

Serial MRI of the brain in asymptomatic patients infected with HIV: results from the UCMMSM/Medical Research Council neurology cohort

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Abstract

Seventy-six homosexual or bisexual men underwent two cranial MRI studies at a mean interval of 13 months; 23 were HIV seronegative, 41 seropositive but asymptomatic (Center for Disease Control (CDC) groups II/III), and 12 had AIDS related complex (ARC)/AIDS (CDC group IV). Agreement between two neuroradiologists was rated as very good for assessment of enlargement of ventricles and good for widening of cerebral sulci and the presence of focal lesions. For assessment of serial studies, the agreement was moderate. The prevalence of cerebral atrophy and focal white matter lesions was no higher in the asymptomatic patients (CDC group II/III) than in appropriate seronegative controls. Some patients with ARC/AIDS showed evidence of developing cerebral atrophy during the study period when serial scans were compared. The imaging evidence supports the other data obtained from this cohort, which suggest that no significant CNS involvement occurs in HIV infection before the development of ARC/AIDS.

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The neurological manifestations such as meningitis,¹ a cauda equina syndrome,² myelitis,³ and encephalitis⁴ that may accompany HIV seroconversion suggest that, at least in some patients, the virus enters the nervous system early in the course of the disease. Furthermore, studies on CSF show cytochemical abnormalities in up to two-thirds of asymptomatic patients in the Center for Disease Control (CDC) groups II/III; HIV can be cultured from CSF in one third of these.⁵

HIV encephalopathy or the AIDS dementia complex has been estimated to occur in 6.5%–66% of patients with AIDS.^{6,7} This wide range reflects variables such as patient selection bias, criteria used for diagnosis, and the stage of disease. Clinically there is a decline in cognitive function often associated with motor and behavioural dysfunction. The diagnosis is one of exclusion of conditions such as depressive pseudodementia, metabolic derangement, opportunistic infections,

and tumours. Although there are no pathognomonic clinical, neurophysiological, or CSF tests, imaging studies may help to support a diagnosis of HIV encephalopathy.

The commonest finding on CT is one of sulcal widening or ventricular dilatation, or both. MRI may show evidence of diffuse white matter lesions on T-2 weighted images.⁸

The issue of subclinical neurological involvement in the asymptomatic patient infected with HIV is still contentious and has important medical, social, and political implications as almost 10 million people are thought to be infected with the virus worldwide. MRI is more sensitive than CT and has proved useful in the investigation of neurologically symptomatic patients with AIDS.⁹ We argued that the detection of early subclinical encephalopathy might be possible with such investigative techniques in asymptomatic patients. If so, such imaging could be used to assess progression of disease and response to treatment, and also to help in elucidating the pathogenetic mechanisms involved in HIV infection.

In 1987, the University College and Middlesex Hospital School of Medicine/Medical Research Council Neurology cohort study was set up to detect the earliest signs of neurological dysfunction in HIV infected patients without symptoms (CDC II/III). To detect such changes the protocol includes serial MRI, neurological assessment, and a battery of neurophysiological and neuropsychological tests. This paper presents the results of the serial imaging performed. Cross-sectional data on the other assessments and a preliminary account of the early MRI findings have been published previously.¹⁰

Methods

PATIENTS

A total of 127 homosexual or bisexual men were recruited. Of these, 101 subjects have had MRI and 76 have undergone repeat imaging at a mean interval of 13 (range 11–23) months. Repeat imaging has not been performed on the remaining 25 subjects (three seronegative, 18 asymptomatic, and four AIDS related complex (ARC)/AIDS) because of death (five); withdrawal from the study (nine); psychological trauma, usually claustrophobia, associated with the procedure

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(five); and imaging not yet performed (six).

At the time of the first MRI study the CDC classification of the 76 subjects who underwent imaging twice was 23 HIV seronegative; 53 HIV seropositive of whom 41 were asymptomatic (CDC group II/III); 12 ARC/AIDS (CDC group IV) (table 1). During the study period six patients asymptomatic in the first study progressed to ARC/AIDS (table 2). For the purpose of this study, the asymptomatic group included subjects with persistent generalised lymphadenopathy and those with oral hairy leucoplakia, which was usually minimal and often transient. The ARC/AIDS group included the CDC group IVA (constitutional disease) and CDC group IVC-2 (oral candida). Patients with AIDS were defined by the CDC groups IVB, IVC-1, and IVD.

