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Magnetic Resonance Imaging Morphometric Analysis of Cerebral Volume Loss in Human Immunodeficiency Virus Infection

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• **Magnetic resonance imaging was used to compare male subjects seropositive for antibody to human immunodeficiency virus type 1 (HIV positive), with and without medical symptoms, with two groups of men who were seronegative (HIV negative). The control subjects included men at high risk for exposure to HIV-1 and those at low risk. None of the HIV-positive subjects met criteria for HIV-associated dementia or had detectable opportunistic brain disease. Quantitative image-analytic techniques were used to estimate volumes of ventricular and cortical cerebrospinal fluid, cerebral white matter, and cortical and subcortical gray matter structures. Relative to low-risk group control subjects and asymptomatic HIV-positive subjects, nondemented but medically symptomatic HIV-positive subjects showed significant increases in cerebrospinal fluid, reduced volume of cerebral white matter, and reduced cerebral gray matter volumes. Unexpectedly, however, some cerebrospinal fluid increases and gray matter volume decreases were present in the seronegative high-risk control subjects as well.**

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The high prevalence and numerous symptoms of central nervous system involvement in acquired immunodeficiency syndrome (AIDS) have been well documented.[1-6] Apart from the focal forms of pathologic findings associated with opportunistic infections and primary lymphomas, a distinct human immunodeficiency virus (HIV)–related dementia syndrome has been recognized, initially termed "AIDS dementia complex,"[2] and more recently defined as "HIV-associated dementia."[7] Early histologic examination of these cases focused attention on the prominent abnormalities in the subcortical white matter,[3] including gliosis, pallor, and the presence of macrophages and multinucleated giant cells. Such areas of subcortical damage have been shown to contain HIV antigens and provirus.[8-10] More recently, significant cortical changes also have been observed in several pathology studies of HIV encephalitis, including neuronal loss,[11-13] loss of synaptic density, and vacuolation of dendritic processes.[13]

Using in vivo brain imaging methods, the presence of cerebral atrophy, ie, enlarged cerebrospinal fluid (CSF) spaces, and signal abnormalities in the white matter have been associated with HIV infection in living patients, particularly with the more advanced stages of infection.[14-20] Previous work by our group defined four types of abnormalities that can be detected by magnetic resonance imaging (MRI) in patients with AIDS and AIDS-related complex. These include the following: focal areas of high-signal intensity, primarily in the white matter and subcortical gray, visualized best on T_2-weighted images; confluent areas of high signal, occurring with less frequency and generally only in late-stage disease; solitary areas of high signal; and enlargement of cortical sulci and ventricular dilatation, with or without the above-mentioned abnormalities.[20,21]

Magnetic resonance imaging has proved to be a sensitive tool for assessing white matter changes and cerebral atrophy associated with HIV encephalopathy, as well as for detecting focal abnormalities due to opportunistic infections and lymphoma.[14,22,23] However, because standard clinical MRI interpretation rarely detects structural abnormality in patients with AIDS who do not have major neurologic symptoms,[24] we have begun to apply quantitative morphometric analyses to determine if subtle changes might be revealed before they can be appreciated reliably by clinical neuroradiologic means.

In our ongoing research program, MRI is performed annually on all HIV-positive subjects and control subjects, and more frequently on symptomatic subjects; however, the results to be presented herein are from initial baseline examinations only. We compared men seropositive for HIV type 1 (HIV positive), with and without medical

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Table 1.—Summary of Subject Characteristics*				
	Seropositive		Seronegative	
	Symptomatic (N=31)	Asymptomatic (N=67)	High-Risk Control (n=39)	Low-Risk Control (n=26)
Age, y	33.4±4.1	34.5±6.7	34.5±6.8	35.1±6.1
Education, y	15.2±1.8	15.0±2.4	15.1±2.2	15.5±2.1

*Values are means±SDs.

symptoms, with men from the same risk group who were seronegative (HIV negative). In addition, we examined a group of men who were seronegative and not known to be members of any group "at high risk" for exposure to HIV. No subjects with diagnosed neurologic disorders or focal brain abnormalities associated with opportunistic infections, etc, were included.

Quantitative image-analytic techniques were used to estimate volumes of ventricular and cortical CSF to assess the degree of brain volume loss. Then separate volumes of cerebral white matter and cortical and subcortical gray matter structures were obtained to attempt to localize the observed losses.

