

Cross-Sectional Study of Unexplained White Matter Lesions in HIV Positive Individuals Undergoing Brain Magnetic Resonance Imaging

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Abstract

White matter (WM) abnormalities are frequently seen on brain MRI of HIV positive (HIV+) patients. We aimed to determine the prevalence of unexplained WM abnormalities and their associations with HIV disease and cardiovascular risk factors. We conducted a retrospective, cross-sectional study of brain MRI of HIV+ patients conducted between 2004 and 2009 at our center. Clinical and laboratory data were compiled, and images were independently reviewed for WM lesions. Images were obtained from 254 patients: 70% male, 53% white, 40% black, mean age 42 years, median current CD4 count 240 cells/mm³, and 41% not taking antiretroviral therapy (ART). Hyperintense WM lesions were present in 161 patients (63.4%): 89 scans (35.0%) showed diffuse WM signal abnormality (DWMSA), 61 (24.0%) were consistent with small vessel disease (SVD, graded by Fazekas' scale), and 37 (14.6%) showed large asymmetrical focal WM lesions. SVD changes were associated with age and cardiovascular risk factors, and while cerebral SVD may be related to HIV infection, the MRI findings were not associated with HIV-related factors. The only risk factor for DWMSA was black race, and no correlation with cardiovascular risk factors, CD4 count, or clinical presentation was identified. DWMSA are therefore of uncertain neurological significance in HIV+ patients and could represent more than one clinicopathological entity.

Introduction

THE CLINICAL AND RADIOLOGICAL SPECTRUM of central nervous system (CNS) disease in HIV positive (HIV+) patients has evolved since highly-active antiretroviral therapy (HAART) was introduced in 1996, in that the incidence of serious AIDS-defining CNS disease has decreased in countries with good access to HAART,^{1,2} but the prevalence of milder neurocognitive impairment (NCI) in individuals living with HIV has increased and is estimated at 19–69%.^{3–7}

Recent neuroimaging studies have used advanced magnetic resonance imaging (MRI) techniques such as diffusion-weighted (DWI) and diffusion tensor imaging (DTI),^{8–10} volumetric analysis^{11,12} and arterial spin labeling¹³ to explore biomarkers of HIV infection and of NCI in HIV+ patients. In particular, research using diffusion-based techniques suggests that HIV infection and HIV-associated NCI are associated

with increased diffusivity and reduced anisotropy in cerebral white matter (WM).^{8,14} However, there have been few studies using standard clinical diagnostic MRI techniques in recent years. Although early work found little evidence for a difference between the prevalence of focal WM abnormalities in HIV+ patients and seronegative controls,^{15–17} considerable changes have occurred since the 1980s in clinical HIV medicine and MR radiography. Hyperintense WM lesions are often seen in the normal aging population, with a strong association with cerebrovascular disease,^{18–20} though their pathogenesis is not well understood and may be multifactorial.²¹ Their significance in HIV clinical practice, particularly as an incidental finding, remains unclear. There have been recent advances in non-imaging tools used to diagnose and monitor NCI in HIV,^{22–25} using techniques that are reproducible and require less expertise than neuropsychological assessment. However, given some of the uncertainty over

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the longer term clinical importance of mild-to-moderate cognitive difficulties, improved understanding of biomarkers such as structural and functional imaging is vital.

Our main aim was to estimate the prevalence of WM abnormalities, subdivided according to morphology, in patients undergoing brain MRI for clinical reasons. Our second aim was to determine whether unexplained WM lesions (UWML) of different distributions were associated with HIV-related factors (such as degree of immunodeficiency, and ART status) or with cardiovascular risk factors.

Methods

Patient sampling and magnetic resonance imaging

We conducted a retrospective, cross-sectional study in an observational clinical setting. All HIV+ patients undergoing in- or outpatient brain MRI for clinical indications between April 2004 and November 2009 at a single tertiary hospital in London, UK, were identified. MRI was performed at 1.5 Tesla using a standardized clinical protocol that included T1- and T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging, with gadolinium enhancement where clinically appropriate. In patients who had had multiple scans during the sampling period, only the earliest available scan was included.