No subject in the seronegative group was found to be positive on repeated HIV antibody testing. Fourteen of the 23 seronegative subjects were included in a separate virological cross sectional study. Peripheral blood mononuclear cells were negative for proviral HIV DNA in a "nested" polymerase chain reaction for the *gag* and *pol* genes of HIV-1.

There were no significant differences between the groups for age (mean age 36.6 years), alcohol intake, cigarette smoking, and drug use, including cannabis and amyl nitrate. Syphilis serology results obtained from 74 case records showed no significant group differences in the frequency of positive *Treponema pallidum* haemagglutination assay (TPHA), indicative of a history of syphilis.

Table 1 Clinical data on the ARC/AIDS group

| Case number | ARC/AIDS diagnosis | Period between ARC/AIDS diagnosis and scan | Clinical course | Developed atrophy |
|-------------|------------------------------------|--|--|-------------------|
| 1 | PCP | 12 months | Myopathy ?zidovudine related; oesophageal candidiasis | Yes |
| 2 | PCP | 6 months | Shingles; oral candida | Yes |
| 3 | Oral candida | 6 months | Abdominal pain of unknown cause | Yes |
| 4 | PCP | 8 months | Myopathy—treated with steroids for 3 months; CMV retinitis | Yes |
| 5 | Oral candida | 13 months | Well | No |
| 6 | Kaposi's sarcoma | 8 months | Depression; oral candida | No |
| 7 | Oral candida | 19 months | Cryptosporidial diarrhoea | No |
| 8 | Kaposi's sarcoma | 1 month | Well | No |
| 9 | Oesophageal candidiasis | 13 months | Extensive Kaposi's sarcoma | No |
| 10 | Oral candidiasis | 5 months | Well | No |
| 11 | Oral candidiasis | 4 months | Myopathy ?zidovudine related | No |
| 12 | Kaposi's sarcoma; oral candidiasis | 1 month | Dissemination of Kaposi's sarcoma | No |

PCP = *Pneumocystis carinii* pneumonia; CMV = cytomegalovirus.

Table 2 Clinical data on patients who progressed from asymptomatic to ARC/AIDS during the study

| Case number | ARC/AIDS diagnosis | Period between ARC/AIDS diagnosis and scan | Development of atrophy |
|-------------|---|--|------------------------|
| 13 | PCP and acute encephalopathy | 1 week | Yes |
| 14 | PCP | 22 months | Yes |
| 15 | PCP | 3 months | Yes |
| 16 | Oral candida | 1 month | No |
| 17 | Kaposi's sarcoma | 4 months | No |
| 18 | Chronic <i>Herpes simplex</i> ; constitutional symptoms | 10 months | No |

IMMUNOLOGY

Numerous studies have shown β_2 microglobulin concentrations to be a useful marker of immune function.¹¹⁻¹³ β_2 Microglobulin concentrations in this cohort were quantified from stored serum samples by means of a modified radioimmunoassay (Pharmacia β_2 -micro RIA; Pharmacia Diagnostics AB, Uppsala, Sweden).

MRI

Imaging was performed on a 0.5 T scanner with a circularly polarised head coil. Although no formal realignment procedure was used, attempts were made to align each subject in the imager in a similar fashion on each visit. The imaging variables obtained with a slice thickness of 7 mm and an interslice gap of 1 mm were: sagittal plane T1-weighted spin echo (SE) (repetition time (TR)/echo time (TE)) 350/27 ms; transverse plane proton density 2000/27 ms and T2-weighted spin echo 2000/70 ms. Images were obtained with a 256 × 256 matrix. Contrast medium was not used.

RADIOLOGICAL ASSESSMENT

Each set of images was qualitatively assessed independently by two neuroradiologists (ARV and BK), blind to all clinical details except age, which was indicated on each study. The features specifically considered were: (1) cerebral atrophy—defined as ventricular dilatation and/or sulcal widening; (2) the presence of focal lesions classified as single, multiple or diffuse. The location and the presence of mass effect or associated oedema were also noted.

