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Sequential Cranial MR Findings of Asymptomatic and Neurologically Symptomatic HIV$^+$ Subjects

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Purpose: To compare results of a prospective MR and clinical reevaluation of HIV$^+$ asymptomatic and neurologically sympatomatic subjects who had had initially abnormal cranial studies to determine what cranial MR changes occur and how these changes correlate with serial neurologic and neuropsychologic findings. **Patients and Methods:** Thirty-one asymptomatic (n = 20) and neurologically symptomatic (n = 11) subjects seropositive for the human immunodeficiency virus (HIV$^+$) were prospectively reevaluated by cranial magnetic resonance (MR) one to two years following an initially abnormal MR of the brain. **Results:** All 31 HIV$^+$ subjects with initial abnormal MR had abnormal follow-up scans (showing atrophy and/or white matter lesions). Twenty-seven showed no progression of MR abnormalities (among whom were 18 with minimally abnormal scans who remained asymptomatic with improved or static neuropsychologic performance). Of the four subjects with scan changes (all with clinically suspected HIV encephalopathy), one showed MR, clinical, and neuropsychologic test improvement; the remaining three showed MR (n = 3), neurologic (n = 3), neuropsychologic (n = 1) worsening and autopsy (n = 1) confirmed the presence of HIV-1 containing multinucleated giant cells in the brain. **Conclusions:** This study suggests that: 1) Progression of intracranial MR abnormalities due to HIV-1 is seen only in a minority of HIV$^+$ subjects over a 1- to 2-year time period, only in those neurologically symptomatic, and correlates with clinical deterioriation. 2) Minor cerebral MR abnormalities seen in HIV$^+$ subjects who remain neurologically asymptomatic do not change over a 1- to 2-year period. 3) Although HIV is known to infect the brain early, it may, nevertheless, not routinely do significant anatomical damage early on in the disease, as based on MR criteria.

Index terms: Acquired immunodeficiency syndrome (AIDS); Brain, magnetic resonance

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It has been well established that the human immunodeficiency virus (HIV-1) infects neurologic tissue early (1–4). However, what remains controversial is whether HIV causes any significant functional or structural abnormalities during the period that an HIV seropositive (HIV$^+$) individual is neurologically asymptomatic (5–16). While some clinical studies comparing asymptomatic HIV$^+$ subjects to HIV negative (HIV$^-$) controls with regard to neurologic and neuropsychologic performance have shown mild functional central nervous system (CNS) impairment (5–11), others have not (6–10, 12). Similarly, with regards to CNS imaging studies, particularly magnetic resonance (MR), structural abnormalities have been reported at a variable incidence at study entry, making it difficult to know the significance of these findings, in particular for the neurologically asymptomatic HIV$^+$ individual (6, 8, 12, 16). Since time-interval studies hold the key to determining the clinical relevance of these early imaging brain abnormalities in HIV$^+$ asymptomatic persons and since few such studies have been done, we undertook our current investigation. We performed

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a prospective MR and clinical reevaluation of those HIV$^+$ asymptomatic subjects who had had an initially abnormal cranial MR at study entry 1 to 2 years and compared those results to findings obtained in a similar fashion in neurologically symptomatic HIV$^+$ individuals.

Methods

From an initial study group of 216 asymptomatic and neurologically symptomatic HIV$^+$ subjects having cranial MR at entry into a multidisciplinary longitudinal study of the neurologic complications of HIV infection, 56 were found to have an initial abnormal scan. Out of these 56, 31 subjects were prospectively rescanned between 13 to 33 months later (average:18 months). Unavailability (n = 6), losses to follow-up, (n = 12), and death (n = 7), precluded the remaining 25 from being rescanned. MR findings on the follow-up visit in the 31 rescanned subjects were compared to those on the initial visit and correlated with serial neurologic (n = 31) neuropsychologic (n = 24), laboratory (n = 31), and autopsy data (n = 1). Seven subjects were unavailable for repeat neuropsychologic testing. Due to cost restrictions, no MR scans were performed on HIV$^-$ controls. The time interval between the most recent neurologic evaluation and the second MR scan was: same day to 3 months: n = 22; between 4 to 6 months: n = 9. The time interval between the repeat neuropsychologic testing and the second MR scan was: same day up to 3 months: n = 12; between 4 to 6 months, n = 6; 7 to 13 months, n = 6.

Details concerning the specific laboratory and clinical tests that were performed routinely in all participants in the overall longitudinal study have been previously reported (16). On initial entry into the larger longitudinal study, none of the 216 HIV$^+$ subjects had any known superimposed CNS infection or tumor. The Center for Disease Control (CDC) classification for HIV infection (17) was used to categorize subjects. The neurologically symptomatic group was classified by predominant neurologic illness, ie, encephalopathy, peripheral neuropathy, or myelopathy.

Follow-up MR scans, performed on upgraded 1.0 or 1.5 T Picker Vista HPQ Units (Picker International, Highland Heights, OH), consisted of T1 axial (700/20/2-4), (TR/TE/excitations) and T2 axial and coronal weighted images (WI) (2400/20,80/1). Slice thickness was 5 mm except for 6-mm thick coronal T2WI. The entry MR studies were performed on 0.5 or 1.5 T Picker Vista Units with similar techniques but with 8-mm slices, and single-echo T2WI.

No direct volumetric measurements of the cerebrospinal fluid (CSF) spaces were made. The sulcal and ventricular spaces were considered either normal or consistent with mild, moderate, or severe atrophy by visual inspection. Concerning parenchymal lesions, when they were discrete, their size was recorded. When comparison of the follow-up scan to the initial entry scan was done, a determination was made as to whether any significant changes had occurred, taking into account differences in scan technique. The scans, assessed by three neuroradiologists, were seen without knowledge of the subjects' neurologic status.

Neurologic evaluations (J.R.B.), included a complete history, Karnofsky's score, a mini-mental state examination, and a thorough neurologic examination. Neuropsychologic testing (B.E.L.), included a test battery with 23 measures to assess six cognitive domains: language, visuospatial ability, judgement and reasoning, attention, memory, and motor speed. All of the cognitive measures are well known standard neuropsychologic tasks that have been described elsewhere (18). Serial neuropsychologic testing was also obtained on 40 HIV$^-$ individuals who were participating in the longitudinal study.