The presence or absence of cerebral WM abnormalities, appearing hyperintense on T2-weighted and FLAIR imaging, was first reported by one of two study radiologists (CD and HC), who were blinded to the original clinical presentation and subsequent progress and investigations. Standardization of the classification method between raters was provided by training in the use of the Fazekas Scale, an established and validated method of reporting WM hyperintensities of presumed vascular origin from a single MRI,²⁶ from two experienced neuroradiologists (HRJ and HH). Validation checks included the re-reporting of 35% of the images (randomly selected by computer) by a single radiologist (HC), again blinded to clinical details and the results of the earlier review. The classifications of the remainder were compared with the original clinical report. Any differences between classifications were adjudicated by the lead investigator (HRJ).

WM abnormalities were classified as focal or diffuse. Focal lesions consistent with cerebrovascular small vessel disease (SVD) were graded according to the Fazekas scale, which classifies SVD into four broad categories (0, no WM lesions; 1, small punctate lesions only; 2, early confluent lesions; 3, confluent WM lesions) and takes into account the number of small WM hyperintensities expected for age. The second type of focal WM hyperintensity was large asymmetrical lesions, presumed not of vascular origin. Diffuse white matter signal abnormality (DWMSA) was graded qualitatively as “intense” if with the signal was more intense than gray matter on T2-weighted and FLAIR images, or “subtle” if the signal on T2-weighted and FLAIR images was iso- or hypointense relative to gray matter. Leptomeningeal enhancement, parenchymal enhancement, mass effect and atrophy were also recorded. Patients without gradable MR scans, because of missing sequences or severe movement artefact, were excluded.

Clinical data collection

Clinical and laboratory data were compiled and reviewed by a different investigator (LJH). Patients with WM abnor-

malities were then categorized into those with a definitive, explanatory diagnosis, and those with no explanatory condition identified, based on clinical and laboratory findings close to the date of the MR scan. A diagnosis of HIV encephalopathy, SVD, or viral encephalitis that was made on clinical or radiological grounds after exclusion of other definitive diagnoses but not confirmed by virological or histopathological evidence was not considered to be definitive or explanatory. Patients in the second group (no explanatory condition) were deemed to have UWML. The remaining patients did not have any WM abnormalities visible on standard brain MRI.

Additional data collected included markers of immunodeficiency [current and nadir CD4+ lymphocyte count, current antiretroviral therapy (ART), duration of treatment with ART, HIV-1 viral load (VL), duration of HIV infection] and cardiovascular risk factors (current and previous cigarette smoking, diabetes mellitus, hyperlipidaemia, systemic hypertension, age, sex, previous cardiovascular events, cocaine use). Long-term follow-up data was obtained from case note review, to determine subsequent worsening or emergence of cognitive, motor, or behavioral symptoms.

Statistical analysis

After compiling descriptive clinical and radiological statistics, patients with WM lesions with a definitive, explanatory clinical or microbiological diagnosis were excluded from further analysis. In the remaining patients, those with SVD-type UWML were compared to those without such lesions, using Mantel-Haenszel methods to calculate odds ratios (OR) and 95% confidence intervals (CI). Variables were divided into cardiovascular risk factors (e.g., age, sex, diabetes, hypertension, cigarette smoking) and HIV-related factors (e.g., current and nadir CD4 count, treatment status, duration of infection). Where large numbers of patients had missing data (e.g., cigarette smoking status), “missing” was treated as a separate category in the analysis. Adjusted OR were then calculated using a multivariable logistic regression model incorporating all variables with $p < 0.10$ in the univariate analysis. Statistical significance of the final results was defined by a p value of < 0.05 . A similar analysis was conducted for factors associated with unexplained DWMSA. The longer-term implications of unexplained intense DWMSA were explored by (1) calculating rates of incidence of new or worsening cognitive, motor, or behavioral symptoms, and (2) qualitatively reviewing the clinical histories of patients with this neuroimaging abnormality.

