Comparison of magnetic resonance imaging with neuropathological findings in the diagnosis of HIV and CMV associated CNS disease in AIDS

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Abstract

Objectives—To compare the results of clinical assessment and MRI with neuropathological findings in the diagnosis of HIV and cytomegalovirus (CMV) associated CNS disease.

Methods—A retrospective study of 35 patients infected with HIV who were examined at necropsy between four and 70 (median 20) days after neurological assessment and MRI.

Results—Of the 35 patients, 19 had diffuse white matter hyperintensity on T2 weighted MRI, six of whom also had focal lesions. Nine other patients had focal white matter lesions and seven had changes in cortical atrophy only. Necropsy in the 19 with diffuse white matter hyperintensity showed HIV leukoencephalopathy (HIVLEP) with encephalitis in 10, CMV encephalitis in three, both HIVLEP/HIV encephalitis and CMV encephalitis in one, lymphoma in three, and non-specific inflammation in two. Necropsy in the 16 other patients without diffuse white matter hyperintensity showed CMV encephalitis in six, HIV encephalitis (without HIVLEP) in two, CMV encephalitis and HIVLEP/HIV encephalitis in one, non-HIV associated abnormalities in five, herpes simplex encephalitis in one, and lymphoma in one. CMV DNA was detected in CSF of five of seven patients with CMV encephalitis and in two of two with CMV associated polyradiculopathy but without CMV encephalitis. Diffuse white matter hyperintensity on MRI had a sensitivity of 100%, a specificity of 66.6%, and a positive predictive value of 58% for diagnosis of HIVLEP.

Conclusion—Diffuse white matter hyperintensity on MRI can be due to either HIV or CMV associated pathology or non-specific abnormalities.

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Keywords: HIV leukoencephalopathy; CMV encephalitis; magnetic resonance imaging; necropsy.

Neurological dysfunction has been reported as a clinical manifestation of AIDS in 30%–40% of patients^{1,2} and at necropsy between 75% and 88% of patients with HIV have abnormalities of the CNS.^{3–5} Cerebral infection with HIV itself produces a subacute dementia—so-called “HIV associated dementia complex”—which is asso-

ciated with a range of neuropathological changes including diffuse myelin pallor (HIV leukoencephalopathy), and encephalitis.⁶ The clinical presentation may be difficult to distinguish from the subacute or chronic encephalitis caused by cytomegalovirus (CMV)⁷ and neuroimaging and CSF studies are of uncertain value in differentiating CMV encephalitis and HIV leukoencephalopathy/encephalitis.

Several studies have reported the clinicopathological correlates of these conditions and of other opportunistic infections, including *Toxoplasma gondii*, JC virus, *Cryptococcus neoformans*, and tumours including primary CNS lymphoma (PCNSL).^{8–12} Brain MRI has shown high sensitivity but only moderate specificity in the diagnosis of these conditions. There are few published data which compare the clinical and radiological diagnoses with postmortem findings in unselected patients with HIV and neurological disease. We undertook a retrospective study of 35 HIV positive patients presenting with well documented neurological symptoms and signs in whom we compared the clinical and radiological diagnosis with that subsequently obtained at necropsy.

Methods

We identified 35 patients with HIV presenting to University College London Hospital with neurological episodes between September 1991 and August 1995 who underwent clinical assessment including cranial MRI within 70 days of death and who subsequently had a necropsy.

During the study period a total of 399 patients with HIV had MRI and 74 necropsies were performed on these patients.

Of the 35 patients studied 33 were men (32 were white and homosexual and one was heterosexual and of African origin); the two women were white and heterosexual. Their ages ranged from 27–56 (median 38.8) years and CD4+ T lymphocyte counts (available in 32 patients) ranged from 0–0.32 (median 0.015) $\times 10^9/l$. (normal range 0.35–2.2 $\times 10^9/l$). The median interval between MRI and necropsy was 20 (range 4–70) days.

