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ORIGINAL CONTRIBUTION

Progressive Cerebral Volume Loss in Human Immunodeficiency Virus Infection

A Longitudinal Volumetric Magnetic Resonance Imaging Study

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Objective: To compare rates and anatomical patterns of brain atrophy during 3 stages of human immunodeficiency virus (HIV) disease.

Design: Comparisons of multiple serial brain magnetic resonance images in men without HIV infection and HIV-infected men in Centers for Disease Control and Prevention (CDC, Atlanta, Ga) stages A, B, and C.

Setting: Longitudinal cohort study of the San Diego HIV Neurobehavioral Research Center, San Diego, Calif.

Participants: Eighty-six HIV-1–positive (HIV-positive) and 23 HIV-negative men who were similar in age and risk group. The number of HIV-positive men in each CDC stage was as follows: A, 33; B, 19; C, 34. All HIV-positive men were free of clinically detectable opportunistic neurologic illness.

Main Outcome Measures: Regional volumes of serial magnetic resonance images converted to standardized slope estimates of change in regional volumes of interest.

Results: Medically asymptomatic men (CDC stage A) and medically symptomatic men (CDC stage C) had more rapid loss of cortical tissues than did HIV-negative men as manifested by higher slopes (Tukey honestly significant difference test, $P=.02$ and $P=.001$, respectively) for cortical fluid volume. Accelerated ventricular volume enlargement occurred only in men with CDC stage C disease. Reduction in the volume of white matter was accelerated in participants with CDC stage C disease compared with participants with CDC stage A disease. Of the gray matter regions, only the caudate nucleus sustained accelerated volume loss during CDC stage C disease. Participants whose systemic disease progressed to a higher CDC stage had significantly accelerated ventricular volume increases and caudate atrophy. Rates of cortical and subcortical fluid volume increases and reductions in the volumes of white matter and the caudate nucleus were significantly related to the rate of decline in the $CD4^+$ lymphocyte count.

Conclusions: In the absence of cerebral opportunistic disease, HIV infection causes progressive atrophy within the gray and white matter in the brain. These changes were most severe in the most advanced stage of disease but were evident even in medically asymptomatic HIV-positive persons. Within the gray matter, the caudate nucleus exhibited progressive volume loss linked to disease stage and the rate of decline of the $CD4^+$ cell count. Structural brain changes can begin in the early stages of HIV infection and accelerate during advanced illness.

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NEUROCOGNITIVE disorders in human immunodeficiency virus (HIV) disease range in severity from incapacitating HIV-associated dementia to milder but symptomatic HIV-associated minor cognitive-motor disorders to asymptomatic subtle cognitive impairments revealed as deficits only by detailed neuropsychological testing. These neurocognitive disorders seem to be directly caused by HIV in the brain.[1-6] Because the neurons are not infected by HIV, the neuronal damage responsible for these conditions is probably due to the neurotoxic products of HIV-infected lymphocytes, macrophages, and microglia.[7-9]

In cross-sectional studies, computed tomography and magnetic resonance imaging (MRI) have revealed increased ventricular and sulcal spaces, reduced volumes of gray matter and white matter, and magnetic resonance signal abnormalities in subcortical and cortical regions.[10-18] Generally, more abnormalities are found in patients with late-stage HIV disease[11-13,18] or with HIV-associated dementia.[10,17] In the earlier stages of the disease, abnormalities have been found less consistently. Most studies that have used clinical readings of brain images have detected abnormalities in only a few people with advanced disease.[19-21] More sensitive and reliable image analysis methods may be required to detect earlier, more subtle changes.

The affiliations of the authors appear in the acknowledgment section at the end of the article.

PARTICIPANTS AND METHODS

PARTICIPANTS

We studied 86 HIV-1–positive (HIV-positive) and 23 HIV-negative men participating in the HIV Neurobehavioral Research Center at the University of California, San Diego. The primary risk factor for HIV infection in all civilian participants was homosexuality; HIV risk factors for military participants were sexual behavior or unknown. Participants were excluded if they had a history of a non–HIV-related major medical, neurologic, or psychiatric disorder such as stroke, complicated head injury (ie, loss of consciousness for more than 30 minutes, hospitalization for treatment of neurologic complications, or both), active psychosis, mental retardation, or current alcohol or other substance abuse. The demographic and clinical characteristics of the HIV Neurobehavioral Research Center cohort have been described previously.[24] Participants were selected for the current study if they had undergone 2 or more MRI examinations (range, 2-5) at intervals of at least 6 months and had no evidence of opportunistic infections or neoplasms of the central nervous system at any time based on comprehensive medical and neurologic examinations and MRI examinations of the brain. Characteristics of the study participants at their last MRI time point are summarized in **Table 1**. The study was approved by the institutional review boards of the University of California, San Diego, and the Department of Veterans Affairs Medical Center, San Diego.