Concerning statistical analyses (R.D.), comparisons of changes over time within and among groups were made using repeated measures analysis of variance or a paired Student's *t*-test for continuous variables and McNemar's test for changes for categorical variables. Comparisons of differences among groups at a point in time were made using one way analysis of variance or a two-sample Student's *t*-test for continuous variables and χ^2 tests for categorical variables. When indicated, Fisher's Exact Test was used in place of the χ^2 test. Statistical significance was set at $P < .05$ for all tests.

Results

Clinical Overview

The 31 rescanned HIV$^+$ subjects included 29 men and 2 women, ranging in age from 25 to 61 years, (average, 41 years; median, 40 years). Four subjects were 50 years or older. Primary risk factors for HIV infection included homosexuality or bisexuality, n = 26; blood transfusions, n = 3; and intravenous drug abuse, n = 2. At the time of the second scan, 29 subjects were ambulatory outpatients; one subject was hospitalized; one subject was in a hospice; and 12 subjects were being treated with zidovudine (Retrovir, Burroughs Welcome, Research Triangle Park, NC). Two of the 20 initially asymptomatic subjects had become neurologically symptomatic while three of the 11 subjects who were initially symptomatic (due to an encephalopathy in seven subjects, a myelopathy in one subject, and a peripheral neuropathy in three subjects) had become asymptomatic. A change in CDC classifications was also noted (Table 1). Follow-up CSF viral

TABLE 1: CDC classification of HIV$^+$ subjects at study entry and at time of follow-up MR scan

CDC Classification	Number of Subjects	
	Entry	Follow-up
Group II (normal laboratory values)	2	1
Group II (abnormal laboratory values)	17	11
Group III	1	3
Group IV	11	16

TABLE 2: Follow-up MR scan findings in both asymptomatic and neurologically symptomatic HIV+ subjects[a]

	Subjects' Classification and Number					
	Class 1a A → A (n = 18)	Class 1b A → S (n = 2)	Class 1c S → S (n = 5)	Class 1d S → A (n = 2)	Class 2a S → S (n = 3)	Class 2b S → A (n = 1)
Type of lesion						
Atrophy only	6	1	3	0	1	1
**WML only	9	0	2	0	0	0
Atrophy + WML	3	1	0	2	2	0
Severity of lesion						
Cerebral atrophy	9	2	2	2	3	1
Cortical	9	2	2	2	3	1
Mild	9	2	2	2	0	0
Moderate	0	0	1	0	1	1
Severe	0	0	0	0	2	0
Deep	5	1	1	2	3	1
Mild	5	1	0	2	0	0
Moderate	0	0	1	0	1	1
Severe	0	0	0	0	2	0
Cerebellar atrophy	0	0	0	0	2	0
Location of WML						
Supratentorial	12	1	2	2	2	0
Periventricular	11	1	2	2	2	0
Centrum semiovale	10	0	1	2	2	0
Internal capsule	1	0	0	0	0	0
Infratentorial	0	0	0	0	2	0
Brain stem	0	0	0	0	2	0
Cerebellar white matter	0	0	0	0	0	0
Distribution of WML						
Unilateral	3	1	1	1	0	0
Bilateral	9	0	1	1	2	0
N of WML						
1–4	9	1	1	2	0	0
5–10	1	0	0	0	0	0
11–15	0	0	1	0	0	0
Clustered	2	0	0	0	0	0
Confluent	0	0	0	0	2	0
Size of WML						
<4 mm	10	1	2	1	0	0
5–10 mm	2	0	0	1	0	0
11–15 mm	0	0	0	0	0	0
16–20 mm	0	0	0	0	0	0
Confluent WML (too diffuse to determine exact size)	0	0	0	0	2	0

Note.—WML, white matter lesions; A, asymptomatic HIV+; S, neurologically symptomatic HIV+.

[a] See Results for explanation of groupings.

cultures were negative in 30 subjects and positive for enterovirus in one subject.

MR Findings and Their Correlation with Clinical Data

All 31 HIV+ subjects with initial abnormal MR had abnormal follow-up scans between 1 to 2 3/4 years later, showing atrophy and/or white matter lesions. However, only four subjects had scans that changed while 27 had no scan changes. The presence or absence of scan changes was used to arbitrarily categorize subjects into two major classes for ease of description. The 27 subjects with static MR scans were designated as class 1 subjects and further subclassified into: 1a: neurologically asymptomatic subjects who remained asymptomatic, (n = 18);

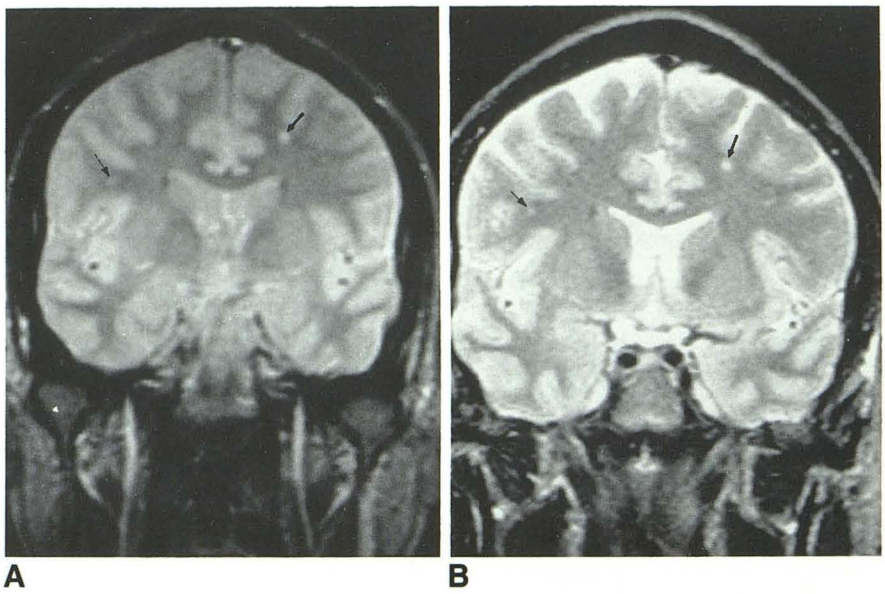

Fig. 1. Neurologically asymptomatic HIV$^+$ subject with unchanged punctate white matter lesions. Initial 0.5 T T2WI showed a few scattered 2–3 mm areas of high intensity signal in the centrum semiovale in this 35-year-old neurologically asymptomatic HIV$^+$ subject, as illustrated in coronal (*A, arrows*), view (2400/80). Twenty-three months later and still asymptomatic, this subject's MR scan revealed no significant changes in any of these small punctate white matter lesions, as illustrated on a corresponding coronal (*B, arrows*) 1.0 T T2WI (2550/80).

