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MRI of the brain in HIV-positive patients: what is the value of routine intravenous contrast medium?

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Abstract Our purpose was to assess the value of routine administration of intravenous gadolinium-DTPA (Gd-DTPA) for cranial MR in a series of human immunodeficiency virus (HIV)-positive patients. Two radiologists retrospectively reviewed 150 consecutive examinations of 104 patients. All patients underwent unenhanced and contrast-enhanced images. Each radiologist independently assessed first the unenhanced images alone and then the pre- and postinjection images together. Then both reviewed the complete study and produced a consensus report. The history, investigations and management were collated separately and were unknown to the radiologists. Contrast-enhanced T1-weighted images showed new focal abnormalities, not seen on the T2-weighted or unenhanced images in 15 (14%) patients, but almost always in the context of abnormal unenhanced images. In only 2 patients (2%) did contrast medium reveal abnormalities when the unenhanced study had been considered normal. In only 1 of these (1%) was the new finding, cytomegalovirus diffuse ependymal enhancement, of clinical importance, although the diagnosis of encephalitis was made on routine examination of cerebrospinal-fluid. The other revealed a toxoplasma lesion in a patient known to have resolving disease. Meningeal disease not suspected on the unenhanced images was shown in 2 patients (2%). In these case the unenhanced images were abnormal in other respects. Intravenous Gd-DTPA was helpful to the radiologist in making a radiological diagnosis in 11 patients (11%), usually by improving characterisation of a lesion seen on the unenhanced images. The contribution of intravenous Gd-DTPA in this series does not warrant recommending its use in every case.

Key words Magnetic resonance imaging · Contrast medium · Human immunodeficiency virus

Introduction

MRI has largely superseded other techniques for cranial imaging in HIV-positive patients. Early studies suggested that unenhanced MRI was more sensitive than CT to intracranial disease in patients with AIDS [1–3], despite recognised limitations of MRI technology then available [3]. Later studies indicated that use of intravenous Gd-DTPA further increased the number of intracranial lesions seen in patients with a range of pathologies [4], particularly metastatic disease [5, 6] and leptomeningeal malignant and inflammatory conditions [7]. Elster et al. [8] found intravenous Gd-DTPA to be 'helpful in depicting or characterizing occult infections and neoplasms in 86% of patients with AIDS or an immune deficient state' [8]. This study was based on a broad range of criteria for usefulness of enhancement or the lack of it.

It would be expected, based on these early studies, that intravenous contrast medium would increase the number of abnormalities seen in HIV-positive patients. However, even contrast-enhanced MRI has limited specificity and in this group investigation for parenchymal or leptomeningeal metastatic disease is not a common problem. Although there are helpful features such as site, number of lesions and enhancement pattern, MRI has limited specificity in differentiating common abnormalities such as toxoplasma infection and lymphoma, even after contrast enhancement. No technique has proved reliable in distinguishing these entities [2, 9–11].

The value of intravenous contrast medium and whether it should be used in all HIV-positive patients has been addressed by two North American studies [12, 13]. In 1993 Tuite et al. [12] examined the value of intravenous Gd-DTPA in 103 consecutive subjects. They reported that of 82 studies with no focal or mass lesions on the unenhanced images, eight showed mass lesions and eight meningeal or ependymal enhancement after contrast medium. This was purported to change management in 23 cases. However, of the eight new mass lesions, five were too small to biopsy or of uncertain significance and demonstration of meningeal or ependymal disease did not affect management. It was concluded that contrast enhancement was useful in the management of selected patients: those with symptoms of meningeal involvement, focal brain lesions or symptoms unexplained by unenhanced imaging. In the same year Jensen and Brandt-Zawadski [13] reported 63 MRI studies in 51 patients, pre- and postinjection images being reviewed together. No study with normal T2-weighted images demonstrated abnormalities after intravenous contrast medium. They concluded that normal T2-weighted images obviated the need for injection. These studies aroused considerable controversy and criticism of methodology [14–16], some commentators expressing the opinion that intravenous contrast medium should be given in every case, though neither study supported this view. Our purpose was to determine the value of intravenous contrast medium for cranial MRI in HIV-positive patients. We sought to find out if 1. intravenous contrast medium revealed new mass lesions or focal enhancement, meningeal or ependymal disease; if 2. the contrast enhanced images are always normal if the unenhanced images appear so; and if 3. intravenous contrast medium increases the confidence of the radiologist in making a specific diagnosis.