At the time of their neurological presentation all patients had been admitted under the care of an HIV/AIDS specialist (RFM or IGW) and were also seen by a neurologist (MJGH); they were investigated according to a unit protocol. In addition to a clinical assessment investigations included MRI performed at 1.5 Tesla on a standard clinical system (Siemens Magnetom 63SP, Erlangen, Germany). Dual echo spin

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echo (TR = 3500 ms, TE = 20/90 ms, NEx = 1, sl = 5 mm) images were acquired with 30 contiguous slices covering the entire cranium. An acquisition matrix of 192×256 , interpolated to 256×256 gave an in plane resolution of 0.9 mm over a 23 cm field of view. The image plane was parallel to the long axis of the temporal lobes. Coronal T1 weighted images were obtained with 5 mm slices, separated by a 1 mm gap, before and after giving 0.1 mMol/kg dimethylglutamine gadopentate (Gd-DTPA; Magnevist, Schering Plough Health Care Ltd) intravenously.

We recorded the duration of symptoms in those presenting with an encephalopathy. Encephalopathy was defined as a presentation of subacute onset over weeks or months of cognitive deficit with decline in motivation or emotional control, or change in social behaviour in the absence of clouding of consciousness or other aetiology.

Lumbar puncture was performed in those patients without a contraindication (such as a mass lesion or midline shift present on MRI). In addition to routine biochemical analysis, CSF was stained histochemically with Gram stain, auramine, Grocott's methenamine silver, indian ink, and mucicarmine, and cultured for bacteria, mycobacteria, and fungi. Assays for cryptococcal antigen (CRAG) and tests for antibodies to *Toxoplasma gondii* and syphilis were carried out. An aliquot of CSF was analysed at the same time for the presence of CMV, varicella zoster virus (VZV), herpes simplex virus type 1 (HSV-1), Epstein Barr virus, and JC virus using nested polymerase chain reaction amplification with oligonucleotide primers to detect CMV *gB*, VZV *gene29*, HSV-1 *gD*, Epstein Barr virus internal repeats, and JC virus T antigen as previously published.¹³⁻¹⁷

All necropsies were performed by SBL and neuropathological examination was carried out by SBL and FS. The brain was removed and fixed in formal saline for two to four weeks. Tissue samples were taken from the frontal, temporal, parietal, and occipital lobes, the basal ganglia, thalamus, cerebellum, midbrain, pons, medulla oblongata, and spinal cord. Additional areas with any abnormalities identifiable by eye were also sampled and processed for light microscopy. Sections were routinely stained with haematoxylin and eosin, Luxol fast blue, and cresyl violet and were impregnated with silver by Glees and Marsland's or Palmagen's methods. Selected sections were also stained with Van Gieson, Gram, Ziehl-Neelsen, periodic acid Schiff, and Grocott's methenamine silver stains.

Neuropathological tissues were specifically examined for evidence of (a) HIV encephalitis, identified by the presence of multiple disseminated foci of microglia and multinucleated giant cells, and of (b) HIV leukoencephalopathy (HIVLEP), by the presence of multinucleated giant cells with considerable damage to white matter with evidence of myelin pallor, an excess of inflammatory cells, and astrocyte gliosis.⁶ In addition, HIV encephalitis was confirmed by immunocytochemistry for HIV structural protein using Anti-p24 antibody (Dako; dilution

1:250). CMV encephalitis was diagnosed by the presence of typical intranuclear and cytoplasmic CMV inclusions on haematoxylin and eosin stains, associated with focal inflammation and necrosis, microglial nodules, and necrotising ventricular ependymitis.¹⁸ In some cases immunocytochemistry for detection of CMV antigen was also performed.

Cranial scans of the 35 patients were rereported, mixed in with scans from patients matched for CD4 + T lymphocyte count who had also presented with neurological symptoms and signs, by two radiologists (MHC and BK) who were experienced in interpreting cranial MRI of patients with HIV. Scans were reported independently by the two radiologists; when there was disagreement, consensus was reached in conference. The radiologists were blinded to the subjects' clinical diagnoses and also who was included in the necropsy study. Predetermined criteria were used to report the MRI; in particular the presence and anatomical distribution of diffuse or focal white matter abnormalities, the degree of atrophy (graded none, mild, moderate, or severe as previously described¹⁹) and the location, number, and nature of any focal lesions was noted. The radiologists were asked to provide a diagnosis or differential diagnosis based on the cranial MRI.