Incidental finding such as arachnoid cysts found in two subjects were not classified as abnormal. In cases of disagreement between the observers, the images were reviewed jointly and an attempt at a consensus decision was made. If no agreement was reached the study was excluded from further analysis.

At a separate session each radiologist reviewed both sets of images to assess whether any change had occurred. Specific note was made of any change in cerebral atrophy. Changes in the focal lesions were classified as: (1) lesions only on the second study; (2) increase, decrease, or no change in the number of lesions; (3) increase or decrease in the size of the lesions. Again, in cases of disagreement, an attempt at consensus was made.

STATISTICAL METHODS

The data were analysed with the Statistical Package for the Social Sciences (SPSSX). Group analyses were carried out with the χ^2 test and the Kruskal-Wallis test was used to analyse the cerebral atrophy and alcohol data. The degree of interobserver agreement was calculated with the kappa statistic, which takes into account the probability of a chance agreement.¹⁴ To interpret the κ values as an indicator of the degree of agreement the levels used were: less than 0.20 poor, 0.21 to 0.40 fair, 0.41 to 0.60 moderate, 0.61 to 0.80 good, and 0.81 to 1.00 very good.

Results

CROSS SECTIONAL ANALYSIS: FIRST STUDY

The degree of agreement between the two radiologists was very good ($\kappa = 0.90$) for enlargement of ventricles, and good for the presence of focal lesions ($\kappa = 0.76$) and for widening of cerebral sulci ($\kappa = 0.67$). After the consensus meeting, three studies (one seronegative and two asymptomatic patients) were excluded from analysis because no agreement could be reached. One further study was excluded because a birth injury was thought to account for a parenchymal abnormality. Table 3 shows the results from the 72 studies that were analysed.

Cerebral atrophy

Cerebral atrophy was present in 6/22 (27%) seronegative patients and 5/38 (13%) asymptomatic patients. No evidence of atrophy was found in the ARC/AIDS patients. Further analysis showed that the presence of atrophy, irrespective of HIV infection, was associated with a significantly higher mean intake of alcohol (atrophy 55.3 units/week, no atrophy 33.1 units/week; $p < 0.01$). There were no significant associations between the presence of atrophy and age, or use of cannabis or amyl nitrate. With β_2 -microglobulin as a marker of immune function no significant correlation was found between the presence of atrophy in the group of patients infected with HIV and the concentrations of β_2 microglobulin.

Focal lesions

Focal white matter lesions were present on 10 studies: 7/22 (32%) seronegative patients, 2/38 (5%) asymptomatic patients, and 1/12 (8%) with ARC/AIDS. Lesions were single in eight cases (six seronegative, one asymptomatic, and one ARC/AIDS). Multiple lesions were found on one asymptomatic subject and one who was seronegative. No correlation was found between the presence of focal lesions and age, a positive TPHA test, alcohol intake, or use of amyl nitrate, cannabis, or cigarettes. The patients infected with HIV had no significant association with concentrations of β_2 microglobulin.

Cerebral atrophy and focal lesions

Two seronegative and two asymptomatic subjects had cerebral atrophy and focal lesions in the first study. The lesions were multiple in one seronegative patient.

LONGITUDINAL ASSESSMENT OF CHANGE

Seventy-six repeated studies were analysed from 23 HIV seronegative, 35 asymptomatic, and 18 subjects with ARC/AIDS; the last group included six who had been asymptomatic on entering the study.

The degree of agreement between the radiologists was moderate for change in cerebral atrophy ($\kappa = 0.41$) and change in focal lesions ($\kappa = 0.58$); there was total agreement ($\kappa = 1.0$) for a change in size of the focal lesions. After discussion, only one set of images from a seronegative patient was excluded from further analysis because no agreement could be reached.