1b: neurologically asymptomatic subjects who developed peripheral neuropathy (n = 2); 1c: neurologically symptomatic subjects who remained symptomatic, (n = 5); and 1d: neurologically symptomatic subjects who became asymptomatic at the time of the second MR, (n = 2). The four subjects whose MR scans changed, all of whom were neurologically symptomatic at study entry, were designated as class 2 subjects and also subdivided. Subclass 2a consisted of three subjects with worsening scans (with increased sulcal and ventricular size in three subjects and greater extension of confluent white matter lesions in two subjects) and increasing encephalopathy. Subclass 2b was composed of one subject who had an improved scan and resolved encephalopathy. The MR findings on the follow-up scans in these different classes of HIV$^+$ subjects are summarized in Table 2 and are further elaborated below, where they are correlated with neurologic and neuropsychologic data.

Class 1: HIV$^+$ Subjects with Static MR Scans (n = 27)

Class 1a: Neurologically asymptomatic subjects who remained asymptomatic (n = 18). These 18 subjects had unchanged follow-up MR scans that showed stable minimal cortical atrophy in nine and minimal lateral ventricular dilatation in five, and unchanged small non-mass producing supratentorial white matter lesions in 12 (Figs. 1 and 2). The areas of high intensity signal on the T2WI in the white matter in nine subjects were few in number and small, under 4 mm. In the three subjects having a larger number of white matter abnormalities, the lesions were slightly larger in size in two subjects, but still under 1 cm. Follow-up neuropsychologic testing done in 16 subjects showed no change in 20 measures and significant improvement in three subskills, including abstractions (Shipley abstractions:t = 2.1; degrees of freedom (*df*) = 15, *P* = .05); line orientation, (Benton Judgment of Line Orientation: t = 2.9, *df* = 15, *P* = .01); and delayed recall of semantically related words, (California Verbal Learning Test, (CVLT): t = 3.7, *df* = 15, *P* = .002).

Class 1b: Neurologically asymptomatic subjects who became neurologically symptomatic (n = 2). These two subjects developed a mild peripheral neuropathy by the time of the second MR scan. Their follow-up scans showed no progression of either minimal atrophy (n = 2) or of the associated few punctate supratentorial white matter lesions (n = 1). Follow-up neuropsychologic evaluation, done in one, showed mild worsening on similarities, design fluency, and immediate recall of semantically related words and figural designs. The scores, however, were relative to his initial presentation, and at no time did this subject show evidence of functional impairment.

Considering the subjects in classes 1a and 1b together, 17 had serial neuropsychologic evaluations. When compared to the performance of the 40 HIV$^-$ control subjects, the follow-up test scores in these initially neurologically asymptomatic HIV$^+$ subjects showed relative impairment in lan-

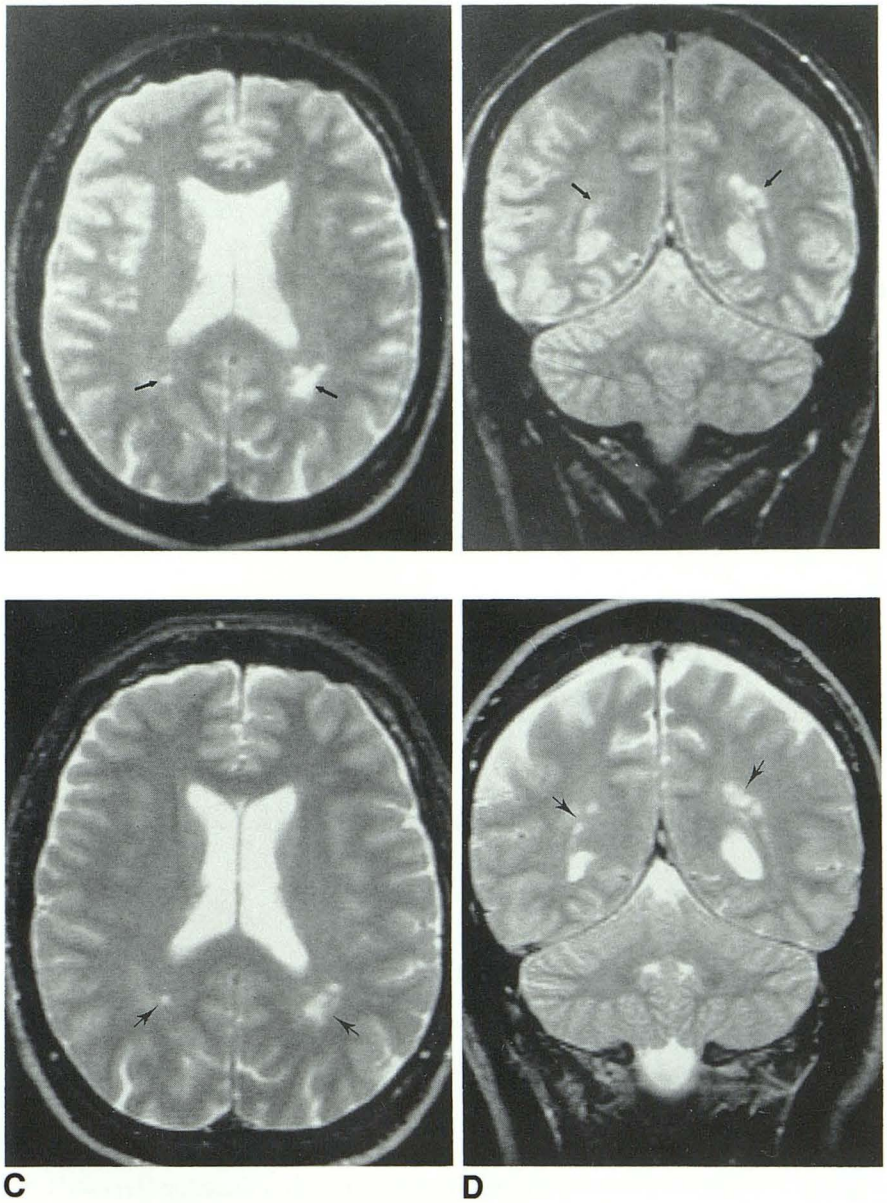

Fig. 2. Neurologically asymptomatic HIV$^+$ subject with unchanged small clustered white matter lesions. This 46-year-old neurologically asymptomatic HIV$^+$ subject had an MR scan at study entry that showed multiple small clustered white matter lesions in the periventricular white matter (*arrows*) on 0.5 T T2WI in (*A*) axial (2400/80) and (*B*) coronal (2300/80) views. Twenty-seven months later, the MR scan on 1.0 T T2WI in (*C*) axial and (*D*) coronal (2200/80) views in this still asymptomatic subject showed no significant changes in the white matter lesions (*arrows*).