Methods and materials

We reviewed all HIV-positive patients referred for cranial MRI over a 2.5-year period. There were 92 men (mean age 38 ± 9 years) and 12 women (mean age 37 ± 11 years). We excluded 34 MRI examinations of 28 patients because intravenous contrast medium was not given or, in three cases because the images were not available. However complete studies performed on another occasion were available for 18 of these 28 patients. We thus had 150 examinations performed on 104 patients.

All MRI was performed at 1.0 T. A standard protocol of an axial T2-weighted sequence (fast spin-echo, echo train 5, effective TE/TR 90/4500 ms) followed by coronal T1-weighted (14/660) images before and after intravenous contrast medium was performed in each case. Slice thickness was 5 mm with 0.2 mm gap and a 190 × 256 matrix. A standard dose (0.1 mmol/kg) of intravenous Gd-DTPA was used.

All images were reviewed by an experienced neuroradiologist (T.C.S.C.) and an experienced MRI radiologist (J.B.B.). At the time of review, a few of the studies had previously been seen by one reader (J.B.B.) and none by the other (T.C.S.C.). All were reviewed without any clinical information, except the knowledge that the patient was HIV positive and his or her age. If a patient had undergone more than one study these were not reviewed consecutively. Each radiologist independently assessed first the unenhanced images alone and then all the images together. Afterwards the two readers reviewed the images together and produced a consensus report.

Each radiologist first independently assessed the images with the following scoring system:

Unenhanced images	
Cerebral/cerebellar atrophy	present/absent
Diffuse white matter disease	present/absent
Number of focal high signal lesions (T2-weighted images)	0 to 5 +
Number of mass lesions	0 to 5 +
Meningeal disease	present/absent
Ependymal disease	present/absent

Then images before and after contrast medium were scored together:

Number of mass lesions	0 to 5 +
Meningeal disease	present/absent
Ependymal disease	present/absent
Number of focal areas of enhancement	0 to 5 +

The presence of new lesions demonstrated with contrast medium and not seen on T2- or unenhanced T1-weighted images was recorded. The most likely diagnosis based on the MRI alone was recorded.

The consensus reading recorded the same features as above, whether new abnormalities were revealed by intravenous contrast medium and whether these were helpful in determining a diagnosis, by changing the suspected diagnosis or increasing the degree of certainty.

The final diagnosis in each patient was based on all clinical, laboratory and radiological data and response to treatment, derived from patient records. Investigations included MRI, serology, cerebrospinal fluid (CSF) analysis with polymerase chain reaction (PCR) study for cytomegalovirus (CMV), JC (JCV), Epstein-Barr (EBV), herpes simplex and *Varicella zoster* viruses. Tissue diagnoses were available from three cranial and two tonsillar biopsies and five autopsies.

Table 1 Final diagnoses determined from all available data after the episode. In some cases more than one diagnosis was given

Intracranial pathology	Examinations	Patients
Cerebral toxoplasmosis	31	14
AIDS-dementia complex/ encephalopathy	27	19
Progressive multifocal leukoencephalopathy	13	11
Psychiatric diagnosis	9	7
Cryptococcosis	9	7
Old injury/surgery	7	5
Non-Hodgkin's lymphoma	5	4
Vascular	4	4
Herpes simplex	3	2
Cytomegalovirus	3	2
Korsakoff's psychosis	2	2
Migraine	2	2
Neurosyphilis	1	1
Extracranial cause		
Viral myeloradiculopathy	3	3
Peripheral neuropathy	2	2
Mononeuritis multiplex	1	1
Sinusitis	6	6
Various non-neurological	4	3
No pathology identified	28	24

Results

The final diagnoses in the population as determined from all available data after the disease episode are recorded in Table 1, the consensus reading of the images in Table 2, and the reasons contrast enhancement was found helpful in 14 cases and the correlation between the radiological and final diagnosis in Table 3. A comparison between the individual readings of the two radiologists is shown in Table 4.

Does contrast enhancement reveal new mass lesions or focal enhancement, meningeal or ependymal disease, not seen on unenhanced images?

Contrast enhancement showed focal abnormalities not visible on T2- or unenhanced T1-weighted images in 20 studies (13%) of 15 patients (14%) on the consensus reading (Fig. 1). There was disagreement between the independent readings on whether additional new lesions were seen after contrast enhancement on three studies. In none of these was contrast medium helpful in making a diagnosis; on all three lesions were seen by both readers on the unenhanced images.