Table 3 Summary of results

| | Seronegative | Asymptomatic CDC III/III | ARC/AIDS CDC IV | χ^2 |
|--|--------------|-----------------------------|--------------------|-------------|
| First study: | | | | |
| Atrophy | 6/22 (27) | 5/38 (13) | 0/12 | NS |
| Focal lesions | 7/22 (32) | 2/38 (5) | 1/12 (8) | $p < 0.05$ |
| Second study: | | | | |
| Development/ increase in atrophy | 1/22 (4) | 1/35 (3) | 7*/18 (39) | $p < 0.005$ |

*Including 3/6 patients who progressed from asymptomatic to ARC/AIDS during the study. Numbers in parentheses are percentages. NS = non-significant.

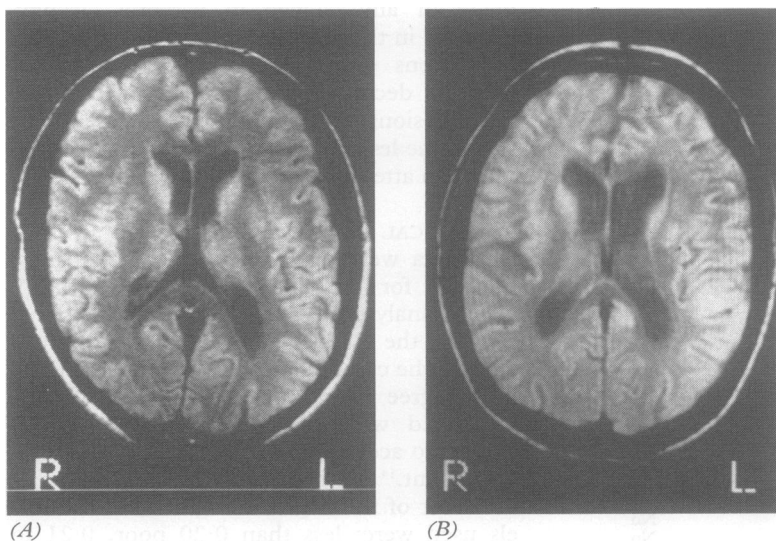


Figure 1 (A) Axial proton density (TR 2000/TE 27) image in a patient with ARC/AIDS showing normal appearance; (B) 13 months later the ventricles are larger.

Increase or development of cerebral atrophy

An increase in cerebral atrophy was found in 1/22 (4%) of seronegative patients. Atrophy developed during the study in only 1/35 (3%) asymptomatic patient but also in 7/18 (39%) patients with ARC/AIDS, of whom three had progressed from being asymptomatic to ARC/AIDS during the study period (fig 1).

The patients who developed cerebral atrophy were not significantly older, and did not have a higher alcohol intake or a longer time interval between the two MRI studies than those who did not develop similar changes.

Change in focal lesions

Lesions were seen only on the second study in HIV positive subjects: one asymptomatic and four ARC/AIDS; in two of the second group, the lesions were classified as diffuse (fig 2). Two seronegative subjects and two with ARC/AIDS had fewer lesions on the repeat MRI. No changes in focal lesions were seen in three seronegative patients and one asymptomatic patient. The numbers were too small for statistical analysis.

Development of cerebral atrophy and focal lesions

One patient with ARC/AIDS and two asymptomatic patients who had progressed to ARC/AIDS, after normal first studies, developed both cerebral atrophy and lesions in the

