Cerebral Single-photon Emission Computed Tomography Abnormalities in Human Immunodeficiency Virus Type 1–Infected Gay Men Without Cognitive Impairment

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Objective: To determine whether technetium Tc 99m exametazime single-photon computed emission tomography (SPECT) can distinguish gay human immunodeficiency virus (HIV)–positive subjects, both with and without mild cognitive impairment, from gay HIV-negative control subjects.

Design: Twenty HIV-positive subjects (12 without cognitive impairment and eight with mild cognitive impairment) and 10 HIV-negative subjects underwent neurological, neuropsychological, magnetic resonance imaging, and technetium Tc 99m exametazime SPECT examinations.

Setting: Subjects were recruited from a natural history study of gay men with HIV infection.

Patients: Subjects from the cohort who had previously participated in a magnetic resonance imaging study were selected for the SPECT study.

Main Outcome Measures: The SPECT scans were rated as abnormal if focal defects, confirmed by a horizontal profile analysis, were seen.

Results: Sixty-seven percent of HIV-positive subjects without cognitive impairment, 88% of HIV-positive subjects with mild cognitive impairment, and 20% of HIV-negative subjects had abnormal SPECT scans (P<.05 for both HIV-positive groups when each group was compared with HIV-negative subjects).

Conclusion: Compared with gay HIV-negative control subjects, focal SPECT defects are seen with an increased frequency in HIV-positive gay men without cognitive impairment and in HIV-positive gay men with mild cognitive impairment.

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FUNCTIONAL BRAIN imaging using single-photon emission computed tomography (SPECT) in patients with both early and advanced stages of human immunodeficiency virus (HIV) type 1–associated dementia complex (ADC) has shown focal cortical or subcortical perfusion defects that are associated with a heterogeneous pattern of cortical uptake.1-9 However, findings from studies of SPECT in HIV infection are difficult to interpret because many have included parenteral drug users as subjects,7,9 and the perfusion pattern in HIV-negative subjects with long-term intravenous drug use cannot be distinguished from the abnormal SPECT pattern that is seen in HIV infection.10

The current study was designed to test the hypothesis that technetium Tc 99m exametazime SPECT could distinguish HIV-positive gay men, with or without mild cognitive impairment, from HIV-negative gay men.

RESULTS

The subjects are described in Table 1. Only the CD4 lymphocyte count was significantly different between HIV-negative subjects and HIV-positive subjects (mean CD4 lymphocyte count difference, 6.1×10^9/L; P<.01). Twenty-five percent of the HIV-positive subjects were medically asymptomatic, 45% had mild medical symptoms, and 30% had AIDS-related complex. The CD4 lymphocyte count fell with advancing medical clinical stage (CD4 lymphocyte count: medically asymptomatic HIV-positive subjects, 3.6×10^9/L; HIV-positive subjects with mild medical symptoms, 3.5×10^9/L; and HIV-positive subjects with AIDS-related complex, 1.3×10^9/L).

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METHODS

SUBJECTS

Subjects were recruited from a cohort of volunteers from gay men's organizations. A majority of the subjects were recruited into the cohort via word of mouth, though two announcements were placed in gay monthly newsletters and one in a newspaper.

The following inclusion criteria for the cohort were used: (1) age between 18 and 60 years, (2) gay or bisexual men who did not self-administer parenteral drugs more than 10 times since 1982 by self-report, (3) prior knowledge of HIV status, and (4) fluency in English.

The following exclusion criteria were used: (1) the Centers for Disease Control and Prevention National Surveillance Criteria for acquired immunodeficiency syndrome (AIDS) at the time of enrollment (1988), with the exception of AIDS dementia and esophageal candidiasis; (2) presence of an encephalopathy that was unrelated to HIV infection; (3) presence of a chronic neurologic disorder that antedated HIV infection (eg, Gilles de la Tourette's syndrome); and (4) presence of a major psychiatric disorder that antedated HIV infection (eg, schizophrenia).

Two hundred seven gay men were enrolled in the cohort, beginning in March 1988, and they were seen every 6 months. From this cohort, 118 men were recruited for a longitudinal magnetic resonance imaging (MRI) study that began in September 1989. Thirty-one subjects who participated in the longitudinal MRI study were sequentially enrolled for the SPECT study, under the following constraints: (1) We attempted to rule out subjects who had a history of depression, psychosis, or cocaine or crack use in the psychiatric evaluations prior to the visit in which they were enrolled. (2) For HIV-positive subjects, we recruited a small number of subjects who had mild cognitive impairment in the preceding visit, to serve as a comparison group for the HIV-positive subjects without cognitive impairment. (3) All subjects volunteered for the study and gave informed consent. One subject was excluded from the analysis because he was HIV negative, but he had focal neurological signs on physical examination.