SUBJECTS, MATERIALS, AND METHODS

Subjects

Four groups of subjects were examined in this study. One group consisted of HIV-positive subjects either having symptoms and signs that met criteria for frank AIDS defined by the Centers for Disease Control and Prevention (CDC), ie, CDC stage IV, excluding IV-C2 (n=22), or having an absolute T4 cell count of 200 mm^3 or less (n=9).[25] The 31 men in this group were classified as "HIV-positive symptomatic." A second group (N=63) consisted of men classified as CDC stages II, III, and IV-C2 who were not significantly immunosuppressed (ie, T4 cell counts >200). While these men could have lymphadenopathy and certain other relatively minor medical symptoms, as a shorthand, we classifed them as "HIV-positive asymptomatic" to distinguish them from the seropositive, symptomatic group with more advanced disease. For both of these groups, HIV infection was established by a repeatedly positive enzyme-linked immunosorbent assay and a confimatory test for HIV-1 antibody.

The third group consisted of 39 men from a high-risk population who were seronegative for HIV. They were comparable in age, education, and alcohol or drug abuse histories to the two seropositive groups (we classifed these as "HIV-negative high-risk controls"). A second control group (n=26) consisted of men recruited for other neuropsychiatric studies within the Department of Psychiatry at the University of California at San Diego (classified as "HIV-negative low-risk controls"). All of these control subjects had medical and psychiatric screening, the extent of which varied from a single interview to assess medical and psychiatric history to screening that consisted of medical history, physical examination, and structured psychiatric examination. The four groups were very closely matched for age and education (Table 1).

Subject Selection Criteria

The first three groups described above were participants in the San Diego HIV Neurobehavioral Research Center (HNRC). The HNRC performs multidisciplinary assessments of HIV-positive and HIV-negative high-risk men to determine the etiology, pathogenesis, and natural history of HIV-associated neurobehavioral complications. Subjects undergo the following: comprehensive medical examination, laboratory testing, and CDC staging by infectious disease specialists; structured neurologic examinations; full neuropsychologic testing; and structured psychiatric evaluations by research psychiatrists, in addition to the neuroradiologic study to be described below. The fourth group, or HIV-negative low-risk subjects, were originally recruited as control subjects for other neuropsychiatric studies.

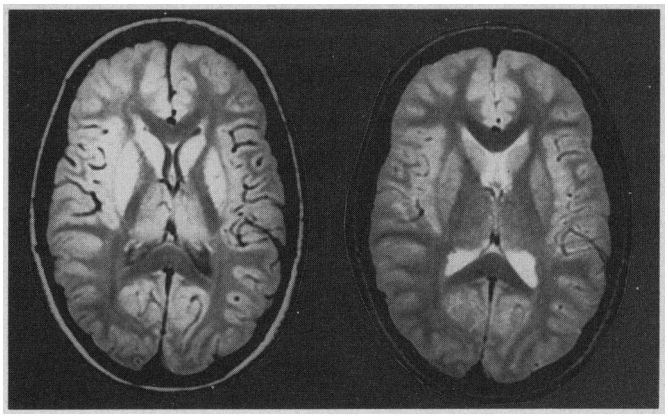

Fig 1.—*Representative images from the standard protocol. Left, Axial section, spin echo 2000/25; right, axial section, spin echo 2000/70. Sections are 5 mm thick, matrix 256×256, with 2.5-mm gaps between images. A field of view of 24 cm was used.*

The HNRC participants are men, aged 18 to 49 years, who do not have histories of significant intravenous drug use or transfusion; therefore, they are presumed to be seropositive or "at risk" by virtue of sexual exposure. Additional exclusions were as follows: presence of clinically evident neurologic complications related to HIV (ie, CDC IV-B cases were ineligible) at time of enrollment; other neuromedical conditions that might independently influence neurocognitive performance or increase likelihood of finding neuroradiologic abnormalities unrelated to HIV (examples, head injury with loss of consciousness exceeding 30 minutes; history of or current neurologic disorder such as epilepsy, encephalitis, congenital or developmental neurobehavioral condition; metabolic or endocrine diseases, eg, diabetes or thyroid disorder; cardiopulmonary disorders, eg, history of myocardial infarction; or hypertension requiring medical treatment). Although, as stated earlier, no clinically demented subjects were included, one subject complained of significant impairment during the baseline neurologic examination. The patient was deemed to be depressed rather than demented, due to findings from psychiatric and neuropsychologic evaluation; therefore, he is included. However, this patient subsequently did become clinically demented.