PROCEDURES

All participants underwent comprehensive baseline and follow-up medical and neurologic examinations. Participants with AIDS were examined semiannually and others, annually. General physical and standardized neurologic examinations[24] were conducted by a neurologist or by a specially trained clinical research nurse under the supervision of subspecialists in the Neurology and Infectious Disease departments. In addition, a general medical history was taken, and current and past medications were recorded on standardized forms. Blood specimens were obtained for hematologic and immunologic studies, including T-cell subsets and β_2-microglobulin (β_2M). Based on the clinical history, the stage of HIV infection was classified according to 1993 criteria of the Centers for Disease Control and Prevention (CDC, Atlanta, Ga).[28] The stages are as follows: A, asymptomatic; B, history of opportunistic infections not classically associated with AIDS or not life threatening; and C, history of opportunistic infections that are AIDS defining.

In addition to examining participants as classified by CDC stages, a secondary set of analyses was performed on HIV-positive participants according to whether their HIV disease progressed during the study. Participants whose CDC clinical stage changed during the MRI study period as a result of additional HIV-related illnesses (eg, from CDC stage A to CDC stage C) were designated as progressors. Participants with no change in the CDC classification during the study were designated as nonprogressors. Participants classified in CDC stage C at the first MRI examination were excluded from this comparison because their disease could not progress to a more advanced stage.

Serum $CD4^+$ lymphocyte counts were measured by flow cytometry.[29] The levels of β_2M in milligrams per liter were determined using a commercially available enzyme immunoassay (Pharmacia Diagnostics, Fairfield, NJ). β_2-Microglobulin is a low molecular weight protein present in the plasma membrane of all nucleated cells, with the exception of neurons, and is noncovalently bound to class I (self-recognition) major histocompatibility complex molecules. The serum level of β_2M has been shown to be a marker of disease stage and a predictor of subsequent disease progression.[30-33]

MRI PROTOCOL

Magnetic resonance imaging examinations were performed as part of the annual or semiannual medical and neurologic examinations. The MRIs were obtained using a 1.5-T superconducting magnet (Signa, General Electric, Milwaukee, Wis). An asymmetrical multiple echo-spin-echo pulse sequence was used to obtain axial images of the entire brain (TR [repetition time], 2000 ms; TE [echo time], 25 and 70 ms). This imaging protocol was used in a standardized fashion for all participants at all time points. Samples were 5-mm sections centered at 7.5-mm intervals. Two registered image sets were obtained, each highlighting different tissue characteristics; the proton density–weighted image effectively discriminated gray and white matter, and T_2-weighted images discriminated brain and CSF. **Figure 1** (A and B) shows sample images from a participant in the study.

IMAGE ANALYSIS

Image processing was performed in the Brain Image Analysis Laboratory, University of California, San Diego. To reduce potential bias in the anatomical analyses, images for this study were interspersed with image sets from other studies after elimination of identifying information. Details of the image-analysis approach used in this study are published[18,34] and are briefly summarized in the following paragraphs.

In a previous study using volumetric analysis of brain MRIs, Jernigan et al[18] reported cerebral volume loss in medically symptomatic HIV-positive persons. These volume losses were regional, primarily in the temporal limbic cortex, the cerebral white matter, and the caudate nucleus and were consistent with those identified by other groups.[10,16,17] Heindel et al[22] also showed that regional volume loss evident on postmortem MRI correlated with the regional severity of HIV infection. Specifically, volume losses in the striatum and cerebral cortex and increased signal abnormality in the white matter were related to higher brain viral burden as measured by intensity of immunostaining for HIV envelope protein.[22] This regional distribution of cerebral damage is consistent with the *subcortical* pattern of

The digital images were processed by trained image analysts using software developed in the Brain Image Analysis Laboratory on a DOS-based platform. Briefly, each pixel location within a brain section image was classified into 1 of 4 categories, including gray matter, white matter, CSF, and T_2-signal hyperintensity (Figure 1, C). This was accomplished in 2 steps. First, 2 new linear combinations of pixel values were computed to optimize distinctions between gray and white matter and between CSF and brain, respectively. Second, classification criteria, which were adjusted section by section based on white matter signal values (from samples chosen by image analysts), were applied to individual images. Image analysts then designated anatomical regions on all sections. Images were transformed spatially into a standard plane of section using the corpus callosum and interhemispheric fissure as landmarks.