The biannual assessments of the cohort have been described in detail elsewhere\textsuperscript{11,12} and are summarized below.

MEDICAL EVALUATION

Medical evaluation included an examination by a physician, a complete blood cell count, and CD4 and CD8 lymphocyte counts. After review of these data, the medical status of each subject was classified as either HIV negative, HIV positive asymptomatic, HIV positive with mild symptoms (primarily enlarged lymph nodes), AIDS-related complex, or AIDS.\textsuperscript{11}

NEUROLOGICAL AND PSYCHIATRIC EVALUATIONS

All neurological evaluations were performed by neurologists who were blind to HIV serostatus. Subjects underwent a structured neurological examination.\textsuperscript{11} A summary score to reflect the overall degree of neurological disability was calculated based on a modified version of the Kurtzke Disability Status Scale for Multiple Sclerosis (ie, the Kurtzke score).\textsuperscript{11,4} A Kurtzke score of 0 indicated a neurological examination with normal results, and a score of 1 indicated no disability and minimal signs, such as frontal release signs or Babinski's sign. A detailed psychiatric assessment was also performed, without knowledge of the subject's serostatus.\textsuperscript{15}

NEUROPSYCHOLOGICAL EVALUATION

Neuropsychological testing was performed, blind to the subject's serostatus, and this testing assessed memory, language, executive or "frontal lobe" function, attention, visuospatial function, and motor speed.\textsuperscript{11} Performance on each

<table>
<thead>
<tr>
<th>Table 1. Subjects Stratified by Serostatus*</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>HIV- 10</td>
<td>38.6 (8.9)</td>
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<tr>
<td>HIV+ 20</td>
<td>39.2 (8.2)</td>
</tr>
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</table>

* HIV indicates human immunodeficiency virus; minus sign, negative; and plus sign, positive.
† Score according to a modified version of the Kurtzke Disability Status Scale for Multiple Sclerosis.
‡ P<.01.

No HIV-positive subject had a focal neurological examination. Four HIV-positive subjects had a psychiatric diagnosis of depression, and one HIV-positive subject had psychosis. Eight HIV-positive subjects had abnormal findings from their neuropsychological examinations. Seven subjects met criteria for HIV-1-associated minor cognitive or motor disorder, and one subject met criteria for ADC stage 1.\textsuperscript{20} All HIV-negative subjects had normal findings from their psychiatric and neuropsychological examinations.

There was no significant difference in the frequency of atrophy or the number of white-matter hyperintensities on MRI scans between HIV-negative and HIV-positive subjects. No opportunistic infections or neoplasms were seen.

The interobserver reliability for all three raters for SPECT scan classification was good, as indicated by a κ index of 0.46 (P<.01). Table 2 shows that SPECT scans were abnormal in 15 (75%) of the 20 HIV-positive subjects and in two (20%) of the 10 HIV-negative subjects. Focal defects were seen in all cortical areas, as well as in the basal ganglia, thalamus, and cerebellum in HIV-positive subjects. No specific cortical or subcortical region predominated. By restricting analysis to HIV-positive subjects, abnormal SPECT scans were not seen more frequently in subjects with a CD4 lymphocyte count of less than 2×10^9/L than in subjects with a CD4 lym-
The test was compared with norms for age- and education-matched populations and then rated as normal, borderline (at least 1 SD below the expected mean), or defective (at least 2 SDs below the expected mean). Cognitive impairment was defined as abnormal if there was a defective performance on one test or a borderline performance on two tests.

MRI SCANS

For all subjects, an MRI scan was performed within 1 year of the SPECT study. Scans were performed on a 1.5-T system. The imaging protocol consisted of T1-weighted axial and coronal scans (repetition and echo times, 3500 and 80 milliseconds, respectively), with a slice thickness of 5 mm and a 4-mm separation between slices. Images were acquired in a 512×512 matrix. The MRI scans were evaluated by one neuroradiologist who had knowledge of each subject’s age but who was blind as to all other clinical data, including serostatus. Atrophy, small areas of high-signal intensity, and larger focal lesions were recorded. Atrophy was rated as absent or mild (normal) or moderate or severe (abnormal). Small foci of high-signal intensity (≥3 mm and <2 cm), diffuse foci of high-signal intensity (≥2 cm), and focal lesions that were consistent with opportunistic infections, neoplasms, strokes, or arteriovenous malformations were also noted.