Results

Table 1 gives results from MRI and CSF analyses, together with the patients' clinical diagnoses (at the time of their admission with neurological symptoms and signs) and the necropsy findings. In reporting the MRI appearances there was agreement for 28 patients and a consensus in seven patients.

DIFFUSE WHITE MATTER HYPERINTENSITY ON MRI

Cranial MRI of 19 patients showed diffuse white matter hyperintensity on T2 weighted images; six patients also had focal lesions (table 1). Of the remaining 16 patients without diffuse white matter hyperintensity nine had focal lesions. Cortical atrophy was present in 14 of the 19 with diffuse white matter hyperintensity and in 12 of the 16 patients without it. The diffuse white matter hyperintensity was patchy in 15 patients, some scans showing more pronounced abnormalities in some areas (table 1). In four patients, all of whom had HIVLEP/HIV encephalitis, the diffuse white matter hyperintensity was extensive and more confluent. Table 2 shows the relation between the MR abnormality of diffuse white matter hyperintensity and the presence or absence of pathology associated with CMV and HIV.

Twelve patients had MRI abnormalities but no pathology associated with CMV or HIV. Five of these had diffuse white matter hyperintensity on MRI (table 2). Neuropathological changes in these patients included focal lymphoma in three (one of whom (16) had a cerebral vasculitis), and non-specific inflammation in two patients. In the seven other patients without diffuse white matter abnormalities on MRI neuropathological findings were microin-

Table 1 MRI abnormalities, CSF findings, and clinical and necropsy diagnoses

Patient No	White matter changes			CSF abnormalities	Clinical diagnosis	Neuropathological findings
	Atrophy	Focal	Diffuse			
Diffuse white matter abnormalities:						
1	+	0	+	VZV DNA +	HADC, toxic confusional state	HIVLEP + HIVE
2	++	0	+(peritrigonal)	Not done	HADC, CMV retinitis	Non-specific abnormalities
3	+	0	+(peritrigonal)	Not done	HADC, confusion secondary to <i>E coli</i> septicaemia	HIVLEP + HIVE
4	++	0	+	—	HADC	HIVLEP + HIVE
5	0	0	+	Not done	HADC, CMV encephalitis and retinitis	CMV encephalitis/ependymitis
6	+	0	+	—	HADC	HIVLEP + HIVE
7	++	0	+	CMV DNA +	HADC, CMV retinitis	CMV encephalitis/ependymitis
8	+++	0	+(periventricular)	CMV DNA +	HADC or CMV encephalitis	HIVLEP + HIVE CMV encephalitis/ependymitis
9	+	0	+(external capsule)	Not done	HADC	HIVLEP + HIVE
10	++	0	+	—	HADC, chronic renal failure	HIVLEP + HIVE
11	0	0	+	—	HADC	HIVLEP + HIVE
12	+++	0	+	CMV DNA +	HADC, CMV retinitis	CMV encephalitis/ependymitis
13	++	0	+(peritrigonal)	CMV DNA + EBV DNA +	HADC, CMV polyradiculopathy, CMV retinitis	Cerebral lymphoma
Focal and diffuse abnormalities:						
14	+	+(both hemispheres)	+(parietal/s frontal)	—	HADC, PML	HIVE, PML
15	+++	+(cerebellum)	+(brainstem parietal)	—	HADC	Non-specific abnormalities Cerebellar astrocytoma
16	++	+(ventricular ependyma)	+(parietal/frontal)	EBV DNA +	Lymphoma	Cerebral lymphoma and cerebral vasculitis
17	+	+(temporal lobe)	+	EBV DNA +	HADC	HIVLEP + HIVE
18	0	+(basal ganglia cerebellum periventricular ependyma)	+(peritrigonal)	Not done	Lymphoma HADC, CMV retinitis	Cerebral lymphoma Lymphoma
19	0	+(basal ganglia brain stem)	+(frontal/corpus collosum)	<i>C neoformans</i> + corpus collosum	HADC, <i>C neoformans</i> meningitis	HIVLEP + HIVE <i>C neoformans</i> meningitis
Focal abnormalities:						
20	++	+(splenium)	—	Not done	HADC, CMV retinitis	HIVLEP + HIVE CMV encephalitis/ependymitis, PML
21	0	+(peripheral and periventricular)	—	—	Toxoplasmosis or lymphoma	HSV encephalitis
22	0	+(deep central white matter, cerebellum)	—	JC virus DNA +	PML	PML
23	++	+(basal ganglia)	—	—	HADC	Multiple cerebral microinfarcts and demyelination
24	+	+(internal capsule)	—	Not done	Cryptococcaemia	CMV encephalitis/ependymitis
25	+	+(periventricular caudate cerebral hemisphere)	—	EBV DNA +	Lymphoma	Lymphoma, HIVE
26	+	+(splenium)	—	Not done	HADC CMV retinitis	CMV encephalitis/ependymitis
27	0	+(pons)	—	Not done	HADC	Non-specific microglial nodules
28	0	+(deep central white matter)	—	Not done	Confusion secondary to Hickman line infection, CMV retinitis	Diffuse gliosis
No focal or diffuse abnormalities:						
29	++	—	—	CMV DNA +	HADC, CMV polyradiculopathy	CMV encephalitis/ependymitis
30	++	—	—	CMV DNA +	CMV retinitis, CMV encephalitis	CMV encephalitis/ependymitis
31	+	—	—	CMV DNA + EBV DNA +	CMV polyradiculopathy	Disseminated cerebral lymphoma
32	+	—	—	—	HADC	CMV encephalitis
33	+	—	—	—	Confusion secondary to <i>P aeruginosa</i> septicaemia, CMV retinitis	CMV encephalitis/ependymitis
34	+	—	—	Not done	HADC	HIVE
35	+	—	—	—	Confusion secondary to hepatorenal failure	Scanty microinfarcts (non-HIV related)