Pixel counts for each anatomical measure were corrected for age and cranium size by using estimates derived from a large group of healthy control participants studied at the Brain Image Analysis Laboratory. Volumes were expressed as *z* scores computed as the deviation of values for each participant from the values for age- and cranium size–matched healthy control subjects.[18]

Volumetric measures of interest were CSF, total cortical gray matter, white matter, and subcortical gray matter regions. Within the CSF, separate measures of cortical (sulcal) CSF and subcortical (ventricular) CSF volumes were made. In addition to total cortical gray matter, 2 measures subdividing the limbic cortex (the mesial temporal lobe) from the remaining cortex (other than the mesial temporal lobe) were obtained. The mesial temporal lobe included the uncus, amygdala, hippocampus, and parahippocampal gyrus. The subcortical gray matter regions, which were all separately measured, included the caudate nuclei, lenticular nuclei, anterior diencephalon (including hypothalamic and septal structures), and posterior diencephalon (thalamus). Also measured were the total and abnormal white matter. Abnormal white matter was defined as areas within the deep white matter or periventricular white matter that were categorized by the tissue classification algorithm as frank signal hyperintensities (ie, that had high signal values outside the ranges of gray matter, white matter, and CSF) or were categorized by the tissue classification algorithm as gray matter but were located in areas in which the presence of gray matter could be ruled out. This method classified all frank signal hyperintensities observable on proton density– or T_2-weighted images as abnormal white matter and included additional pixels not obviously abnormal on the filmed images. **Figure 2** shows a series of 3 fully processed brain sections across 2 time points in an HIV-positive study participant.

COMPUTATION OF STANDARDIZED SLOPE ESTIMATES

Estimates of the rate of change for each of the MRI measures, the $CD4^+$ lymphocyte count, and the levels of β_2M were derived using a flexible collection of routines in the S-Plus (StatSci, Seattle, Wash) language.[35] These routines were based on an empirical Bayesian treatment of a set of statistics from a preliminary least-squares analysis of the data and were performed recursively. Such a procedure is necessary because a least-squares approach is insufficient to estimate slopes that originate from variable numbers of samples obtained over variable periods. This method allows variance components to be estimated using restricted maximum likelihood and uses error estimates to determine the shrinkage of individual slopes toward a common mean such that values that potentially contain more error (fewer time points sampled) are shrunk more than estimates containing less error (more time points sampled). These slopes have the mathematical optimality property of best linear unbiased prediction.

To aid interpretation of the slopes data, they were standardized based on the HIV-negative group. Thus, by definition, for each of the standardized slope measures, the HIV-negative group had a mean of 0 and an SD of 1, while for the HIV-positive participants, individual slopes indicated deviations from the HIV-negative group.

DATA ANALYSIS

The primary goal of the study was to evaluate the rate of cerebral atrophy at different stages of HIV infection. Thus, we first studied the relationship of CDC stage at the last imaging time point to the longitudinal estimates of cerebral volumes (standardized slopes) of cortical sulcal CSF, ventricular CSF, and white matter using 1-way analysis of variance. When significant effects of the CDC stage were obtained, planned comparisons between all groups were made using the Tukey honestly significant difference test. When these analyses indicated significant effects, we studied the additional MRI measures of individual gray matter regions and abnormal white matter to characterize the regional pattern of progressive loss of brain volume.

In a secondary set of analyses, the volumetric brain MRI slopes of the progressors and nonprogressors were compared. To reduce type I errors from multiple comparisons, a level of significance of .01 was used for this secondary set of analyses.

Finally, to evaluate possible relationships between the longitudinal changes in brain volumes and the cellular and biochemical markers of the disease state in the HIV-positive participants, Pearson correlations between brain volumetric slopes and the slopes of $CD4^+$ lymphocyte counts and β_2M levels were computed.

neurocognitive dysfunction observed in many HIV-positive persons.[23-27] This pattern consists of declines in attention, executive functions, psychomotor speed, learning, and memory retrieval and resembles the neurocognitive changes in Huntington disease.