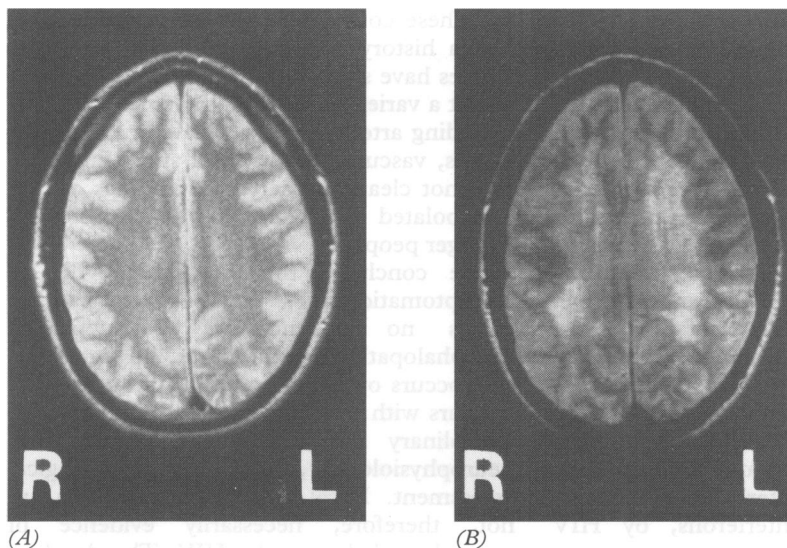


Figure 2 (A) Axial T2 weighted spin echo (TR 2000/TE 70) image showing normal appearance in an asymptomatic HIV positive patient; (B) after 18 months, during which the patient had developed AIDS, there are diffuse white matter abnormalities.

white matter. These were diffuse in two of the studies and at a single focus in the other.

No subject with atrophy only at the first study developed focal lesions at the second. Conversely, one patient with ARC/AIDS who had a focal lesion at the first study developed cerebral atrophy but with resolution of the focal lesion on the repeat study.

Discussion

In 1987, Grant *et al*, using a battery of neuropsychological tests, suggested that asymptomatic patients infected with HIV showed evidence of subtle neurocognitive dysfunction; MRI also revealed a high prevalence of atrophy and abnormalities in subcortical white matter in a small group of patients with ARC/AIDS.¹⁵ This was put forward as further evidence for parenchymal brain damage by HIV. Seronegative controls were not included, however, in this part of the study. Subsequently, larger studies which accounted for confounding variables such as mood and had appropriate seronegative controls, and used a similar battery of tests, have shown no such psychometric deficit in asymptomatic patients. The Multicentre Aids Cohort Study (MACS) concluded that the prevalence of dementia and other HIV related neurological disorders was very low in asymptomatic homosexual men infected with HIV.¹⁶ Furthermore, follow up of this group over a period of 18 months showed no evidence of decline.¹⁷ The issue of subclinical HIV encephalopathy in asymptomatic patients, however, remains controversial. In 1990, Wilkie *et al* found significant abnormalities of information processing and certain verbal memory tests in an asymptomatic group infected with HIV compared with seronegative controls.¹⁸ Although neuropathological data have been sparse in this asymptomatic group, a recent study of patients infected with HIV dying of causes unrelated to their HIV disease described changes, some of which are

found in the brains of patients dying with AIDS, including myelin pallor and reactive astrocytosis. Thus although multinucleate giant cells, the pathological hallmark of HIV encephalitis, and viral antigens such as p24 were not found, there is a suggestion that subtle neuropathological changes may indeed be occurring during the clinically asymptomatic stages of HIV infection.¹⁹

Due to the subjectivity of radiological reporting, some workers have found poor agreement between those interpreting MRI studies particularly with respect to the presence of atrophy.²⁰ With the κ statistic, we found that the degree of agreement was good for assessment of the cerebral sulci and the presence of focal lesions. Agreement was excellent for enlargement of ventricles. When assessing for any change between serial studies, however, the agreement was only moderate. Altogether three sets of images were excluded from the cross sectional study and one from the longitudinal study because of lack of agreement between the two radiologists, which was not resolved at a consensus meeting.

This study may be criticised technically on two aspects. Firstly, using 7 mm thick slices with a 1 mm gap results in partial volume effects and it is possible to overlook lesions. Secondly, no formal method was used to ensure accurate alignment for serial studies. As the techniques used applied to all three subject groups, these drawbacks should not detract from the final group results obtained and the conclusions drawn.

In the cross sectional study, we found no significant difference in the prevalence of cerebral atrophy between seronegative controls, asymptomatic patients infected with HIV, and patients with ARC/AIDS. The presence of atrophy correlated with alcohol intake. In the patients infected with HIV, there was no correlation between atrophy and the degree of immunosuppression as indicated by the β_2 -microglobulin concentration. Serial MRI studies over a period of 13 months showed the development of cerebral atrophy in some of the ARC/AIDS group, including a number who had progressed from being asymptomatic to having ARC/AIDS during the study. With quantitative methods of radiological assessment McArthur *et al* have shown an association between an increase in the ventricular/brain and bicaudate ratios and the degree of immunosuppression using the T-helper lymphocyte count as a marker of immune state.²¹

Although prolonged use of steroids has been implicated as a cause of the brain shrinkage seen on CT,²² only two patients in this study were prescribed high doses of prednisolone and only for a short period during bouts of severe *Pneumocystis carinii* pneumonia. One further patient was on prednisolone for three months for myopathy—the second scan, showing the development of atrophy, was performed five months later.