Sample size was determined pragmatically according to available data, as the study was primarily a prevalence study. All statistical calculations were carried out using STATA SE12 software (StataCorp, Texas, USA).

Ethics approval

The Chairman of the Local Research Ethics Committee (LREC) (National Research Ethics Service Committee London–Camden and Islington) determined that this project did not require LREC approval as all data used in the present study were accrued from patients who were undergoing routine, clinically indicated investigations, and no information was collected that was not available in clinical records.

TABLE 1. AGE, SEX AND HIV-RELATED CHARACTERISTICS OF STUDY PATIENTS (n=254)

	Median (IQR)	Number (%)
Age	42.2 (35.9–48.3)	
Male		178 (70.1)
Ethnic group		
White		134 (52.8)
Black		102 (40.2)
Other/mixed		18 (7.1)
Route of infection		
Heterosexual		117 (46.1)
MSM		108 (42.5)
Vertical		7 (2.8)
IVDU/other/not known		22 (8.7)
Nadir CD4	100 (40–210)	
Current CD4	240 (100–440)	
Current treatment status ^a		
Suppressed on ART		94 (37.0)
Early treatment		25 (9.8)
Failed treatment		28 (11.0)
Off ART		104 (40.9)
Not known		3 (1.2)
Years since diagnosis of HIV	4.6 (0.6–11.0)	
Total duration of ART in years	3.8 (1.1–8.0)	

^aSuppressed on ART = HIV-1 viral load (VL) less than 50 copies/mL; early treatment = VL greater than 50 copies/mL but duration of antiretroviral therapy (ART) less than 3 months; failed treatment = VL greater than 50 copies/mL and duration of ART greater than 3 months.

ART, antiretroviral therapy; IQR, inter-quartile range; IVDU, intravenous drug user; MSM, men who have sex with men.

Results

Demographic and clinical characteristics

During the study period, 254 HIV+ individuals underwent brain MRI and had complete, gradable images. The main characteristics of these patients are shown in Table 1. Cardiovascular risk factors (not tabulated) were as follows: 98 (38.6%) current or ex-smokers, 95 (37.4%) non-smokers; 15 (5.9%) diabetic; 60 (23.6%) hyperlipidemia; 40 (15.7%) systemic hypertension, 183 (72.0%) normotensive; 32 (12.6%) cocaine users, 85 (33.5%) did not use cocaine; 29 (11.4%) with previous cardiovascular disease. Cardiovascular variables were frequently missing from the notes: 61 (24.0%) smoking status not recorded, 31 (12.1%) presence or absence of systemic hypertension not available; 137 (53.9%) cocaine use not recorded.

The clinical indications for brain MRI were focal neurological symptoms or signs (n=63, 24.8%), complicated headache (severe in intensity, or associated with other neurological symptoms or fever) (n=42, 16.5%), chronic or subacute symptoms of cognitive impairment (n=33, 13.0%), multi-system illness (n=33, 13.0%), acute confusion or behavioral change (n=32, 12.6%), seizures or blackouts (n=26, 10.2%), and chronic uncomplicated headaches (23, 9.1%). The indication could not be determined from available clinical records in 2 patients. Of the 254 patients, 113 (44.5%) had lumbar puncture during the same clinical episode as the brain MRI. Cerebrospinal fluid (CSF) HIV VL was measured in 38 (33.6%) of those undergoing lumbar puncture and 21 had detectable (>50 copies/mL) CSF VL, although only 2 of the 21 patients had a concurrent undetectable plasma VL.