To date, no investigators have reported the longitudinal effects of HIV on the brain using volumetric MRI techniques. We hypothesized that HIV-infected persons would lose cerebral volume and have corresponding increases in cerebrospinal fluid (CSF) volume compared with an HIV-negative control group. Furthermore, we predicted that greater rates of loss would occur in participants with acquired immunodeficiency syndrome (AIDS) compared with participants

Table 1. Demographic and Immunologic Characteristics of Study Participants*

Characteristics	HIV-Negative Control Participants (n=23)	HIV-Positive Participants by CDC Stage A (n=33)	B (n=19)	C (n=34)	P
Demographic					
Age at first visit, y	36.9±8.2	34.1±5.9	35.3±6.8	34.6±4.9	.23
Education, y	14.7±2.6	15.2±2.5	14.1±2.0	14.9±1.9	.88
White, %	82.6	90.9	89.5	88.2	.47
Duration of follow-up, y	1.6±0.6	1.7±0.7	1.7±0.7	1.6±0.9	.96
Clinical					
$CD4^+$ lymphocytes/$\times 10^9$/L	0.83±0.17	0.50±0.23	0.42±0.20	0.28±0.27	<.001†
$CD4^+$ standardized slopes	0.00±1.0	−2.7±1.8	−3.8±1.9	−4.1±1.4	<.001
β_2-Microglobulin, mg/L	1.5±0.6 (n=23)	2.9±1.2 (n=28)	3.2±2.1 (n=18)	2.2±0.4 (n=30)	<.001‡
β_2-Microglobulin standardized slopes	−0.0±1.0 (n=23)	1.3±1.7 (n=31)	1.6±2.3 (n=19)	3.2±2.1 (n=32)	<.001§

*Unless otherwise noted, values are given as mean±SD. P values were calculated by analysis of variance unless otherwise indicated. HIV indicates human immunodeficiency virus; CDC, Centers for Disease Control and Prevention. For definitions of stages, see the "Procedures" section of the "Patients and Methods" section of the text.

†For the $CD4^+$ lymphocyte count, planned pairwise comparisons using the Tukey honestly significant difference indicated the HIV-negative group differed significantly from each of the other groups and that the CDC stage A group differed significantly from the CDC stage C group.

‡For the β_2-microglobulin level, planned pairwise comparisons using the Tukey honestly significant difference indicated that the CDC stage C group differed from each of the other groups, the HIV-negative group differed from each of the other groups, but the CDC stage A group and the CDC stage B group did not differ from each other.

§For the β_2-microglobulin standardized slopes, planned pairwise comparisons using the Tukey honestly significant difference indicated that the CDC stage C group differed significantly from each of the other groups and that the CDC stage B group differed significantly from the HIV-negative group.

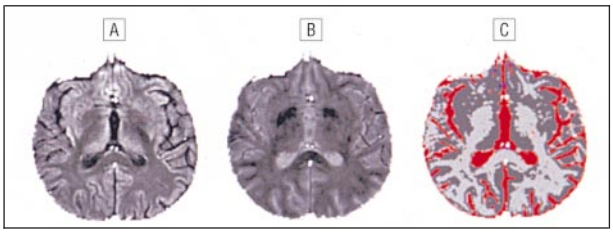

Figure 1. *The standard protocol used in all magnetic resonance examinations included in the study. Each image shown is from the same section of the same participant. A, Proton density–weighted image; B, T_2-weighted image; and C, segmented image.*