SPECT SCANS

Image acquisition began 30 minutes after intravenous injection of 20 mCi of technetium Tc 99m exometazime (Ceretec, Amersham, Ltd, Amersham, England). Data were acquired on a dedicated brain scanner (SME 810x, Strichman Medical Equipment, Boston, Mass) by employing 2 to 3 million counts per slice and by covering the complete cranial volume at 6-mm axial slice spacing. An 800 collimator was used. System resolution was 8-mm full-width half maximum. Transverse slices were reconstructed by two-dimensional deconvolution with iterative attenuation correction, and coronal and sagittal views were generated as required.

The SPECT scans were independently evaluated by three readers (N.S., I.P., and R.L.V.H.) who were blind to the serostatus of the subjects, and a consensus diagnosis was then obtained. Studies were evaluated by using a horizontal profile analysis to quantify the degree of asymmetry in radioactive tracer activity in a comparison of left with right sides. Results of studies were defined as normal or abnormal based on the presence and number of focal defects. A focal defect was defined as a 20% or greater asymmetry in radioactive tracer activity based on a side-to-side comparison in the axial plane. A focal abnormality was considered to be significant when it was confirmed on an adjacent axial slice and also in the coronal plane. Scans were rated as normal if no or one focal defect was seen. Scans were rated as abnormal if two or more focal defects were seen.

STATISTICAL ANALYSIS

Neuropsychological, MRI, and SPECT data were collapsed into two categories: normal or abnormal. The agreement between readers with respect to SPECT scan classification was evaluated by using the k statistic. The significance of group differences for quantitative data (eg, age, education, and CD4 lymphocyte count in HIV-positive and HIV-negative subjects) was assessed with t tests. For categorical data (eg, the Kurtzke score), the Wilcoxon Rank Sum Test was performed. To compare proportions (eg, frequencies of neuroimaging test abnormalities), Fisher’s Exact Test (two tailed) was used. Simple odds ratios (ORs), OR adjusted for age and log CD4 lymphocyte count using logistic regression, and OR stratified by cognitive impairment were calculated to assess the association of a positive serostatus and abnormal SPECT scans. The In CD4 lymphocyte count was used because the distribution of the CD4 count was skewed. In addition, logistic regression was used to assess the value of SPECT scans as predictors of positive serostatus or abnormal neuropsychological testing results.

The phagocyte count of greater than 2×10⁹/L. None of the four HIV-positive subjects with depression had a decreased uptake in the frontal lobes although three had focal defects in the right temporal lobe. Compared with HIV-negative subjects, the odds of having an abnormal SPECT scan were 12 times higher for HIV-positive subjects (95% confidence interval [CI], 1.9 to 76.4). After adjusting for age and log In CD4 lymphocyte count using logistic regression, the OR remained significant (OR, 52; 95% CI, 3.3 to 807.5).

Eight (67%) of the 12 HIV-positive subjects with normal neuropsychological test results had abnormal SPECT scans. The Figure shows the transaxial plane images of an HIV-positive subject with normal neuropsychological testing results. Focal defects are noted in the right frontal lobe, right part of the thalamus, and left part of the cerebellum. Logistic regression modeling for an abnormal SPECT scan in HIV-positive subjects with normal neuropsychological testing results, as compared with that in HIV-negative subjects, revealed an OR of 8 (95% CI, 1.1 to 56.8). Seven (88%) of the eight HIV-positive subjects with abnormal neuropsychological testing results had abnormal SPECT scans. Logistic regression modeling for an abnormal SPECT scan in HIV-positive subjects with abnormal neuropsychological testing results, as compared with that in HIV-negative subjects, revealed an OR of 28 (95% CI, 2.1 to 379.3). There was no significant difference in the frequency of abnormal SPECT scans between HIV-positive subjects with abnormal neuropsychological testing results and HIV-positive subjects with normal neuropsychological testing results.

Because one subject met criteria for ADC (stage 1), a subanalysis was performed by removing this subject from the statistical analysis. In this subanalysis, as compared with that in HIV-negative subjects, the OR for an abnormal SPECT scan in all HIV-positive subjects (OR, 11; 95% CI, 1.8 to 71.6) and the OR for an abnormal SPECT scan in HIV-positive subjects with abnormal neuropsychological testing results (OR, 24; 95% CI, 1.7 to 330.8) remained significant.