The pathogenic mechanisms underlying the development of cerebral atrophy in AIDS

are unresolved. HIV is not restricted to subcortical white matter. Sinclair *et al* have found HIV proviral sequences in cortical grey matter.²³ In the study by Post *et al*, cortical atrophy on CT or MRI was found to be a useful indirect marker of cortical HIV involvement.²⁴ More recently, Everall *et al* showed a 38% loss of frontal cortical neurons even in the absence of HIV encephalitis in the brains of patients with AIDS.²⁵ This raises the possibility that the atrophy in AIDS may be due, in part, to indirect effects of the virus. Possible mediators include toxic HIV gene products such as the HIV envelope glycoprotein gp 120, which may interfere with neuronal cell function or cause cell death. Other postulated mechanisms include production of cytokines, such as interleukins, tumour necrosis factor, and interferons, by HIV infected macrophages.

We found that single focal white matter lesions occurred significantly more often in seronegative patients (7/22; 32%) than in the asymptomatic patients (2/38; 5%). Although no correlation was found between a positive TPHA and focal white matter lesions, this may be misleading: with increasing immunosuppression the TPHA may revert to negative.²⁶ In the HIV infected patients (CDC groups II/III and IV) no significant association with β_2 microglobulin concentrations was found. The presence of cerebral atrophy at the first study was not predictive for the development of focal lesions at the second. The MACS study reported a 24% (15/62) prevalence of focal white matter lesions in a group of homosexual men uninfected with HIV, which is similar to our finding of 32%²⁰; however, 26% (33/128) of their asymptomatic HIV infected group, compared with our finding of 5%, also had evidence of these white matter lesions. As in our study, no significant changes occurred over a 12 month period.

There is a lack of data on brain MRI studies in healthy low HIV risk subjects within the age group of our cohort. One such study found an 11% prevalence of white matter lesions in the 30 to 39 age group.²⁷ A higher rate of 22% with presumed incidental white matter lesions was found in patients aged 21–40 years referred to a neurological centre.²⁸ It is argued that the incidence of MRI abnormalities may be higher in homosexual men, reflecting a history of extensive recreational drug use and exposure to a wide variety of infections including sexually transmitted diseases such as syphilis and *Herpes simplex* virus infections. With ultra low field MRI and a computer assisted classification procedure, Sonnerburg *et al* described white matter lesions in 58% of asymptomatic men infected with HIV and 55% of HIV seronegative homosexual men. No such abnormalities were found in a group of heterosexual men and women.²⁹

The aetiology and significance of these focal white matter lesions is still not clear. In the healthy elderly population high signal foci in white matter were found in 30 to 80%.^{28 30}

and these correlated with age, hypertension, and a history of stroke.²⁸ Postmortem MRI studies have shown that these focal areas represent a variety of neuropathological changes, including arteriosclerosis, dilated perivascular spaces, vascular ectasia, and small infarcts.³¹ It is not clear whether these findings can be extrapolated to account for the foci seen in younger people.

We conclude, therefore, that MRI in asymptomatic HIV seropositive patients shows no evidence of a subclinical encephalopathy. Furthermore, no deterioration occurs over a period of 13 months. This concurs with the other findings of this multidisciplinary study including neurological, neurophysiological, and neuropsychological assessment. Focal white matter lesions are not, therefore, necessarily evidence of parenchymal damage by HIV. The development of cerebral atrophy may be seen in some patients with ARC/AIDS, including some who have only recently become symptomatic. Issues to be considered include collecting more data on a young population at low risk for HIV infection, to answer the question as to whether homosexual men have a higher prevalence of MRI abnormalities irrespective of HIV infection and determining whether quantitative MRI will be more sensitive to subclinical encephalopathy in asymptomatic patients infected with HIV than the qualitative methods described in this study.

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