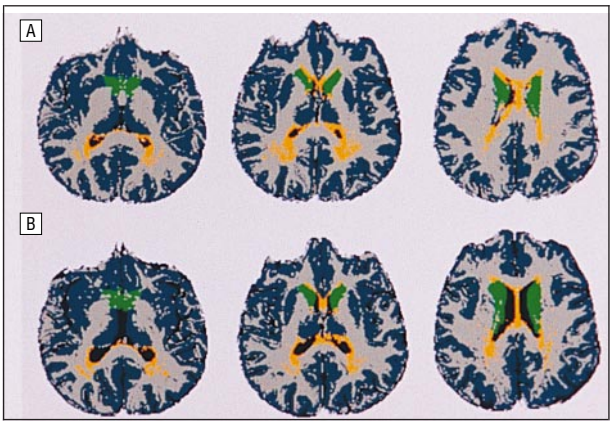

Figure 2. *Three matched axial sections through the ventral cerebrum at each of 2 time points in a human immunodeficiency virus–positive participant with medically symptomatic (Centers for Disease Control and Prevention stage C) disease. A, Results of the baseline examination. B, Results of an examination 18 months after baseline. The z scores for volumes at baseline vs 18 months, respectively, were as follows: ventricular cerebrospinal fluid, −0.53 vs 1.87; cortical sulcal cerebrospinal fluid, 0.19 vs 3.02; white matter, −0.10 vs −1.42; abnormal white matter, 1.23 vs 0.58; and caudate nuclei, −2.01 vs −2.95. Blue indicates gray matter; gray, white matter; black, cerebrospinal fluid; yellow, abnormal white matter; and green, the caudate nucleus.*

with asymptomatic HIV infection. Finally, based on findings from cross-sectional studies, we expected that the most substantial parenchymal losses would be evident in the caudate and lentiform nuclei and the subcortical white matter.

RESULTS

EFFECTS OF DISEASE STAGE

Volume of Cerebrospinal Fluid Spaces

Group comparisons of standardized slopes for cortical sulcal and ventricular CSF–filled spaces are given in **Table 2** and **Figure 3**. The overall analyses of variance were statistically significant (P=.001) for both CSF volumetric measures. These results are consistent with progression of cortical and central atrophy in HIV-infected patients.

Planned pairwise comparisons showed that the rate of progression of cortical atrophy was significantly greater in participants with CDC stage A disease and those with CDC stage C disease than in HIV-negative control participants. A similar tendency was noted for subcortical atrophy, but in this analysis, a statistically significant difference in slope was found only between participants with CDC stage C disease and HIV-negative control participants (Table 2 and Figure 3).

White Matter

Comparisons of the white matter slopes between groups indicated that the white matter group difference was due to accelerated atrophy in the participants with CDC stage C disease compared with the participants with CDC stage A disease (Table 2 and Figure 3). No other group comparisons of white matter volume were statistically significant.

Table 2. Standardized Slopes for CSF and White Matter Volumes for HIV-Positive Participants*

Brain Area	CDC Stage A (n=33)	CDC Stage B (n=19)	CDC Stage C (n=34)	Group Differences
Cortical sulcal CSF†	0.93±1.33	0.46±1.12	1.70±1.38	C greater change than HIV-negative or B; A greater change than HIV-negative
Ventricular CSF†	0.83±1.42	0.61±0.96	2.20±2.14	C greater change than HIV-negative, A, or B
White matter‡	0.21±1.09	0.27±1.25	−0.49±0.88	C greater change than A

**Values are given as mean±SD. Positive slope values indicate increasing volumes (cortical sulcal and ventricular CSF). Negative slope values indicate decreasing volumes (white matter). All slopes are normalized to the HIV-negative group slope of 0. CSF indicates cerebrospinal fluid; HIV, human immunodeficiency virus; and CDC, Centers for Disease Control and Prevention. For definitions of stages, see the "Procedures" section of the text.*

†P<.001 by analysis of variance.

‡P<.05 by analysis of variance.