Prevalence of WM abnormalities, and associated clinical and imaging findings

Overall, 161 scans (63.4%) showed WM abnormalities (Table 2). These included: DWMSA in 89 scans (35.0%),

TABLE 2. SUMMARY OF ABNORMALITIES DETECTED IN SCANS OF HIV+ PATIENTS UNDERGOING BRAIN MAGNETIC RESONANCE IMAGING (n=254)

	Patients with WM abnormalities with explanatory diagnosis, n (%)	Patients with unexplained WM abnormalities, n (%)	Patients with no WM abnormalities, n (%)	Total, n (%)
Number of patients	66 (26.0)	95 (37.4)	93 (36.6)	254 (100)
Diffuse WM signal abnormality				
Subtle	4 (1.6)	51 (20.1)	0	55 (21.7)
Intense	21 (8.3)	13 (5.1)	0	34 (13.4)
Any	25 (9.8)	64 (25.2)	0	89 (35.0)
Focal WML (SVD)				
Fazekas grade 1	15 (5.9)	32 (12.6)	0	47 (18.5)
Fazekas grade 2	2 (0.8)	9 (3.5)	0	11 (4.3)
Fazekas grade 3	1 (0.4)	2 (0.8)	0	3 (1.2)
Any grade of SVD	18 (7.1)	43 (16.9)	0	61 (24.0)
Large, focal WML (non-SVD)	32 (12.6)	5 (2.0)	0	37 (14.6)
Cerebral atrophy	26 (10.2)	38 (15.0)	19 (7.5)	83 (32.7)
Meningeal enhancement	8 (3.1)	4 (1.6)	3 (1.2)	15 (5.9)
Mass lesion				
Single	3 (1.2)	4 (1.6)	7 (2.8)	14 (5.5)
Multiple	14 (5.5)	2 (0.8)	7 (2.8)	23 (9.1)

Percentages are expressed as a proportion of the entire study sample. SVD, small vessel disease; WM, white matter; WML, white matter lesions.

TABLE 3. ANALYSIS OF ASSOCIATIONS BETWEEN EXPOSURE VARIABLES AND SMALL VESSEL DISEASE-TYPE LESIONS (FAZEKAS GRADE 1–3), AFTER EXCLUSION OF PATIENTS WITH EXPLAINED WHITE MATTER LESIONS ($n = 192$)

	Crude odds ratio (95% CI)	p Value	Adjusted odds ratio ^a (95% CI)	p Value
<i>Demographic variables</i>				
Age				
< 35 years	1.0			
35–50 years	4.39 (1.22–15.8)	0.014		
> 50 years	8.32 (1.92–36.0)	0.0007		
Per + 1 year	1.05 (1.01–1.09)	0.007	1.05 (1.01–1.09)	0.012
Male				
Female	1.79 (0.86–3.73)	0.11		
Ethnicity				
White	1.0			
Black	1.70 (0.83–3.49)	0.14		
Other/mixed	1.28 (0.32–5.10)	0.73		
Route of infection or risk group				
Heterosexual	1.0		2.22 (1.04–4.71)	0.038
MSM	0.55 (0.26–1.15)	0.10	(Heterosexual vs. other routes)	
Vertical	0.49 (0.05–4.48)	0.52		
IVDU/other	0.56 (0.14–2.19)	0.40		
<i>Immunodeficiency and HIV-related variables</i>				
Nadir CD4 count				
> 350 cells/mm ³	1.0			
200–350 cells/mm ³	0.62 (0.15–2.61)	0.51		
< 200 cells/mm ³	0.56 (0.15–1.99)	0.36		
Current CD4 count				
> 350 cells/mm ³	1.0			
200–350 cells/mm ³	1.23 (0.50–3.03)	0.65		
< 200 cells/mm ³	0.95 (0.43–2.09)	0.90		
Change in CD4 count relative to nadir				
Current = nadir	1.0			
Increased 1–100 cells/mm ³	1.08 (0.43–2.70)	0.87		
Increased 100–250 cells/mm ³	1.23 (0.45–3.36)	0.69		
Increased > 250 cells/mm ³	0.83 (0.32–2.15)	0.71		
Suppressed on ART ^b				
Early treatment ^b	0.84 (0.24–2.91)	0.78		
Failed treatment ^b	1.26 (0.42–3.80)	0.68		
Off ART	0.65 (0.30–1.45)	0.29		
Not known	2.94 (0.17–51.1)	0.44		
Time since diagnosis of HIV				
< 1 year	1.0			
1–5 years	1.65 (0.64–4.26)	0.29		
> 5 years	1.02 (0.43–2.40)	0.97		
Total duration of treatment				
Never treated	1.0			
< 1 year	1.15 (0.39–3.38)	0.80		
1–5 years	1.50 (0.60–3.71)	0.38		
> 5 years	1.45 (0.59–3.58)	0.42		
Not known	4.21 (0.24–74.6)	0.29		
<i>Cardiovascular risk factors</i>				
Cigarette smoking status				
Non-smoker	1.0			
Ex- or current smoker	0.64 (0.28–1.43)	0.27		
Not available	0.94 (0.40–2.21)	0.90		
Nondiabetic				
Diabetic	4.64 (1.16–18.6)	0.017	3.17 (0.74–13.6)	0.12
Normal lipids				
Hyperlipidemia (+/- treatment)	1.0			
	1.59 (0.74–3.43)	0.23		