The HNRC exclusion criteria for alcohol abuse were as follows: subjects who drank seven or more drinks per day for at least 2 weeks in the month prior to entering the study or 90 days in a row in the year prior to enrollment were excluded.

Imaging Protocol

Magnetic resonance imaging was performed with a 1.5-T superconducting magnet (Signa; General Electric, Milwaukee, Wis) at the University of California San Diego/American Medical International Magnetic Resonance Institute. Two spatially registered images (Fig 1) were obtained simultaneously for each section, using an asymmetric, multiple-echo sequence (repetition time, 2000 milliseconds; echo time, 25, 70 milliseconds) to obtain images of the entire brain in the axial plane. Section thickness was 5 mm with a 2.5-mm gap between successive sections in all instances. A 256×256 matrix and 24-cm field of view were used. For the following discussion of image analysis, the term "pixel" will be used to refer to a single picture element (or signal value) from the image matrix. The term "voxel" will be used to refer to the corresponding three-dimensional volume from which the signal value for a pixel arises.

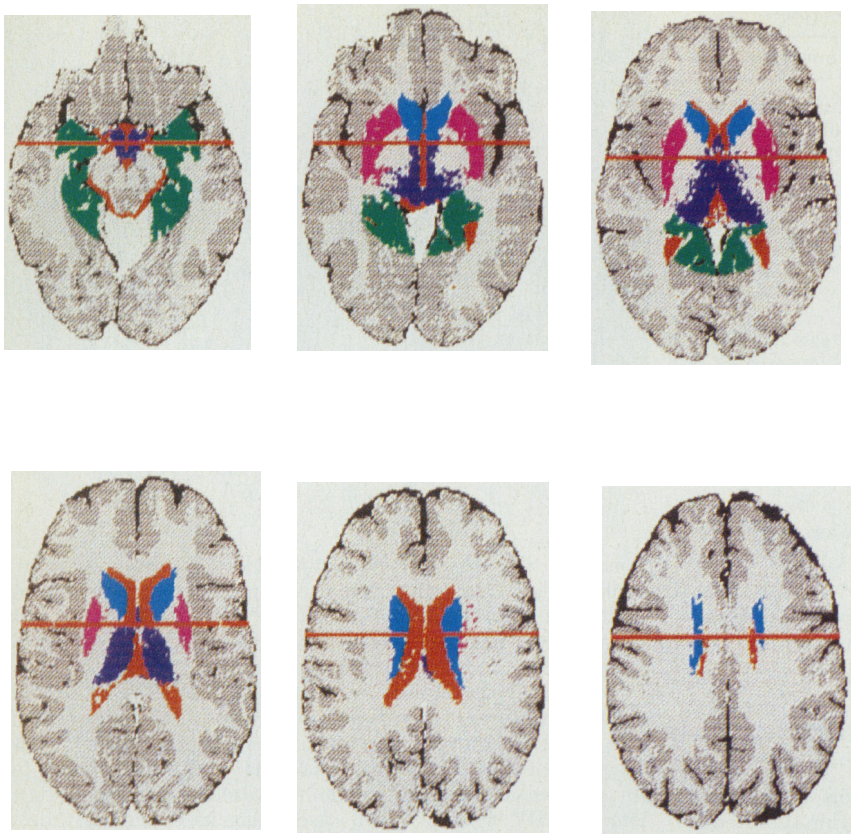

Fig 2.—*Representative, fully processed images. Pixels are classified and regions have been designated using anatomic and some stereotactic criteria. The pixels have been color coded to display the region designations: cerebral cortex, dark gray; temporal limbic structures, green; caudate, blue; lenticular nucleus, magenta; and diencephalon, purple. Ventricular cerebrospinal fluid is coded in red, sulcal cerebrospinal fluid is coded in black, and white matter pixels are displayed herein in light gray. The red line shown within the sections indicates the position of the coronal dividing plane.*