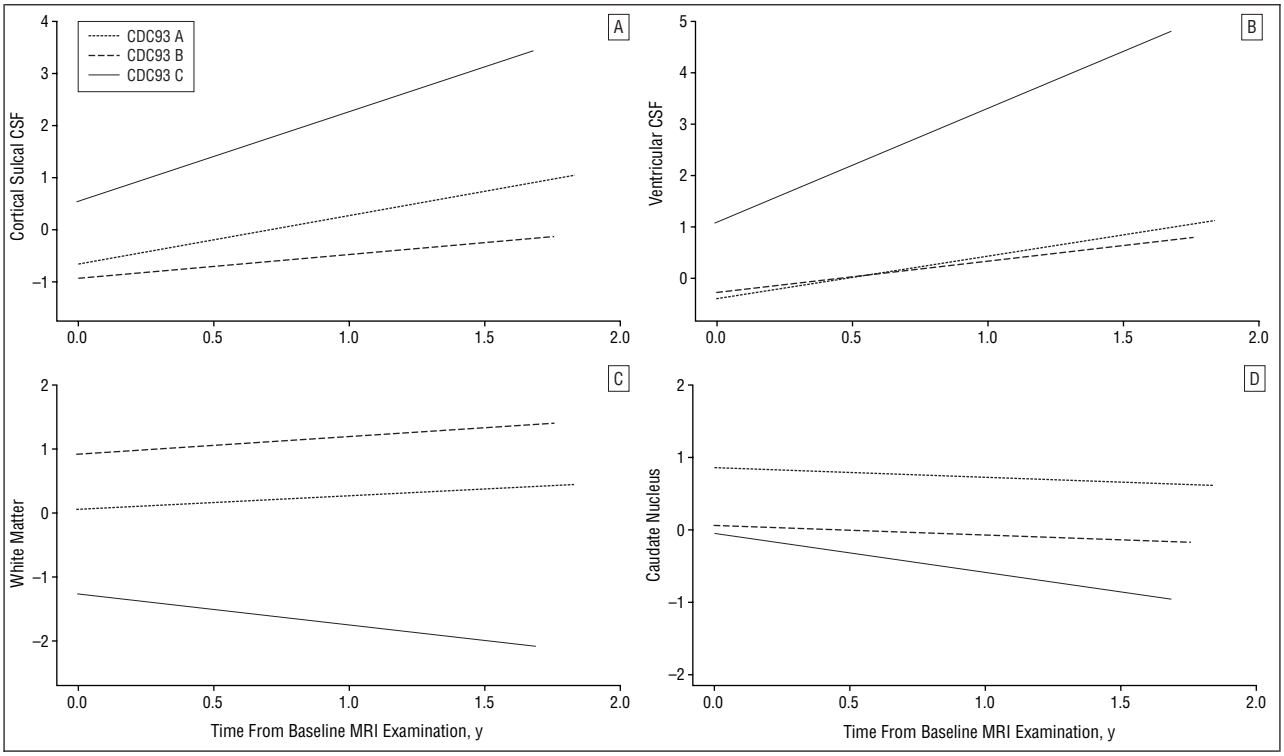

Figure 3. *Mean slopes for the volumes are as follows: A, cortical sulcal cerebrospinal fluid (CSF); B, ventricular CSF; C, white matter; and D, caudate nucleus for human immunodeficiency virus (HIV)-positive participants, standardized to slopes for the HIV-negative control participants. The slopes for the HIV-negative participants are not shown because, by definition, this group had a mean of 0 and an SD of 1. For the cortical sulcal CSF volume, the results for participants with Centers for Disease Control and Prevention stage C disease, 1993 criteria (CDC93 C) differed from those for HIV-negative participants (not shown; by definition, z score of 0) and those with CDC stage B disease (ie, a history of opportunistic infections not classically associated with acquired immunodeficiency syndrome [AIDS] or not life threatening); the results for participants with medically asymptomatic (CDC stage A) disease differed from those for HIV-negative participants. For the ventricular CSF volume, the results for participants with medically symptomatic disease (CDC stage C) differed from the results for all other groups. For the white matter volume, the results for those with CDC stage C disease differed from the results for those with CDC stage A disease. For the caudate nucleus volume, there was a significant effect of group (P=.05); however, no 2 groups differed significantly from each other. MRI indicates magnetic resonance imaging.*

Gray Matter and Abnormal White Matter

To characterize losses in the gray matter that may have contributed to the increases in CSF volume, a set of secondary analyses of gray matter volume slopes was computed (**Table 3**). Analysis of variance was significant for loss of volume in the caudate nucleus (Figure 3), but separate post hoc *t* tests failed to reveal significant differences between participants at various clinical stages. The results of all other analyses of variance for gray matter regions were nonsignificant. Similarly, the result of the analysis of variance for abnormal white matter was nonsignificant.

PROGRESSORS VS NONPROGRESSORS

Progressors showed significantly faster declines in caudate volume and faster increases in ventricular volumes than did nonprogressors (**Table 4**).