Using logistic regression, an abnormal SPECT scan predicted HIV-positive serostatus (P<.01). In addition, an ab-
Multifocal cortical and subcortical SPECT uptake defects can help to distinguish HIV infection from psychiatric disorders, such as psychosis or depression. However, this pattern cannot be distinguished from that seen in long-term intravenous cocaine and heroin use. Tatsch et al reported SPECT abnormalities in both early and advanced stages of HIV infection. More than 50% of the patients with abnormal SPECT findings had normal computed tomographic or MRI scans. However, the risk factor for HIV disease was not defined, and no controls were used as a comparison with the HIV-positive subjects with early infection in this study. Other studies of SPECT in early HIV infection have had a significant proportion of parenteral drug users in their subject population. The SPECT perfusion defects that were observed in long-term intravenous cocaine and heroin users were, in part, reversible with short-term (1- to 4-week) abstinence. The goal in this study was to determine if technetium Tc 99m exametazime SPECT could distinguish gay HIV-positive subjects without cognitive impairment or with mild cognitive impairment from gay HIV-negative control subjects. No subject reported a significant history of active parenteral drug use. The control subjects who were used in this investigation were age matched to the HIV-positive subjects and were in the same HIV-risk group. The presence of SPECT focal defects in two control subjects was unexpected. This may simply reflect the sensitivity of the SPECT technique. However, one of the seronegative control subjects with an abnormal SPECT scan seroconverted 6 months later. No other seroconversions occurred among the seronegative subjects during 1 year of follow-up since the SPECT examinations were performed.

These results show that HIV-positive gay men without cognitive impairment were more likely to have an abnormal SPECT scan than were HIV-negative gay men. The HIV-positive gay men with mild cognitive impairment (minor cognitive/motor disorder), but not ADC, were also more likely to have an abnormal SPECT scan compared with HIV-negative gay men.

There are several limitations to this study. Bilateral focal defects could be missed by side-to-side comparisons for focal abnormalities. In addition, defect size, global reduction in cerebral uptake, and heterogeneous cortical uptake patterns were not considered in the determination of SPECT scan abnormalities. Semiquantitative analysis using cortical region-of-interest/subcortical or cerebellar activity ratios (ie, isolating the activity in a cortical region and comparing it with the activity in a subcortical or cerebellar region) could not be performed because of the presence of focal defects within the subcortical structures and cerebellum. Cerebellar hypoperfusion has been noted in prior studies of SPECT in HIV infection.

The cause of the focal SPECT uptake defects in HIV-positive subjects remains unclear. They may result from direct neuronal damage by the HIV-1 virus23,24 or toxic effects of enzymes or cytokines that are secreted by infected cells. Subcortical demyelination21,22 may lead to a cortical perfusion defect via the mechanism of diaschisis. The HIV-1 virus may directly cause vascular inflammation and damage that reduce flow. Alternatively, the focal defects may not represent true cortical brain defects but rather enlarged cortical sulci due to focal atrophy. Johnson et al reported that 65% of the focal uptake defects that were seen in ADC corresponded to cortical gyri, and 35% of the defects corresponded to cortical sulci when SPECT studies were coregistered with MRI studies.

This study demonstrates that SPECT focal defects may be seen in HIV-1–infected gay men without cognitive impairment and suggests that SPECT results may be predictive of HIV serostatus and neuropsychological performance in HIV-positive gay men. Single-photon emission computed tomography may be a valuable neuroimaging tool in the diagnostic evaluation of cognitive impairment in HIV-positive gay men, and further longitudinal studies to evaluate the role of SPECT in predicting prognosis and response to the treatment of HIV-1–associated cognitive impairment should be performed.

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**Table 2. Number of Normal and Abnormal SPECT Scans and OR for Abnormal SPECT Scans for Subjects Stratified by Serostatus**

<table>
<thead>
<tr>
<th>No. of SPECT Scans</th>
<th>Normal</th>
<th>Abnormal</th>
<th>OR (CI) Unadjusted</th>
<th>OR (CI) Adjusted for Age and in CD4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>8</td>
<td>2</td>
<td>1.0 (reference value)</td>
<td>1.0 (reference value)</td>
</tr>
<tr>
<td>HIV+</td>
<td>5</td>
<td>15</td>
<td>12 (1.9-76.4†)</td>
<td>52 (3.3-807.5†)</td>
</tr>
</tbody>
</table>

*SPECT indicates single-photon emission computed tomography; OR, odds ratio; CI, confidence interval; CD4, CD4 lymphocyte count; HIV, human immunodeficiency virus; minus sign, negative; and plus sign, positive.

†P<.05.
13. Accepted

References