(continued)

TABLE 3. (Continued)

	Crude odds ratio (95% CI)	p Value	Adjusted odds ratio ^a (95% CI)	p Value
Systemic hypertension				
No	1.0			
Yes (+/- treatment)	2.69 (1.14–6.36)	0.019	1.39 (0.54–3.54)	0.49
Not available	0.90 (0.28–2.88)	0.85		
No previous CVD	1.0			
Previous CVD	3.36 (1.31–8.62)	0.0074	3.64 (1.32–10.07)	0.013

^aThe adjusted model included all variables that were statistically significant to a *p* value of <0.10 in univariate analyses.

^bSuppressed on ART=HIV-1 viral load (VL) less than 50 copies/mL; early treatment=VL greater than 50 copies/mL but duration of antiretroviral therapy (ART) less than 3 months; failed treatment=VL greater than 50 copies/mL and duration of ART greater than 3 months.

ART, antiretroviral therapy; CI, confidence interval; CVD, cardiovascular disease; IVDU, intravenous drug user; MSM, men who have sex with men.

72% of which were unexplained, and 62% of which were only subtly hyperintense; focal WM lesions consistent with small vessel disease in 61 scans (24.0%), again mostly (62%) without definite explanatory diagnoses; and large, focal lesions in 37 scans (14.6%), most of which (86%) were in association with a definitive intracranial pathology. The most common diagnoses associated with large, focal lesions in WM were progressive multifocal leucoencephalopathy (PML; 14 cases), toxoplasmosis (8 cases), herpesvirus meningoencephalitis (8 cases), and tuberculosis (6 cases).

Cerebral atrophy was more commonly observed in patients with UWML than those without WM abnormalities. Eight out of thirteen patients (61.5%) with intense DWMSA and 16/51 patients (31.4%) with subtle DWMSA had cerebral atrophy compared to 33/124 (26.6%) without DWMSA (*p*=0.03). Similarly, 6/11 patients (54.5%) with Fazekas grade 2–3 and 15/32 (46.9%) with Fazekas grade 1 had atrophy compared to 36/145 (24.8%) without SVD (*p*=0.002). There was no association between large, non-SVD focal WM lesions and cerebral atrophy.

Factors associated with focal WM lesions

The remaining analyses included only those with UWML (*n*=95) and those with no WM abnormalities (*n*=93). The first analysis explored which variables were most strongly associated with the presence of unexplained, focal WM lesions consistent with SVD in this sample of HIV+ patients (Table 3). This showed that age, previous cardiovascular disease (CVD), diabetes, systemic hypertension, and to a lesser extent heterosexual transmission, were associated with the presence of WM lesions of presumed vascular origin, although only age, route of transmission, and previous CVD remained statistically significant when these five variables were included in a multivariable logistic regression model. There was no association with current or nadir CD4 count, treatment status or duration, or time since HIV diagnosis.