TABLE 3: Neuropsychologic tests showing relative impairment at follow-up of HIV$^+$ classes 1a and 1b compared to HIV$^-$ controls

Tests	Student's *t*-test (61 *df*)	*P* Value
Language tasks		
FAS	t = −2.1	.04
Foods	t = −4.1	<.005
Arithmetic calculations	t = −3.9	.005
Stroop word reading	t = +2.6	<.05
Stroop color reading	t = +3.0	<.005
Memory tasks		
Immediate recall of logical discourse material	t = −2.6	<.05
Delayed recall of logical discourse material	t = −2.7	<.01

Note.—Linear contrast following an analysis of variance between groups; *df*, degrees of freedom.

guage and memory tasks (Table 3). However, since the test scores were within the average range, none of these subjects could be formally classified as functionally impaired.

Class 1c: Neurologically symptomatic subjects who remained symptomatic (n = 5). These five subjects demonstrated a persistent mild encephalopathy in three subjects and a stable myelopathy in two subjects. Their follow-up MR scans remained stable, showing no progression of atrophy or of white matter lesions. However, the MR abnormalities in two subjects were more severe than those seen in classes 1a and 1b: one subject had moderate cortical and deep atrophy and another had 15 small white matter lesions. Serial neuropsychologic evaluations, done in 4

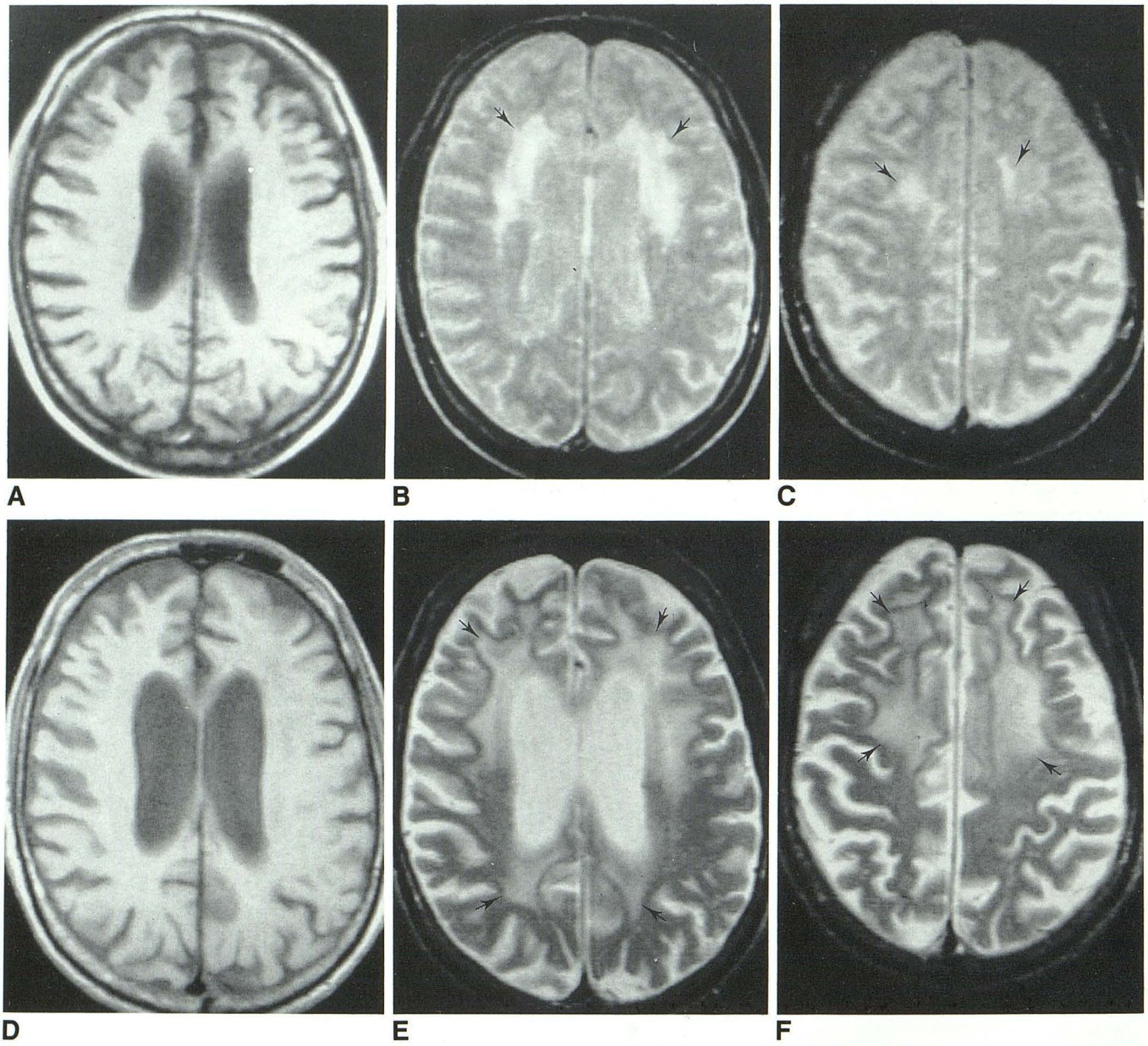

Fig. 3. MR and clinical worsening in a neurologically symptomatic HIV$^+$ subject, a 61-year-old mildly encephalopathic HIV$^+$ subject whose neuropsychologic test battery demonstrated a subcortical dementia. This subject had no hypertension and no active infection with other pathogens. His initial 0.5 T MR on (*A*) T1WI (700–20) showed moderate cortical and deep atrophy associated with periventricular and centrum semiovale confluent white matter lesions, the latter seen on (*B* and *C, arrows*) T2WI (2400/80). Fourteen months later, concomitant with worsening encephalopathy, the follow-up 1.0 T MR showed on (*D*) T1WI (850/20) an increase in size of the sulci and ventricles and on (*E* and *F*) T2WI (2200/80) extension of the white matter lesions (*arrows*).

subjects, showed mild deterioration in two subjects, erratic performance in one subject, and improvement in a mild functional impairment in another. The mild deterioration in one subject was on select language measures, attention and delayed memory and in the other, on visuospatial skills and attention.