Image Analysis

Detailed descriptions of the image-analytic approach used in this study are contained in several articles.[26-29] Image data sets are assigned (random) numeric codes, and all analyses are conducted "blind" to any subject characteristics. Briefly, each pixel location within a section of the imaged brain is classified based on its signal values in both original magnetic resonance images (echo time, 25 milliseconds; echo time, 70 milliseconds) as most resembling CSF, gray matter, white matter, or signal hyperintensity (tissue abnormality). This is accomplished in two steps: first, two new linear combinations of the pixel values are computed to optimize tissue contrast (CSF/brain and gray/white). Then, classification criteria, adjusted separately for each section based on white matter tissue values, are applied to these computed values. The full series of axial images is analyzed, beginning at the bottom of the cerebellar hemispheres and extending through the vertex.

Consistently identifiable landmark points and structural boundaries are then designated on the pixel-classified images by trained image-analysts. The processed image data are transformed spatially so that all locations within the brain images may be identified relative to a common anatomic coordinate system. Some regional boundaries are then defined relative to this coordinate scheme (ie, stereotactically).

To delineate specific gray matter and CSF structures for this study, the operators circumscribed pixels classified as gray matter or CSF that were visually determined to be in the ventricles, cortical sulci, caudate nuclei, lenticular nuclei, diencephalic gray matter structures (which included, but did not separately delineate, the following: mamillary bodies, hypothalamic gray, septal nuclei, and thalamus), and cerebral cortex (including the contiguous amygdala). The operators did not trace the edges of the structures, but, for each region, they defined polygons that included all gray matter or CSF pixels within the structure and excluded those associated with other structures. In some cases, when the subcortical nuclei were contiguous with other areas classified as gray, but clearly not in the structures, boundaries were manually constructed using the filmed images as a guide.

The cortical and diencephalic regions were further subdivided for this study: the mesial temporal lobe (temporal limbic) structures were separated from the remaining cortex, and the functionally distinct hypothalamic and septal structures within the diencephalic region were separated from the bulk of the thalamus based on a stereotactically defined coronal dividing plane. The fully processed images are illustrated in Fig 2. The different regions are color coded as follows: diencephalic areas are purple, caudate nuclei are blue, and lenticular nuclei are magenta. The red line running through each section indicates the position of the coronal dividing plane. This plane divides the hypothalamic and septal structures (lying anteriorly) from the bulk of the thalamus (lying posteriorly). The region designated as temporal limbic structures (uncus, amygdala, hippocampus, and parahippocampal gyrus) is green, and the remaining cerebral cortex is dark gray. Areas within the lenticular nucleus containing significant iron deposits, particularly in the globus pallidus, do not meet the signal criteria for gray matter and thus are excluded from this region. Ventricular fluid is shown in red, sulcal fluid is shown in black, and white matter is shown in light gray.

Volume of the supratentorial cranium was estimated by summing supratentorial voxels (including CSF, signal hyperintensities, gray matter, and white matter) over all sections. The voxels within each of the regions were summed over all sections in which the designated structures appeared. The sum of all supratentorial white matter voxels was also computed.

Statistical Analysis

The MRI measures used in the comparisons of the four groups had been subjected to additional analyses to remove irrelevant variability due to cranium size and age. These adjustments were based on analyses conducted earlier within a larger group of 107 normal control subjects (many, but not all, of the present low-risk control subjects were in this larger normative group). Normal

age-related changes and effects of supratentorial cranium size were estimated for each measure with multiple regression analyses. Previous studies[30,31] have suggested that some relationships between brain structural volumes and age or cranial volume are not linear. For this reason, polynomial regressions were performed to detect significant deviations from linearity. If the simple correlation (linear component) of age with a morphologic measure was statistically significant, a quadratic term (age-squared) was added to the regression. Similarly, if a linear term for the cranial measure contributed significantly, a quadratic term was included. If the addition of such terms significantly increased R-squared, the function was considered to be nonlinear, and the function with both terms was used in the correction formula.

Based on these analyses, new measures were computed for each normal control that expressed the original values as deviations from the values predicted from the subjects' ages and cranium sizes. Similar analyses were then conducted to estimate any age-related change in the variances of the new deviation scores. Finally, formulas were constructed for estimating a subject's deviation from age- and cranium-predicted values in standard deviation units appropriate for the subject's age.