HADC = HIV associated dementia complex; VZV = Varicella zoster virus; HIVE = HIV encephalitis; HIVLEP = HIV leuko-encephalopathy; PML = progressive multifocal leukoencephalopathy; CMV = cytomegalovirus; HSV = herpes simplex virus; EBV = Epstein Barr virus; Atrophy: 0 = none, + = mild, ++ = moderate, +++ = severe; Diffuse = diffuse white matter hyperintensity of T2 weighted images; — = absent, + = present.

Table 2 Correlation between MR abnormalities and the presence or absence of CMV and HIV associated pathology

MRI appearances	HIVLEP+ HIVE	HIVE only	CMV encephalitis	CMV encephalitis HIVLEP+ and HIVE	Non-HIV or CMV associated pathology*	Total
Diffuse white matter hyperintensity:*						
With atrophy	7	0	2	1	4	14
No atrophy	3	0	1	0	1	5
No diffuse white matter hyperintensity:*						
With atrophy	0	2	6	1	3	12
No atrophy	0	0	0	0	4	4
Total	10	2	9	2	12	35

*For pathological details see text and table 1.
HIVLEP = HIV leukoencephalopathy; HIVE = HIV encephalitis; CMV = cytomegalovirus.

farcts in two patients, diffuse gliosis in one (whose scan showed no atrophy), microglial nodules in one, herpes simplex encephalitis in one (21), disseminated lymphoma in one, and progressive multifocal leukoencephalopathy in one.

Of 11 patients with CMV encephalitis at necropsy, 10 also had ventricular ependymitis due to CMV. Of these 10 patients six also had microglial nodules and three others had focal necroses. The one patient without CMV necrotising ventricular ependymitis also had microglial nodules. Cranial MRI showed diffuse periventricular hyperintensity on T2 weighted images in only one of the 11 patients with CMV encephalitis (table 1). This patient (8) had both CMV and HIV associated pathology. In none of the 35 patients was there evidence of periventricular enhancement on T1

weighted images after Gd-DTPA. There was no difference in the duration of encephalopathy. In those with CMV encephalitis the history ranged from three to 52 weeks (median five weeks) and in those with HIVLEP/HIV encephalitis it had lasted three to 50 weeks (median four weeks).