RELATIONSHIP OF CEREBRAL VOLUME CHANGES TO MARKERS OF IMMUNOSUPPRESSION AND PROGNOSIS

Using the results for all HIV-positive participants, longitudinal changes in brain volumes and the cellular and

Table 3. Gray Matter and Abnormal White Matter Slopes for HIV-Positive Participants (Standardized Scores)*

Brain Area	CDC Stage A (n=33)	B (n=19)	C (n=34)
Non–mesial temporal lobe cortex†	−0.21±1.16	0.31±1.17	0.09±1.44
Temporal limbic cortex†	−0.34±0.83	−0.24±1.02	−0.18±1.08
Caudate nucleus‡	−0.13±0.74	−0.15±0.85	−0.55±0.64
Lenticular nucleus	0.13±1.35	−0.43±0.86	−0.02±0.98
Anterior diencephalon	−0.01±1.25	−0.01±1.41	−0.29±1.05
Thalamus	0.06±1.18	0.63±1.04	0.43±1.53
Abnormal white matter	−0.17±2.20	−0.01±2.17	1.34±4.88

**Values are given as mean±SD. No paired comparisons were statistically significant. HIV indicates human immunodeficiency virus; CDC, Centers for Disease Control and Prevention. For definitions of stages, see the "Procedures" section of the "Patients and Methods" section of the text.*

†Non–mesial temporal lobe cortex and temporal limbic cortex contain only 31 cases in CDC stage A.

‡P<.05, analysis of variance.

Table 4. CSF, Gray Matter, and White Matter Slopes by Status of Disease Progression (Standardized Scores)*

Brain Area	Nonprogressors (n=43)	Progressors (n=28)
Cortical sulcal CSF	0.86±1.33	1.36±1.41
Ventricular CSF†	0.72±1.39	1.76±1.76
White matter	0.15±1.03	−0.06±1.12
Non–mesial temporal lobe cortex	−0.02±1.22‡	0.11±1.20
Temporal limbic cortex	−0.27±0.86‡	−0.35±0.93
Caudate nucleus†	−0.05±0.78	−0.58±0.70
Lenticular nucleus	0.08±1.21	−0.29±1.01
Anterior diencephalon	−0.02±1.28	−0.03±1.07
Thalamus	0.20±1.17	−0.48±1.11
Abnormal white matter	−0.18±2.11	−0.06±2.21

**Values are given as mean±SD. CSF indicates cerebrospinal fluid. For definitions of nonprogressors and progressors, see the "Procedures" section of the text.*

†P<.01, t test.

‡Included only 41 participants.

biochemical markers of disease state were correlated. Only the brain areas that showed significant relations to CDC stage (Tables 2 and 3) were included in this analysis. Results indicated that the rate of $CD4^+$ lymphocyte loss was significantly related to the rate of atrophy in each of the 4 brain regions. Specifically, more rapid decreases in the $CD4^+$ lymphocyte count were associated with rapid increases in the volumes of ventricular and sulcal CSF (r_{82}=−0.31, P=.006; r_{82}=−0.33, P=.003, respectively). Rapid decreases in the $CD4^+$ lymphocyte count were also associated with rapid decreases in white matter and caudate volumes (r_{82}=0.24, P=.03; r_{82}=0.28, P=.01, respectively).

For serum β_2M levels, trends suggested possible associations of more rapid increases in β_2M levels with more rapid decreases in caudate volume (r_{81}=−0.22, P=.05) and more rapid increases in β_2M levels with more rapid increases in sulcal volume (r_{81}=0.19, P=.09). Thus, the slopes for the $CD4^+$ lymphocyte count had a more consistent and stronger relationship to the slopes for brain volume than did the levels for β_2M. In summary, rapid declines in the $CD4^+$ lymphocyte count were associated with rapid progression of brain atrophy in the most damaged regions. The data suggest similar, although less robust, relationships between brain atrophy and higher levels of β_2M.

COMMENT

In this study, longitudinal volumetric analyses of brain MRIs revealed progressive atrophic changes linked to the progression of HIV disease. Although the most dramatic progression of structural brain abnormalities was noted in men with CDC stage C disease, significant progression in cortical atrophy was also demonstrated in men with CDC stage A disease. A similar pattern of results was noted for central atrophy, although the rates of increase in the ventricular volume among participants with CDC stage A disease compared with HIV-negative control participants did not differ statistically.