This rather complex data reduction method was used because the resulting measures are considered to have numerous advantages over the simple volumes. In this study, the volumes of brain structures were measured in an attempt to detect atrophy associated with an HIV-related encephalopathy. Within normal subjects, brain size variability, presumably related to body size variability, is a large contributor to the volume variability of most brain structures; and yet, by definition, it is unrelated to neuropathologic processes. Thus, if such variability can be removed, a larger proportion of the remaining variability should be related to abnormal processes. A similar argument applies to the volume variability within normal subjects that is associated with age. This method produces measures of structural volume that are independent of brain size variations and age differences.

A deviant score on these measures has a different meaning than that of more conventional volume measures. Such a score suggests that a structural volume has an anomalous (or improbable) relationship to cranial size, ie, it is too large or too small, given the subject's age. The degree to which results using these measures are comparable with those from neuropathologic studies is unclear. A further advantage of the measures presented herein, however, is that since they represent estimated z scores, they are expressed on roughly equivalent scales; and thus, it is possible to make gross comparisons of the magnitude of change in one structure with that in another. Since these procedures do not correct for other demographic factors, we have statistically compared the mean z scores of the HIV-positive samples with those of the matched HIV-negative control groups, rather than the larger normative group of 107.

The groups were compared on volumes of ventricular CSF, cortical sulcal CSF, and cerebral white matter using one-way analyses of variance, followed, when significant group differences were detected, by post hoc t tests. Then, additional comparisons were made for the volumes of subcortical structures, temporal lobe limbic structures, and cerebral cortex. For these secondary analyses, α was set at .01 for significance. The CSF and white matter analyses test our major hypothesis that volume loss is present in HIV-positive subjects with symptoms of AIDS but without significant clinical neurologic complications. The group comparisons on the gray matter volumes are secondary analyses intended to provide some indication about the regional pattern of these volume losses.

RESULTS

Group comparisons on the CSF and white matter z scores are summarized in Table 2. All analyses of variance are significant. Post hoc group comparisons are summarized in Fig 3. The CSF group differences are primarily due to significant increases in both cortical sulcal and ventricular CSF in the symptomatic HIV-positive group, relative to all other groups. Unexpectedly, post hoc comparisons also revealed a significant increase in cortical sulcal CSF in the HIV-negative high-risk control subjects relative to both the asymptomatic HIV-positive group and the low-risk control subjects. No CSF increases were observed in asymptomatic HIV-positive patients relative to control subjects. Thus, there is definite evidence for brain volume loss in the medically symptomatic patients relative to all other groups, but there is also unexpected evidence of a modest degree of volume loss in the HIV-negative high-risk control subjects as well, as reflected in increased subarachnoid CSF values.

Table 2.—CSF and White Matter Volume z-Scores*

	Seropositive		Seronegative	
	Symptomatic (N=31)	Asymptomatic (N=67)	High-Risk Control (n=39)	Low-Risk Control (n=26)
Ventricles†	1.6±.1.8	0.2±1.3	0.2±1.2	0.0±1.1
Cortical sulci†	2.0±1.4	0.4±1.3	1.0±1.1	0.1±1.2
White matter‡	−0.7±1.5	−0.2±1.2	0.0±−1.0	0.1±1.0

*CSF indicates cerebrospinal fluid; values are means±SDs.
†$P<.001$.
‡$P<.05$.

Post hoc group comparisons on the white matter volumes (Fig 3) suggest that a substantial amount of the volume loss observed in the symptomatic seropositive subjects is due to white matter loss. This group has significant white matter volume reduction relative to all other groups. No other group comparisons reach significance.

The comparisons of the gray matter volume z scores are presented in Table 3. The analyses of variance yielded a significant group difference only on the temporal limbic measure. Although they did not meet our criterion for significance ($P<.01$), there were also trends for differences in caudate ($P<.05$), anterior diencephalon ($P<.10$), and overall cerebral cortex ($P<.10$). The observed pattern of group differences was similar for the temporal limbic, caudate, and cerebral cortex measures. Reductions were observed in HIV-positive symptomatic subjects *and* HIV-negative high-risk control subjects relative to *both* low-risk control subjects and asymptomatic HIV-positive subjects.