The sensitivity of the presence of diffuse white matter hyperintensity on T2 weighted MRI for the diagnosis of HIV leukoencephalopathy was 100% (11/11) and the specificity was 66.6% (16/24). This MR appearance had a positive predictive value of 58% (11/19) and a negative predictive value of 100% (16/16). Figure 1 shows examples of MRI used for assessment of atrophy. Figure 2 shows MR appearances of extensive confluent diffuse white matter hyperintensity on T2 weighted images in a patient with (a) CMV encephalitis and (b) HIVLEP/HIV encephalitis. Figure 3 shows patchy diffuse white matter hyperintensity on T2 weighted images in a patient with (a) CMV encephalitis and (b) HIVLEP/HIV encephalitis.

Analysis of CSF for the presence of CMV DNA was performed in seven of the patients with CMV encephalitis. Five of these patients had detectable CSF CMV DNA. Of these patients one (8) also had HIVLEP/HIV encephalitis, three (5, 12, and 30) had concomitant CMV retinitis, and one (29) had a CMV associated polyradiculopathy. The two patients (32 and 33) with evidence of CMV encephalitis at necropsy, but no detectable CSF CMV DNA antemortem, had no white matter changes on MRI. CMV DNA was also detected in CSF of two other patients (13 and 31) with lymphoma and no pathological evidence of CMV encephalitis; both had a polyradiculopathy associated with CMV.

FOCAL ABNORMALITIES ON MRI
Lymphoma (n = 5)

Five patients had lymphoma, of whom two patients (13 and 31) had no focal MRI abnormalities. Two patients had periventricular tumour with ependymal spread and one had a solitary temporal lobe lesion. In this patient CSF analysis had shown lymphoma cells. In all five patients Epstein Barr virus DNA was detected in CSF.

Progressive multifocal leukoencephalopathy (n = 2)

Two patients had progressive multifocal leukoencephalopathy and both had typical focal MRI signal abnormalities with high intensity on T2 and low intensity on T1 weighted images. JC

Figure 1 MRI used for assessment of atrophy; (A) none, (B) mild, (C) moderate, (D) severe.

Figure 2 T2 weighted MRI showing confluent diffuse white matter hyperintensity in a patient with HIVLEP/HIVE.

virus DNA was detected in CSF from one of these patients. Necropsy confirmed progressive multifocal leukoencephalopathy in both.

Cryptococcal infection (n = 1)

One patient (19) in whom examination of CSF disclosed *Cryptococcus neoformans* had multiple focal lesions within the brain stem and basal ganglia on MRI which were thought to be cryptococcomas. This diagnosis was confirmed at necropsy.

Cytomegalovirus infection (n = 1)

One patient (24) with a focal lesion in the internal capsule had CMV encephalitis and ependymitis. There was no enhancement of the ventricular wall.

Miscellaneous conditions (n = 5)

One patient (23) with MRI evidence of multiple focal lesions in the basal ganglia died with bacterial sepsis, with a background of progressive weight loss and disseminated extracranial *Mycobacterium avium-intracellulare* infection. Necropsy disclosed evidence of multiple cerebral microinfarcts and demyelination. Another patient (15) had a focal cerebellar lesion noted

on MRI which was thought to represent a vascular abnormality. Necropsy disclosed a cerebellar astrocytoma. In a third patient (20) multiple peripheral white matter and periventricular lesions, which enhanced with gadolinium, were identified on MRI. These were thought in life to represent either cerebral toxoplasmosis or lymphoma. Necropsy showed multiple foci of necrotising herpes simplex encephalitis. In this patient DNA amplification of CSF was negative for HSV-1, and also HSV-2 DNA. Another patient (35) had hepatorenal failure; MRI showed only atrophy and CSF analysis was negative. Necropsy showed sparse microinfarcts which were not thought to be related to HIV. The final patient (28) had multiple deep white matter lesions which did not enhance with gadolinium. Necropsy showed changes of diffuse gliosis.

Discussion

This study has sought to define the accuracy with which HIV leukoencephalopathy and encephalitis can be diagnosed by MRI and distinguished from CMV encephalitis in a selected series of patients infected with HIV who underwent necropsy shortly after presenting with neurological disease. The results show that the MRI finding of diffuse white matter hyperintensity on T2 weighted images can arise in the presence of both HIV leukoencephalopathy/HIV encephalitis and CMV encephalitis, or when only non-specific minor changes are found at necropsy. Extensive confluent changes were only seen with HIV pathology but the numbers were small. We conclude that diffuse white matter imaging abnormalities cannot be used to infer specific HIV related pathology even in patients with AIDS presenting with a clinical picture suggestive of HIV associated dementia complex. The lack of MRI abnormality has negative predictive value, however, and should prompt a search for other causes of encephalopathy such as those associated with metabolic disturbance.