Factors associated with unexplained diffuse white matter signal abnormality

The factors associated with unexplained DWMSA, whether subtle or intense, were then assessed. This analysis (not tabulated) showed that while age and cardiovascular risk factors were not associated with DWMSA, there was an as-

sociation with black African race (OR 2.21, 95% CI 1.15–4.22, *p*=0.014) and heterosexual transmission (OR 2.19, 95% CI 1.17–4.11, *p*=0.012). Heterosexual transmission and black race were correlated with one another in this patient population, and this collinearity led to the disappearance of a statistical association of either variable with DWMSA when both variables were included in the same logistic regression model.

The clinical histories of the 13 patients with unexplained DWMSA of high signal intensity (as opposed to subtle) were reviewed in detail (Table 4). The clinical observations demonstrated that most patients had concurrent imaging findings and significant presenting histories, and that a putative diagnosis was usually assigned but often unconfirmed. Six of the 13 patients (46%) had a clinical diagnosis of HIV encephalopathy, but in most cases the MRI appearances were the only supportive evidence, and there was no association between DWMSA and chronic cognitive symptoms as the primary presenting complaint. Eight (62%) of these patients were of black African race, the remainder being white. Most had no new significant neurological symptoms during follow-up, although two patients went on to develop fluctuating neurological symptoms and signs over a period of years, and one developed significant cognitive impairment some years later. This patient was diagnosed with neurosyphilis at the time of brain MRI, a condition not typically associated with neuroimaging findings of this kind.²⁷ Of those with complete subsequent records, those with unexplained intense DWMSA did not experience new or worsening symptoms affecting cognition, behavior, or movement at a greater rate than those with no WM abnormalities (*p*=0.93) or those with subtle DWMSA (*p*=0.63).

Discussion

In this study we found that 62% of HIV+ patients undergoing brain MRI had WM abnormalities using standard imaging techniques in a clinical setting. The most common abnormality was diffuse white matter signal abnormality, mostly subtle in intensity and unexplained after further investigation. White matter hyperintensities of presumed vascular origin²¹ were also commonly seen. Our findings are important given the paucity of published data on cerebral small vessel disease in HIV,^{28,29} the growing proportion of older adults with HIV in many regions, and the frequent difficulties encountered when interpreting the clinical and

TABLE 4. CLINICAL AND LABORATORY CHARACTERISTICS OF 13 PATIENTS WITH UNEXPLAINED DIFFUSE WHITE MATTER SIGNAL ABNORMALITY OF HIGHER INTENSITY