COMMENT

The results of this study confirm and extend earlier imaging reports of brain volume loss in HIV-positive subjects. We observed definite evidence for volume loss only in the medically symptomatic, but neurologically normal, subjects. The results of secondary analyses suggest that this HIV-related volume loss is at least partly attributable to loss of white matter volume. Postmortem studies of frank HIV encephalopathy have revealed neuronal loss, loss of dendritic spines, axonal and dendritic vacuolation, loss of synaptosomes,[13] and reduced synaptic density[32] in these patients. Although the subjects in this study did not have HIV encephalopathies, it is possible that the changes observed in this study reflect an earlier stage of similar neuropathologic processes. Longitudinal observations using MRI, and follow-up autopsy studies, will be necessary to determine if the volume losses we have observed in these neurologically nonsymptomatic persons progress and become associated with frank neurologic signs.

The comparisons of HIV-positive symptomatic with

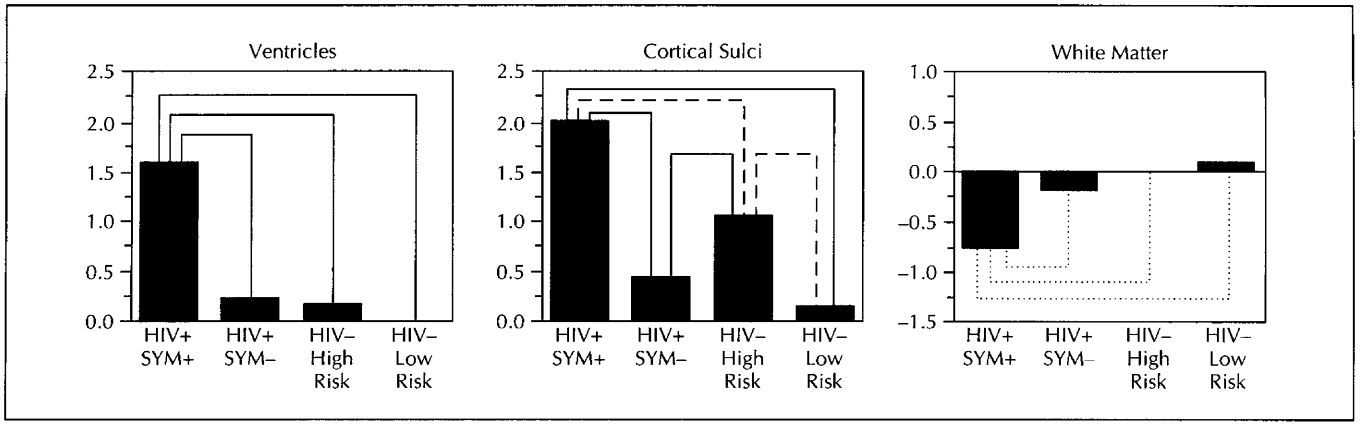

Fig 3.—*Post hoc two-group comparisons of anatomic measures. HIV indicates human immunodeficiency virus; SYM, symptomatic; plus sign, positive; and minus sign, negative. Solid line indicates P<.001; dashed-dotted line, P<.01; and dotted line, P<.05.*

Table 3.—Gray Matter *z*-Scores*

	Seropositive		Seronegative	
	Symptomatic (N=31)	Asymptomatic (N=67)	High-Risk Control (n=39)	Low-Risk Control (n=26)
Cerebral cortex†	−0.6±1.2	−0.1±1.1	−0.6±1.1	−0.2±1.1
Temporal limbic‡	−0.9±1.4	−0.2±1.1	−1.0±1.5	0.1±1.5
Caudate nucleus§	−0.7±1.0	−0.1±1.1	−0.6±1.2	0.2±0.9
Lenticular nucleus	−0.3±0.7	−0.2±1.2	−0.1±1.0	−0.1±0.9
Anterior diencephalon†	0.0±1.1	0.2±1.1	−0.3±1.2	0.3±1.2
Thalamus	−0.4±1.4	−0.3±1.0	0.0±1.0	0.1±1.0

*Values are means±SDs.
†$P<.10$.
‡$P<.01$.
§$P<.05$.