Class 1d: Neurologically symptomatic subjects who became asymptomatic (n = 2). One of these two subjects had an initial peripheral neuropathy that resolved. His MR scan showed persistent mild cortical and deep atrophy and several unchanged white matter lesions, one under 4 mm and the other larger, but still under 1 cm. His follow-up neuropsychologic test scores showed slight improvement on visuospatial functioning and figural memory, but worsened performance on immediate and delayed recall of

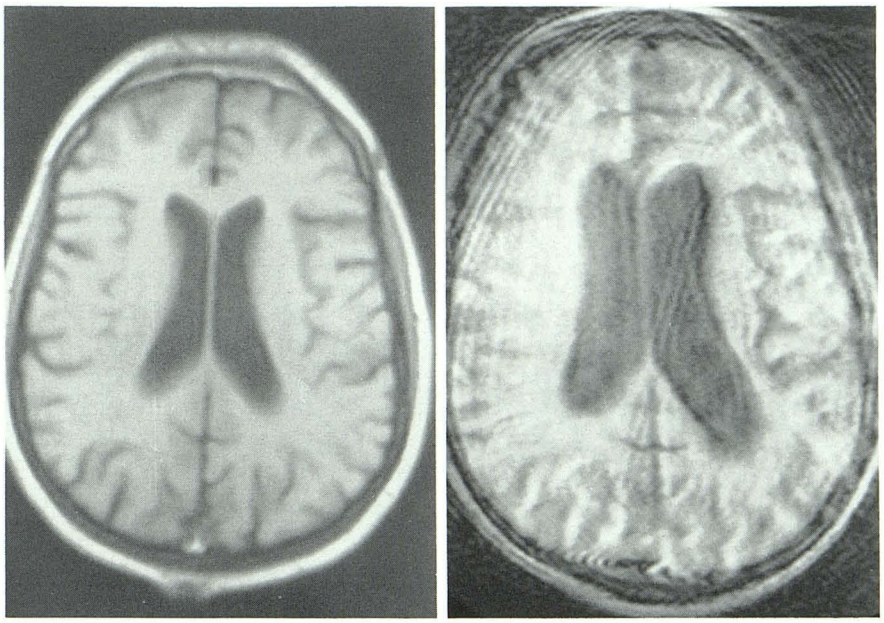

Fig. 4. Neurologically symptomatic HIV$^+$ subject with progressing encephalopathy and MR worsening; 33-year-old HIV$^+$ subject with a predominant encephalopathy (and myelopathy) whose initial 0.5 T MR showed cortical atrophy and lateral ventricular dilation on T1WI in (*A*) axial view (700/20) and periventricular white matter lesions on T2WI (data not shown). Over the ensuing 24 months, the subject deteriorated and, at the time of the follow-up 1.0 T MR scan, was in a hospice. Notice the definite increase in atrophy (*B*) on the T1WI (850–20) despite the patient motion. There was also an increase in white matter lesions (data not shown).

verbal material. The second subject, also initially classified as peripheral neuropathy, became asymptomatic while his scan stayed unchanged with four white matter lesions under 4 mm, with stable mild atrophy, and no follow-up neuropsychologic examinations.

Class 2: HIV$^+$ Subjects with Changed MR Scans (n = 4)

Class 2a: Neurologically symptomatic subjects who worsened (n = 3). Progression of encephalopathy concomitant with worsening of MR abnormalities was seen in all three subjects in this class, all of whom were on zidovudine. The MR abnormalities in two were more severe than those seen in any of the 27 subjects in class 1. The MR scan in the third subject was similar in severity to one of the symptomatic subjects in class 1c. The scans of all three subjects showed either moderate (n = 1) or severe (n = 2) cortical and deep atrophy. Cerebellar atrophy, not present in any of the subjects in class 1, was also seen in two subjects. With respect to white matter lesions, (n = 2), they were more extensive in nature than in any of the other classes studied, being confluent in the periventricular white matter and centrum semiovale and also being present in the brain stem.

The MR scan changes (Figs. 3 and 4) that occurred in these three subjects over a 14 month (n = 2) to 24 month (n = 1) time period included increasing cortical and deep atrophy, from moderate to severe in two subjects and from mild to moderate in one subject and an increase in size of the white matter lesions in both of the subjects with white matter disease. The clinical changes in these subjects included an encephalopathy that progressed from mild to moderate in two subjects and moderate to severe in one subject. Initial neuropsychologic examinations showed subcortical dementia in two subjects, both of whom had elevated serum and CSF p24 antigen values. The other subject, who had serial neuropsychologic examinations, showed a decline in verbal memory with respect to immediate and delayed recall. This latter subject's course was complicated by the ultimate development of disseminated histoplasmosis, resulting in his death. An autopsy revealed HIV multinucleated giant cells characteristic of HIV encephalitis in the brain (Fig. 5), and no intracranial histoplasmosis.