Sex	Age, years	ART status ^a	Nadir CD4 ^b	Current CD4 ^b	Presenting symptoms	Other MRI findings	CSF findings	CNS diagnosis	Subsequent long-term outcome
M	37	Suppressed on ART	80	160	Collapse, dysarthria, unsteady gait	Cerebral atrophy, small focal WM lesions	LP not done	Possible small vessel disease	No further problems (3 years of follow-up)
M	43	Suppressed on ART	240	550	Memory loss	Large focal WM lesions	LP not done	Possible small vessel disease	Difficulties concentrating, low mood, depression, episode of UMN 7 th CN palsy 1 year later
M	42	Suppressed on ART	40	690	Febrile illness; possible vasculitis related to HCV or interferon	Small focal WM lesions	Normal	Possible small vessel disease	Fever resolved with cessation of interferon; no further neurological symptoms over next 5 years
M	54	Off ART	60	60	Few weeks' history of confusion	Cerebral atrophy	CSF HIV VL 33,000 c/mL; plasma HIV VL 560 c/mL	Probable HIVE	Started ART; anxiety symptoms but significant improvement in cognition over next 2 years
F	43	Off ART	160	500	Dystonic tremor of upper limbs	Cerebral atrophy; scan unchanged from 5 years previously	LP not done	Possible long-standing HIVE	Ongoing complaints of memory problems and dizziness over next few months
M	42	Off ART	90	90	Pneumonia, ICU admission, coma	Cerebral atrophy, small focal WM lesions	LP not done	Pneumonia/sepsis with possible HIVE	Became depressed, otherwise did well on ART (5 years of follow-up)
M	42	Early ART	180	530	Chronic headaches	Cerebral atrophy	CSF HIV VL 160,000 c/mL; plasma HIV VL 14,000 c/mL	Probable HIVE	Continued ART and achieved plasma viral re-suppression; uneventful course over next 3 years
M	35	Suppressed on ART	210	260	Seizures	Cerebral atrophy	Normal	Possible HIVE	Uneventful course over next 6 months
F	57	Off ART	70	170	Weak legs, lethargy, weight loss, neck pain	Small focal WM lesions	Normal	Depression; possible HIVE	Possible steroid-responsive encephalopathy diagnosed subsequently; fluctuating neurological syndrome over many years
F	43	Failing ART	40	130	3 weeks of headache and progressive malaise	Nil else	Normal	Possible TB meningitis	Died approx. one year later with intracranial mass of unknown cause
F	34	Early ART	30	280	Subacute history of abnormal behaviour and personality change	Meningeal enhancement	Normal	Possible viral meningoencephalitis	No further problems (4 years of follow-up)
F	31	Failing ART	40	1000	Partial seizures affecting upper limb	Large focal WM lesions	Normal	No diagnosis made	Occasional presentations with disorientation, dyspraxia, unsteady gait, confusion and seizures over next 3 years.
M	49	Suppressed on ART	NK	310	Chronic dizziness and headaches	Nil else	RPR positive; low-grade pleocytosis	Neurosyphilis	Presented with global cognitive impairment 4 years later

^aSuppressed on ART=HIV-1 viral load (VL) less than 50 copies/mL; early treatment = VL greater than 50 copies/mL but duration of antiretroviral therapy (ART) less than 3 months; failed treatment = VL greater than 50 copies/mL and duration of ART greater than 3 months.

^bCD4 + lymphocyte counts expressed in cells/mm³.
 ART, antiretroviral therapy; c/mL, copies per milliliter; CN, cranial nerve; CNS, central nervous system; CSF, cerebrospinal fluid; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIVE, HIV encephalopathy; ICU, intensive care unit; LP, lumbar puncture; MRI, magnetic resonance imaging; NK, not known; RPR, rapid plasma reagin; TB, tuberculosis; UMN, upper motor neuron; VL, viral load; WM, white matter.

pathological importance of subtle or unexplained WM lesions in HIV+ patients. Although we did not directly compare the patients in this study period with a pre-1996 study sample, the proportion of patients with an opportunistic infection was generally low (24%) and a high proportion (59%) had no specific neurological diagnosis. In comparison to our more recent data, a study published in 1995 reported that scans from 188 consecutive untreated HIV+ patients in Germany commonly identified toxoplasmosis (25%), HIV encephalopathy (10%), and PML (5%).³⁰

SVD-type WM lesions were associated with typical cerebrovascular risk factors such as age, diabetes, other CVD, and hypertension. The strong association with age was notable particularly as the age of the patient had already been taken into consideration when classifying SVD lesions, in that scans were graded as normal if the number of lesions seen was typical for the patient's age. There was an association between route of HIV infection and SVD (heterosexual patients had higher odds of having SVD). This could be explained by ethnic and gender differences between risk categories in UK HIV+ patients translating to differences in cardiovascular health. By contrast, diffuse signal hyperintensity was not associated with cardiovascular risk factors, the only positive finding being an association with black race. There was only a weak trend towards subsequent neurocognitive symptoms. Large focal lesions (not typical of small vessel disease) were typically seen in association with inflammatory or space-occupying intracranial pathology. After excluding scans with an explanatory diagnosis, HIV-related factors such as receipt of ART, current and nadir CD4 count, duration of infection and duration of ART, were not associated with WM abnormalities of any distribution.