These results are consistent with the observations that HIV often enters the central nervous system during primary HIV infection and that increased rates of neurocognitive dysfunction are detectable in patients with CDC stage A disease.[24] Both findings suggest that neuropathologic changes commence during the asymptomatic phase of HIV infection. The specific mediators of these changes in brain volume may be virus-encoded proteins (eg, gp120) or, alternatively, neurotoxic products of HIV-infected lymphocytes, macrophages, and microglia.[7,8]

The rate of these anatomical changes correlates with absolute levels and changes in the clinical and immunologic markers of the stage of HIV infection. Participants with CDC stage C disease had more rapid increases in ventricular volume than all other participants. For cortical atrophy as evidenced by an increased volume of sulcal CSF, the participants with CDC stage C and participants with CDC stage A disease had more rapid losses than did HIV-negative participants. The participants with CDC stage C disease also had more rapid cortical loss than did those with CDC stage B disease. This suggests that cortical atrophy may be biphasic, having larger effects in early and late, rather than middle, disease stages. Alternatively, a larger sample may be necessary to detect changes in the middle stage more reliably. The participants with CDC stage C disease also had more rapid loss of white matter volume than did participants with CDC stage A disease, but the rate of loss was not significantly different from the rates for HIV-negative participants or those with CDC stage B disease. One possible reason that the white matter findings were less robust than the CSF findings is that the presence and extent of abnormal signal in the white matter seemed to fluctuate over time, suggesting the possibility of alternating processes of inflammation and atrophy. Of the 2 cortical and 5 subcortical gray matter regions that we examined, only 1, the caudate, showed significant volume loss related to disease progression. Thus, while the loss of gray matter may be generalized, only in the caudate region is this loss of sufficient magnitude to be detected relative to measurement error in a sample of this size. White matter atrophy also makes a major contribution to the overall loss

of cerebral volume, and this may obscure smaller regional changes in gray matter structures.

Several previous cross-sectional studies have suggested that the caudate nucleus is selectively vulnerable in HIV disease.[10,16,17] A longitudinal study used the bicaudate ratio as a measure of caudate atrophy and indicated a significant relationship between a decreased bicaudate ratio and the possible progression of neurocognitive impairment as manifested indirectly by failure to show expected improvements (related to practice) on repeated testing.[36] This association was present for asymptomatic and symptomatic participants but was stronger in the symptomatic group. In addition, studies of neuropathologic effects have shown higher levels of HIV-associated proteins in the basal ganglia than in other gray matter regions.[37,38]

We were surprised that we did not find progressive increases in abnormal white matter volume, because many of the patients in our study had elevated levels of abnormal white matter. Abnormal white matter volumes were highly variable even in the HIV-negative participants. Such high variability would reduce the detectability of a relationship between abnormal white matter and disease stage if a relationship indeed exists. In addition, we have observed fluctuations over time in the amount of abnormal white matter in some HIV-infected persons; such fluctuations could make detection of reliable linear components in abnormal white matter slopes difficult. For example, the participant whose images are shown in Figure 2 had fluctuating z scores for abnormal white matter volume (Figure 2 legend). While such fluctuations may indicate acute processes occurring in the central nervous system, our slopes were not computed so as to reveal such nonlinear trends.

Given the findings of the effects of disease stage on the volumes of CSF, white matter, and caudate, but not on other gray matter regions, we compared participants in whom the disease progressed with those in whom the disease did not progress. Only rates of ventricular expansion and caudate loss differed significantly between progressors and nonprogressors. Because ventricular CSF surrounds the basal ganglia, losses in volume of the caudate nucleus are probably important to ventricular expansion during disease progression. Whether this acceleration of caudate atrophy is linked to increasing cerebral viral burden or to other HIV-related immunopathologic processes that coincide with disease progression remains to be determined.

Declining $CD4^+$ lymphocyte counts are strong predictors of vulnerability to opportunistic infections and of mortality. We found that rapid $CD4^+$ cell depletion correlated with accelerated cerebral volume loss in each of the 4 volumetric measures that had been shown to be linked to disease stage.

Several types of selection bias probably occurred in this study. For example, participants in whom more severe or incapacitating disease developed may have dropped out of the study, and those with opportunistic infections of the central nervous system were excluded. Because the remaining participants may represent persons with generally less severe disease, we may have underestimated the rates of atrophy in the men with AIDS. Also, because our participants were men whose mode of HIV acquisition was predominantly sexual, our findings may not apply to intravenous drug users or to women.

The results of our study indicate that HIV is associated with progressive brain atrophy. Some of these atrophic changes are noted to progress even in persons with CDC stage A disease, and atrophy is accelerated in advanced HIV disease. The gray matter of the caudate nuclei, the region previously reported to be the most heavily infected by HIV, shows the most dramatic volume loss, suggesting the possibility that the degree of regional viral burden may be associated with corresponding atrophic change.

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