Class 2b. Neurologically symptomatic subject who improved (n = 1). The one subject in this class was a 32-year-old man in CDC class IV, subgroup B, on zidovudine, who was classified initially as mildly encephalopathic. His initial neuropsychologic evaluation showed borderline performance on arithmetic calculations, conceptual set shifting, and abstraction ability. His design fluency was impoverished and he exhibited mild memory difficulties. His initial MR (Figs. 6A–6C) showed moderate cortical and deep atrophy and confluent white matter lesions. Follow-up 16

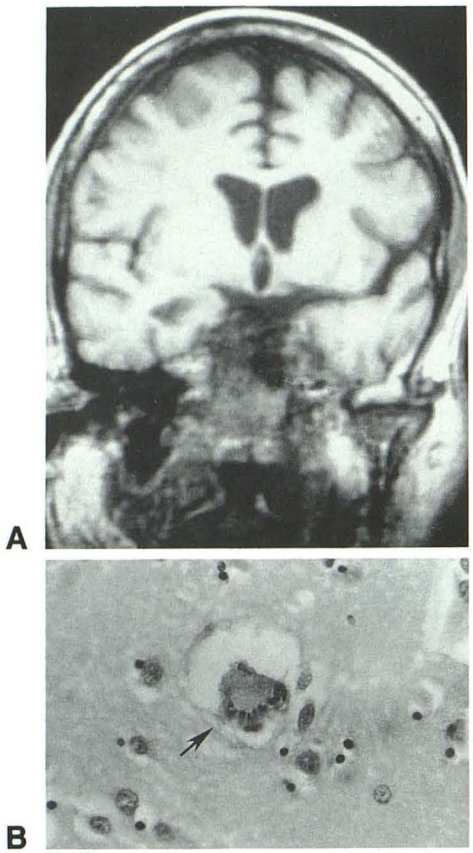

Fig. 5. Neurologically symptomatic HIV$^+$ subject with mild clinical and MR worsening with autopsy correlation. Follow-up (*A*) coronal T1WI (700–20) in this encephalopathic subject showed enlargement of the cortical sulci and lateral and third ventricles. At autopsy, as illustrated on the light microscopic image (original magnification × 125), microglial nodules and multinucleated giant cells (*arrow, B*) characteristic of HIV encephalitis were found.

months later on zidovudine and α-interferon revealed that his neurologic symptoms had resolved and neurologic examination was unremarkable. His follow-up neuropsychologic evaluation showed improvement on select neuropsychologic measures, including word fluency, word retrieval, arithmetic calculations, and visuospatial skills. MR at this time showed stable atrophy and virtual resolution of the white matter lesions (Figs. 6D–6E).

Statistical Correlations between MR, Neurologic, and Neuropsychologic Evaluations

Statistical analysis of MR findings with clinical data in these 31 rescanned HIV$^+$ asymptomatic and neurologically symptomatic subjects revealed the following. There was no statistically significant correlation using χ^2 analysis between findings of atrophy, white matter lesions, or both atrophy and white matter lesions and the following variables: 1) age; 2) sex; 3) race; 4) ethnicity; 5) education; 6) zidovudine therapy; 7) history of head injury; 8) history of hypertension; 9) history of diabetes; 10) history of syphilis; 11) serum fluorescent treponemal antibody absorption (FTA-ABS) values; 12) CSF FTA-ABS values; 13) CSF Venereal Disease Research Laboratory (VDRL) values; 14) and all the neurologic tests save one. Abnormal postural stability to threat correlated significantly with the presence of white matter lesions, ($P = .02$). Similarly there was also no significant correlation between the MR findings cited above and CD4 counts (cluster designation-helper inducer subset) grouped in the following way: less than 200; 200–400; and above 400 cells/mL. There was a statistically significant correlation between CDC classification class IV, subgroup C-2 (class IV, subgroup C-2 in CDC classification system indicates one of the following secondary infectious diseases: oral hairy leukoplakia, multidermatomal herpes zoster, recurrent salmonella bacteremia, nocardiosis, tuberculosis, or oral candiasis (thrush)) and white matter lesions ($P = .02$).

Follow-up neuropsychologic testing, comparing HIV$^+$ subjects with white matter lesions only and those with atrophy only, revealed that the atrophy group performed significantly worse, learning fewer words after 5 trials ($t = -3.2$, $df = 19$, $P = .005$) and recalling fewer words on both the immediate ($t = -2.4$, $df = 18$, $P = .03$) and delayed ($t = -2.7$, $df = 17$, $P = .02$) recall conditions of CVLT. These HIV$^+$ subjects with atrophy only also had more difficulties on the color word interference condition of the Stroop ($t = 2.7$, $df = 10$, $P = .02$). No analysis was performed on the subjects with both atrophy and white matter lesions since there were only three subjects who had serial neuropsychologic tests.

Comparison of the follow-up neuropsychologic test scores in the HIV$^+$ persistently asymptomatic, HIV$^+$ persistently neurologically symptomatic, and HIV$^-$ control subjects revealed a pattern of mean response showing the HIV$^-$ control subjects performing the best, followed by asymptomatic HIV$^+$ subjects in the middle, and lastly the neurologically symptomatic HIV$^+$ subjects. The statistically significant test score differences in these three groups are summarized in Table 4. Memory was the task that most clearly differentiated the groups, with the HIV$^-$ control subjects performing