Limitations of the study include its retrospective design and the high likelihood of selection bias due to this being a study of normal clinical practice. Another important limitation is the use of qualitative neuroradiological classification. While we believe that our use of the Fazekas scale—a methodology that is well-established in the neuroradiological literature for grading cerebral SVD—included sufficient validity checks to reach a high level of accuracy, we accept that some random or systematic error could have occurred. Also, the classification of “diffuse” versus “intense” WM lesions may be somewhat subjective as quantitative analysis of signal intensity was not done in this study. Bearing this in mind while interpreting our findings relating to DWMSA, we feel that our classification represents the descriptive findings that may arise in the course of clinical practice. Additionally, data were incomplete in several areas: only a minority of patients had lumbar puncture, and even fewer had measurement of CSF HIV viral load, making complete correlation between imaging and CSF abnormalities impossible. Sampling of the CSF for measurement of viral nucleic acid titers is now generally recommended in HIV+ patients with neurological or cognitive complaints³¹ and has become standard practice at our center since the period of this study. Also, cardiovascular risk data were often missing—particularly smoking status—and more likely to have been recorded in those perceived to be at higher risk (e.g., older men). In analysis, the study lacked an HIV-negative or an asymptomatic HIV+ control group, so we could not determine whether HIV status was independently associated with UWML, nor if the lesions

were caused by premature or accelerated aging in HIV+ patients. Also in the analysis, as numbers of patients within particular subgroups were small, it was difficult to determine the prognostic importance of unexplained WM lesions in HIV.

Using routine clinical data from within the last decade, this study echoes the findings from studies performed in the 1980s, prior to the availability of HAART and using MR scanners of lower field strengths.^{15–17} In these earlier descriptions, WM lesions were no more frequent or progressive in HIV+ men than in HIV-negative controls. There have since been numerous small cross-sectional studies using advanced techniques such as DWI and DTI, which have provided further evidence for WM abnormalities as correlates of both HIV infection and of HIV-associated neurocognitive impairment. There is a lack of data from prospective longitudinal and clinical studies in order to translate those findings into clinical practice, but it may be that diffusion-based techniques are required to be able to fully interpret the significance of DWMSA in patients who have had other diagnoses excluded.

It is likely that focal hyperintense WM lesions in HIV+ patients undergoing neuroimaging are very similar in nature to the WM changes seen in normal aging and, more extensively, in patients with small vessel disease. If it is assumed that such lesions are vascular in origin, their presence in HIV+ patients requires them to be treated similarly to the general population, in whom there is likely to be an association with future cerebrovascular events, vascular dementia and frailty.^{19,20,32–36} It is possible that HIV+ patients experience accelerated cerebrovascular aging or faster progression of SVD, but there are few imaging studies of cerebrovascular disease in the HIV+ population, and none published to date with an HIV-seronegative control group. The Hawaii Aging with HIV Cohort has produced the only published work on cerebral small vessel disease to date and describes a 48% prevalence of moderate WM disease among HIV+ patients without neurological disease,²⁹ with a strong association with age and a modest association with hypertension.^{28,29} The association between NCI and cerebrovascular risk factors in HIV+ patients^{37,38} and the similarity between the domains affected in vascular dementia and HIV-associated neurocognitive disorders^{35,38–40} raise the intriguing possibility that NCI in HIV is in some way vascular in etiology. Previous work has established the high burden of large-vessel atherosclerotic disease in HIV, including ischemic stroke,^{41–44} subclinical endothelial dysfunction, and increased carotid intima-media thickness,⁴⁵ femoral and carotid artery plaques detectable on ultrasound,⁴⁶ and coronary artery disease.⁴³ The growing proportion of older HIV+ patients⁴⁷ makes small- and large-vessel cerebrovascular disease an important area for the clinical research agenda in future.

Acknowledgments

We are grateful to the following people for their assistance with data collection: Gareth Askey, Laurence Dufaur, Augusto Braga Fernandez, Ruth Fish, Derek Phillips.

Author Disclosure Statement

The authors declare no conflict of interest.

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