HIV-positive asymptomatic and low-risk control subjects suggest that among the gray matter structures examined, at least the limbic cortical structures of the temporal lobe and the caudate nuclei might be affected by the virus. However, the presence of similar abnormalities in the seronegative high-risk control subjects complicates the interpretation of the gray matter losses in the symptomatic subjects.

One critical methodologic question is which of the groups is the most appropriate control for determining the nature and extent of HIV-related abnormalities. Although gray matter reductions were present in HIV-negative high-risk control subjects, they are unlikely to be related to risk behaviors per se, since they were absent from the asymptomatic HIV-positive group drawn from the same population. The fact that the white matter volume reductions were specific to the HIV-positive symptomatic group suggests that the process by which gray matter losses occurred in this group is probably different than that in the high-risk control subjects.

Others have reported the presence of abnormal findings in HIV-negative control subjects.[19,24,33] While we attempted to exclude subjects (HIV-negative high-risk and HIV-positive subjects) who might have had sources of subclinical neurologic insults unrelated to HIV, it is possible that we were not fully successful in this regard. For example, some of the volume changes (eg, more CSF) might reflect short-term effects of heavier alcohol consumption that were not so intense as to qualify for alcohol dependence (a definite exclusion). It is also possible that differences in use of substances that were not specific exclusions, eg, inhalational nitrites, could contribute to subtle MRI abnormalities in high-risk control subjects. The fact that HIV-positive subjects in the asymptomatic phase had fewer abnormalities than did the high-risk control subjects suggests that significant self-selection factors operating in these groups may be playing a role. Unfortunately, attempts to identify any such factors have so far been unsuccessful.

Whatever the source of MRI "abnormality" in high-risk control subjects, we would expect it to be static in nature or even likely to improve (if related to short-term alcohol or other drug effects). In contrast, if data from the neurologically intact but medically symptomatic subjects are reliable, the possibility exists that such changes will gradually progress not only in the symptomatic group, but they also might begin to appear in the later stages of the "asymptomatic" period. The longitudinal investigation in which we are engaged should help sort out some of these possibilities and, hopefully, yield more definitive information about the nature and location of early HIV-related processes within the central nervous system.

In summary, MRI morphometric analyses reveal that HIV-positive persons who are medically symptomatic or immunosuppressed, but who are free of clinical neurologic signs, nevertheless manifest significant increases in cortical sulcal and ventricular CSF, as well as volume loss in white matter and cerebral gray matter structures. Such changes were not observed in HIV-positive asymptomatic persons. It remains to be determined whether such MRI changes bear any relationship to the cognitive deficits present in some HIV-positive individuals or whether they progress in those CDC IV subjects who have development of frank neurologic complications.

The San Diego HNRC group is affiliated with the University of California, San Diego, the Naval Hospital, San Diego, and the San Diego Veterans Affairs Medical Center, and includes the following: Igor Grant, MD, Director; J. Hampton Atkinson, MD, Co-Director; Robert A. Velin, PhD, Center Manager; Edward C. Oldfield III, MD, James

L. Chandler, MD, Mark R. Wallace, MD, and Joseph Malone, MD, Co-Investigators Naval Hospital, San Diego; J. Allen McCutchan, MD, Principal Investigator Medical Core; Stephen A. Spector, MD, Principal Investigator Virology Core; Leon Thal, MD, Principal Investigator Neurology Core; Robert K. Heaton, PhD, Principal Investigator Neuropsychology Core; John Hesselink, MD, and Terry Jernigan, PhD, Co–Principal Investigators Imaging Core; J. Hampton Atkinson, MD, Principal Investigator Psychiatry Core; Clayton A. Wiley, MD, PhD, Principal Investigator Neuropathology Core; Richard Olshen, PhD, and Ian Abramson, PhD, Co–Principal Investigators Biostatistics Core; Nelson Butters, PhD, Principal Investigator Memory Project; Renée Dupont, MD, Principal Investigator Single Photon Emission Computed Tomography Project; Thomas Patterson, PhD, Principal Investigator Life Events Project; Sidney Zisook, MD, Principal Investigator Mood Project; Dilip Jeste, MD, Principal Investigator Psychosis Project; Hans Sieburg, PhD, Principal Investigator Dynamical Systems Project; and James D. Weinrich, PhD, Senior Investigator.

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