None of the patients in our study showed evidence of periventricular enhancement, after Gd-DTPA, on T1 weighted images, and only one, who had HIV leukoencephalopathy/HIV encephalitis, had periventricular hyperintensity on T2 weighted images. These findings are surprising as 10 of the 11 patients in our study who had CMV encephalitis also had necrotising ventricular ependymitis. It has been suggested previously that periventricular hyperintensity on T2 weighted MRI might be specific for CMV encephalitis.²⁰ By contrast are the results of Holland *et al* who compared cases of CMV encephalitis and HIV related encephalopathy confirmed by necropsy.⁷ Six of the 14 patients with CMV underwent MRI; in one patient the appearances were normal and in five of the six there was periventricular hyperintensity. Three showed atrophy and three had meningeal enhancement, a finding not seen in our series. In eight of the 17 cases of HIV related pathology reported by Holland *et al* there had been an MRI study. Three were normal, four showed only atrophy, and two

Figure 3 T2 weighted MRI showing patchy diffuse white matter hyperintensity in a patient with (A) CMV encephalitis and (B) HIVLEP/HIVE.

had diffuse changes in white matter. Three of the eight patients showed periventricular hyperintensity. The lack of specificity of the MRI findings was clear.⁷

Previous studies have suggested the detection of CMV DNA in the CSF of patients with HIV is strongly associated with neurological disease related to CMV.^{21,22} In one prospective study by Gozlan *et al* of 164 consecutive patients with HIV undergoing lumbar puncture 26 had neurological disease associated with CMV (encephalitis in 12, mononeuritis multiplex in nine, and polyradiculopathy in five), in 10 of the 12 cases of encephalitis the diagnosis was confirmed at necropsy. In 24 of those 26 patients CMV DNA was detected in CSF; by contrast, CMV DNA was detected in only four patients without CMV associated neurological disease, giving a sensitivity of 92%, a specificity of 94%, and a negative predictive value of 97%.²¹ Another prospective study²² similarly reported a strong association between detection of CMV DNA in CSF and CMV encephalitis and polyradiculopathy. CMV retinitis without CNS involvement is not thought to be associated with CMV DNA in the CSF.²³ In this study, although not all patients had CSF analysis the detection of CMV DNA in the CSF was also linked to CMV related pathology. Of 11 patients with CMV encephalitis seven had CSF analysis, disclosing CMV DNA in five. The two with negative CSF findings also had no changes of diffuse white matter abnormality on MRI, so highlighting the limited diagnostic usefulness of the combined investigational approach (CSF and MRI).

In three of the five patients in our study with focal lesions on MRI due to lymphoma the diagnosis had been suspected in life on the basis of characteristic periventricular tumour with ependymal spread in two patients and a focal lesion in one.¹¹ In all five patients Epstein Barr virus DNA was detected in CSF. By contrast this investigation was negative in the other patients without lymphoma, thus confirming the usefulness of Epstein Barr virus DNA detection for diagnosis of lymphoma.¹⁶ Both patients with progressive multifocal leukoencephalopathy had typical MRI appearances⁹; in addition, detection of JC virus DNA in CSF confirmed the diagnosis in life in one patient.

The inclusion of patients with non-specific neuropathological findings at necropsy within this series is important because it emphasises that non-HIV associated neurological pathology may occur in patients with HIV. Another aspect of this study is that it underscores the importance of necropsy in this patient group, to better relate clinical and radiological abnormalities to actual pathology.^{24,25}

In conclusion, diffuse white matter signal abnormalities on MRI in patients with HIV do not enable discrimination between HIV and CMV associated pathology or non-HIV related abnormalities in individual cases. A combined investigational approach with MRI and detection of CMV DNA in CSF is further limited by the sensitivity and specificity of the molecular technique.

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