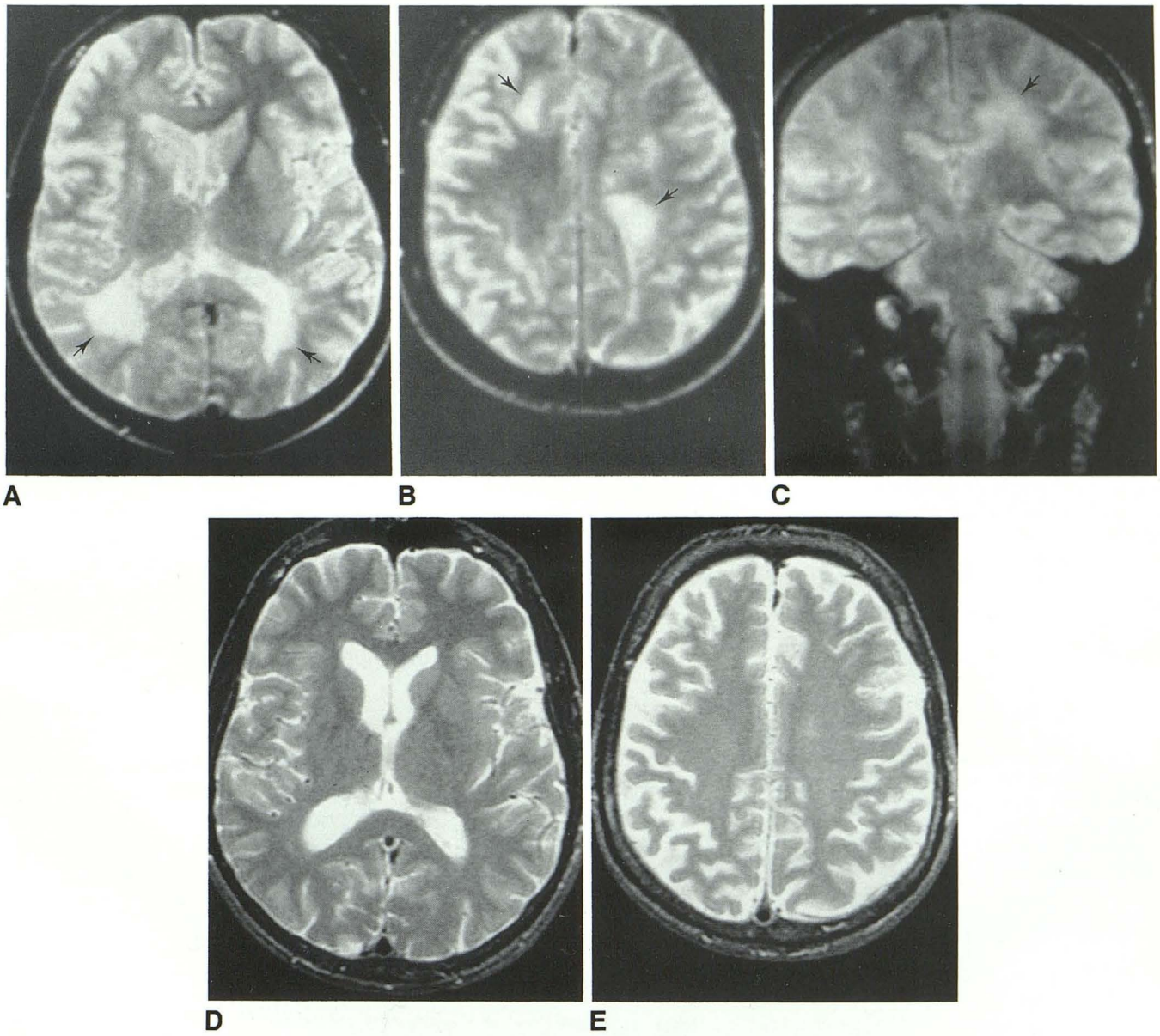

Fig. 6. Initially neurologically symptomatic HIV$^+$ subject with MR and clinical improvement. Initial MR in this 33-year-old HIV$^+$ subject with mild encephalopathy demonstrated on 0.5 T T2WI in (*A* and *B*) axial (2400/80) and (*C*) coronal (2400/80) views confluent white matter lesions (*arrows*) in the periventricular white matter and centrum semiovale and moderate atrophy. A follow-up scan 16 months later while the subject was on zidovudine and α-interferon showed almost total resolution of white matter lesions as verified on (*D* and *E*) axial (2550/80) T2WI. This subject's neurologic examination became normal and his neuropsychologic studies showed selected measure improvements.

best on memory tasks, followed by the neurologically asymptomatic, and lastly, by the neurologically symptomatic HIV$^+$ subjects.

Discussion

HIV infects the brain and, in one-third of AIDS patients, eventually causes a progressive motor and cognitive dysfunction that may culminate in a profound subcortical dementia (19–22). This clinical encephalopathy may be antedated by subtle cognitive impairments that may be detected on comprehensive neuropsychologic test batteries and detailed neurologic examinations. The particular neuropsychologic tasks that have been found to be impaired in AIDS have been those requiring concentration, information processing efficiency, problem solving, abstraction, visuospatial skills, and fine motor control (5, 9, 23). When compared to seronegative controls, mental flexibility and speed of central processing have been found to be reduced and slowed in

TABLE 4: Comparative analysis of follow-up neuropsychologic performances between persistently HIV$^+$ asymptomatic and neurologically symptomatic subjects and HIV$^-$ control subjects

I. Persistently asymptomatic HIV$^+$ (n = 16) subjects vs HIV$^-$ controls (n = 40)
Asymptomatic HIV$^+$ subjects performed significantly worse than HIV$^-$ control subjects on seven of 23 test measures including:
- A. Foods verbal fluency: t = −2.9, *df* = 54, *P* = .006
- B. Proverb interpretation: t = −2.0, *df* = 54, *P* = .05
- C. Wais-R Arithmetic: t = −3.1, *df* = 54, *P* = .003
- D. Verbal memory:
  1. Immediate recall of logical discourse material
     LMP-IR[a]: t = −2.0, *df* = 54, *P* = .047
  2. Delayed recall of logical discourse material
     LMP-DR[b]: t = −2.2, *df* = 54, *P* = .033
- E. Timed reading scores
  1. Word condition of the Stroop: t = 2.9, *df* = 54, *P* = .006
  2. Color reading condition of the Stroop: t = 3.1, *df* = 53, *P* = .003

II. Persistently neurologically symptomatic HIV$^+$ subjects (n = 5) vs HIV$^-$ control subjects (n = 40)
Neurologically symptomatic HIV$^+$ subjects performed significantly worse than HIV$^-$ control subjects on the following measures:
- A. Vocabulary: t = −2.1, *df* = 43, *P* = .004
- B. Proverb interpretation: t = −2.9, *df* = 43, *P* = .006
- C. Shipley abstractions: t = −21, *df* = 43, *P* = .046
- D. Memory
  1. Immediate recall of logical discourse material
     LMP-IR: t = −3.2, *df* = 43, *P* = .003
  2. Delayed recall of logical discourse material
     LMP-DR: t = −3.9, *df* = 43, *P* = .001
  3. Immediate recall of semantically related words (5th trial)
     CVLT-5:t = −2.2, *df* = 43, *P* = .037
  4. Immediate recall of semantically related words (after interference)
     CVLT-IR: t = −2, *df* = 43, *P* = .022
  5. Delayed recall of semantically related words
     CVLT-DR: t = −2.9, *df* = 43, *P* = .006
  6. Immediate recall of figural material
     Benton: t = −3.8, *df* = 43, *P* = .001
- E. Visuospatial judgements: t = −2.1, *df* = 43, *P* = .047
- F. Timed reading scores
  1. Color reading condition of the Stroop: t = 2.9, *df* = 43, *P* = .005
  2. Color word interference condition of Stroop: t = 2.9, *df* = 42, *P* = .006

III. Persistently neurologically symptomatic HIV$^+$ subjects (n = 5) vs persistently asymptomatic HIV$^+$ subjects (n = 16)
Neurologically symptomatic HIV$^+$ subjects performed significantly worse than the asymptomatic HIV$^+$ subjects on the following measures:
- A. Memory
  1. Delayed recall of logical discourse material
     LMP-DR: t = −3.0, *df* = 19, *P* = .008
  2. Immediate recall of semantically related word list
     CVLT-IR: t = −2.1, *df* = 19, *P* = .049
  3. Delayed recall of semantically related word list
     CVLT-DR: t = −2.8, *df* = 19. *P* = .011
- B. Visuospatial judgements: t = −2.4, *df* = 19, *P* = .027

[a] LMP-IR: Wechsler Memory Scale—Logical Memory Passages Subtest, immediate recall.
[b] LMP-DR: Wechsler Memory Scale—Logical Memory Passages Subtest, delayed recall.

symptomatic HIV$^+$ patients (5, 10, 23, 24). Whether cognitive dysfunction exists in the asymptomatic HIV$^+$ individual, however, and whether it can be detected and measured in the asymptomatic period, remains controversial (10, 11, 23).

