS. However, after separating them into the herein-defined groups, we did find significant differences. Although all mean values lie within the normal range, patients in group 3 had significantly higher mI/Cr ratios than those of groups 1 and 2. The size and placement of regions of interest in our patients may also account for the relative variability of data despite the significant but relatively small differences between groups. Focusing exclusively on the striatum (which was impossible in our experimental setting) might have led to more significant differences. However, the fact that we can detect significant differences between the electrophysiologically defined groups in this study makes the explanation we suggest even more probable.

Chang and coworkers recently described an increased Cho/Cr ratio in the midfrontal white matter and...
Highly active antiretroviral therapy has been found to improve metabolic dysregulation.6 Psychomotor slowing may also respond to antiretroviral therapy.12,14 Since all but 3 of our patients received HAART, therapy may account for the relatively small degree of differences between our patient groups. However, if our finding of only slight metabolic disturbances is due to the therapeutic effect of HAART, it would imply that electrophysiologic motor testing may be more sensitive than MRS in detecting early signs of HIV-1-associated central nervous system disease at least in the basal ganglia. Other regions of interest including the frontal white matter must therefore be examined. Although the mean CD4 cell counts in our patients were within expected asymptomatic ranges, the groups did differ with regard to CT values and mI/Cr ratios in the basal ganglia. These findings are in good agreement with those of Price and coworkers,13 who described that CD4 cell counts, HIV-1 RNA plasma levels, and neurologic impairment are independent predictors of mortality. Hypothetically,9 the course of HIV-1 MMDs could begin with increased cerebral blood flow followed by functional deficits. The patients in our group 2 were most likely in this pathogenetic phase. More sustained pathologic psychomotor slowing (group 3) would be accompanied by progressive gliosis and more marked metabolic dysregulation. A final hypometabolic phase with neuronal loss and clinical manifestation of HIV-1 dementia would follow. Obviously, such a hypothesis stresses the urgent need for continuous follow-up examinations of patients, especially to determine the points in individual pathogenesis that are therapeutically accessible.

### Table 2. Group Statistical Comparison Between Patients and Control Subjects*

<table>
<thead>
<tr>
<th>MRS Variable</th>
<th>HIV-1–Seronegative Control Subjects (n = 14)</th>
<th>HIV-1–Seropositive Patients (Groups 1-3) (n = 32)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA/Cr</td>
<td>1.48 ± 0.17</td>
<td>1.51 ± 0.14</td>
<td>.52</td>
</tr>
<tr>
<td>Cho/Cr</td>
<td>0.73 ± 0.13</td>
<td>0.74 ± 0.10</td>
<td>.70</td>
</tr>
<tr>
<td>mI/Cr</td>
<td>0.52 ± 0.14</td>
<td>0.53 ± 0.09</td>
<td>.81</td>
</tr>
<tr>
<td>Glx/Cr</td>
<td>0.80 ± 0.19</td>
<td>0.84 ± 0.32</td>
<td>.64</td>
</tr>
<tr>
<td>NAA/Cho</td>
<td>2.07 ± 0.33</td>
<td>2.07 ± 0.34</td>
<td>.98</td>
</tr>
<tr>
<td>mI/Cho</td>
<td>0.74 ± 0.27</td>
<td>0.72 ± 0.18</td>
<td>.87</td>
</tr>
</tbody>
</table>

*Values are mean ± SD. MRS indicates magnetic resonance spectroscopy.

### Table 3. Group Statistical Comparison Among Patient Groups 1 to 3*

<table>
<thead>
<tr>
<th>MRS Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA/Cr</td>
<td>1.55 ± 0.09</td>
<td>1.45 ± 0.10</td>
<td>1.52 ± 0.19</td>
<td>.34</td>
</tr>
<tr>
<td>Cho/Cr</td>
<td>0.72 ± 0.08</td>
<td>0.77 ± 0.09</td>
<td>0.75 ± 0.12</td>
<td>.76</td>
</tr>
<tr>
<td>mI/Cr</td>
<td>0.50 ± 0.08</td>
<td>0.48 ± 0.10</td>
<td>0.57 ± 0.07</td>
<td>.03</td>
</tr>
<tr>
<td>Glx/Cr</td>
<td>0.72 ± 0.23</td>
<td>0.74 ± 0.15</td>
<td>0.98 ± 0.40</td>
<td>.10</td>
</tr>
<tr>
<td>NAA/Cho</td>
<td>2.18 ± 0.29</td>
<td>1.91 ± 0.24</td>
<td>2.08 ± 0.39</td>
<td>.23</td>
</tr>
<tr>
<td>mI/Cho</td>
<td>0.70 ± 0.13</td>
<td>0.64 ± 0.18</td>
<td>0.79 ± 0.19</td>
<td>.12</td>
</tr>
</tbody>
</table>

*Values are mean ± SD. See footnote to Table 1 for explanation of groups and first footnote to Table 2 for explanation of abbreviations.

†Analysis of variance. P < .05 was considered significant.

in the basal ganglia as well as an elevated mI/Cr ratio and mI concentration in the basal ganglia. Importantly, these changes normalized with HAART. Most of our patients were also treated with HAART, which may explain the relatively small differences between our groups. Untreated patients may show more significant differences. Higher Cho concentrations were also found in subcortical brain regions early in HIV-1 disease when individuals were clinically and neuropsychologically asymptomatic, whereas low NAA levels were only found in subcortical brain regions in individuals with severe neuropsychological impairments.7 Conversely, MMDs are not associated with a decrease in NAA.9 We conclude that sustained HIV-1 MMDs even with HAART may be associated with altered mI/Cr ratios. Myoinositol has been identified as a glia-specific marker that may participate in the osmoregulatory system in astrocytes.8 Disturbances in astrocyte function may therefore play an important role in the pathogenesis of sustained HIV-1 MMDs. Interestingly, another MRS study of patients without HIV-1–associated dementia showed a statistically significant increase in mI/Cr ratios in white matter compared with normal control subjects.9 That group may well have consisted of patients with pathologic psychomotor slowing. In contrast, the demented group in that study showed almost normal levels of mI/Cr in both gray and white matter and a significant decrease in NAA/Cr in gray matter compared with both the control subjects and patients without dementia.9

### REFERENCES


©2001 American Medical Association. All rights reserved.