With regard to imaging studies of the CNS in HIV infection, there has been an excellent clinical-radiographic correlation in those with neurologic symptoms felt to be caused by HIV. Progression of white matter lesions and cortical and deep atrophy on MR and CT have correlated well with

progression of dementia (5, 16, 25, 26, 29, 30). However, in neurologically asymptomatic subjects, both the incidence of MR abnormalities and their clinical significance have been debated. Cranial MR abnormalities in HIV^+ asymptomatic subjects at entry into longitudinal studies investigating the neurologic complications of HIV have been reported in as few as 13% (16) and in as many as 63% of subjects (6).

Some investigators have correlated these MR abnormalities, consisting of atrophy and/or white matter lesions, to early neurologic dysfunction while others have seen no clear cut relationship between early clinical difficulties and these MR abnormalities (5–16). McArthur et al (6), for example, found MR imaging abnormalities in 63% of 270 asymptomatic HIV^+ subjects, but demonstrated no difference in the frequency of MR abnormalities between this HIV^+ group and a group of 193 HIV^- individuals. They also found no differences in the prevalence of neuropsychiatric symptoms or in neuropsychologic performance in these HIV^+ and HIV^- groups (6). Maravilla et al, however, felt that the high percentage of cranial MR abnormalities in their 36 HIV^+ asymptomatic subjects correlated well with early neuropsychiatric difficulties such as abstract concept formation and immediate visual memory function (27). Levin et al, on the other hand, while finding a general slowing of information processing rate in all HIV^+ groups, found a significant deviation from the performance of normal controls in only CDC classification group IV patients (12). In this study, MR quantification of cerebral atrophy correlated directly with speed of response so that the more severe the cerebral atrophy, the slower was the speed of information processing, with the most abnormal speed occurring in patients in CDC group IV.

These conflicting results have remained unreconciled due to the fact that few long-term follow-up MR studies have been done. On a preliminary study of the follow-up MR and clinical evaluations of 35 neurologically asymptomatic HIV^+ subjects performed after a 6-month interval only minimal progression of MR and neuropsychologic abnormalities was found (28). In this study, six subjects had punctate areas of increased signal on T2WI in the white matter which worsened, while one subject had an increase in sulcal and ventricular size. A diffuse increase in white matter signal seen in six subjects on initial MR remained unchanged. Neuropsychologic studies in these 35 subjects were stable or improved (from practice effect) in some areas but tended to decline in the Paced Auditory Serial Addition Test. A greater deficit in immune function, as evidenced by absolute value and percentage of T4, was seen in the small group who had worsening MR abnormalities. Goethe et al also found a correlation between immunocompromise, neuropsychologic deficits, and MR abnormalities in asymptomatic HIV^+ subjects, although their report was based on initial entry MR scans and not on serial scans (9).

In our study, we found no significant changes in minor cerebral abnormalities on MR scans over a 13- to 33-month time period in neurologically asymptomatic HIV^+ subjects who were participating in a multidisciplinary longitudinal study of the neurologic complications of HIV. MR scans, mildly abnormal at study entry, remained mildly abnormal 1 to 2 years later, with either minimal enlargement of the CSF spaces, small white matter lesions, or both. The white matter lesions were usually punctate, under 5 mm in size, and few in number. Only occasionally were they clustered or between 5 to 10 mm in size. Most of these small high intensity signal areas seen in the supratentorial white matter on T2WI resembled those designated in common parlance as "UBOs." Such punctate hyperintense white matter areas, seen on dual-echo images, appeared no different, when not seen in clusters, than what has been previously reported in the literature in neurologically normal HIV^- persons (6, 31, 32). Thus, despite the lack in our study of MR scans for comparison in HIV^- control subjects, reports in the literature support our contention that the majority of the white matter changes in these neurologically asymptomatic HIV^+ subjects are in fact similar to those in neurologically asymptomatic HIV^- persons. With respect to the finding of atrophy in our asymptomatic HIV^+ subjects, it was always minimal and, without volumetric measurements, might even be considered by some to be within the range of normal variation.

Concerning the neuropsychologic test scores in this same neurologically asymptomatic HIV^+ group, they either remained stable or improved over the same 1- to 2-year time period. Cognitive function was within the range of normal. Thus, despite a mild relative impairment in language and memory tasks when compared to the HIV^- control group, these asymptomatic HIV^+ subjects could not be formally classified as functionally impaired.

Concerning the neurologically symptomatic HIV^+ subjects in our study, the most marked MR

abnormalities were seen in this group. Moderate and severe cortical atrophy, confluent and more extensive white matter lesions, and both supra- and infratentorial white matter lesions were evident only in this symptomatic population. Neuropsychologic testing also revealed, with respect to memory tests, that the worst performance was in these neurologically symptomatic subjects, when compared to the neurologically asymptomatic HIV^+ and HIV^- control subjects.

Of the 31 rescanned asymptomatic and neurologically symptomatic HIV^+ subjects in our study, the only four who demonstrated scan changes were those with an encephalopathy. Progression of MR abnormalities paralleled neurologic and neuropsychologic worsening in three subjects and, conversely, MR improvement in one subject correlated with clinical improvement.

Despite the need for a larger sample size and longer time intervals between scans to verify our results, our study leads us to speculate that the minor cerebral abnormalities seen on MR in neurologically asymptomatic HIV^+ subjects either may not, in some individuals, be related to HIV or, if in fact related to HIV, may act in a stable manner for relatively long periods of time (1 to 2 years).

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