Meningeal thickening judged as pathological was seen on three unenhanced studies (2%) in 2 patients (2%) (Fig. 2). After contrast medium, pathological thickening or enhancement was seen in six studies (4%) of the same two patients (2%). There was disagreement between readers about assessment of meningeal disease in two unenhanced and two contrast-enhanced studies. In none of these cases was contrast medium judged of diagnostic help on consensus reading. Where meningeal disease was seen only after injection, there were focal lesions on the unenhanced images.

There was 100% concordance between readers regarding the presence or absence of diffuse ependymal enhancement, present in only one case, and not suspected on the unenhanced images.

Table 2 Consensus reading of scans

MRI findings	Examinations (patients)	
	Unenhanced	Contrast-enhanced
Normal	33 (27)	32 (26)
Cerebral atrophy only	21 (19)	20 (18)
Diffuse white-matter disease	18 (15)	
Focal high-signal lesion on T2-weighted images	74 (46)	
Mass lesions present	30 (21)	29 (20)
Focal lesions present and not seen on unenhanced images		20 (15)
Meningeal disease	3 (2)	6 (2)
Ependymal disease	0 (0)	1 (1)
Arachnoid cyst	1 (1)	1 (1)
Bilateral subdural collections	1 (1)	1 (1)

Table 3 Additional diagnostic value of intravenous contrast medium to observers in 14 examinations of 11 patients with normal or abnormal unenhanced images

Value of Gd-DTPA to radiologist	Examinations	
	unenhanced images normal	unenhanced images showed focal lesions
Features favour toxoplasmosis		6
Features favour lymphoma		1
Characterises progressive multifocal leukoencephalopathy		4
Characterises white matter disease		1
New toxoplasmosis lesion	1	
Ependymal enhancement and focal areas of enhancement	1	
Agreement of consensus radiology reading with final diagnosis	2 (all cases)	12 (all cases)

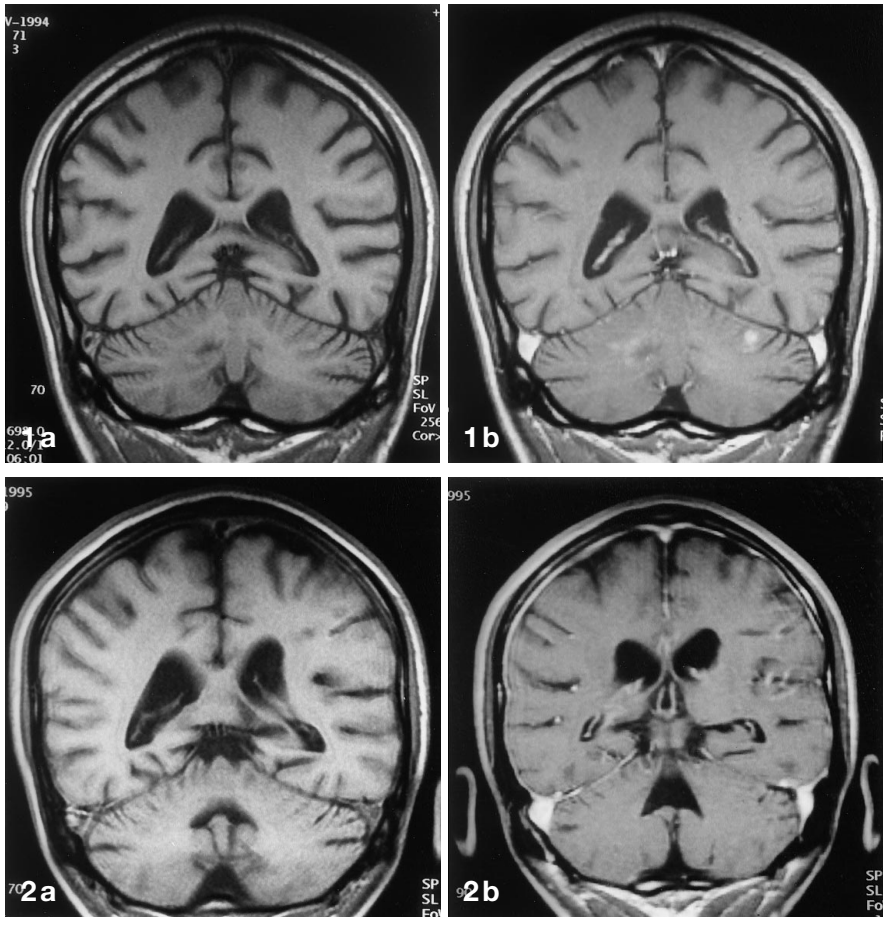

Fig. 1 a, b Toxoplasmosis in a 30-year-old man. **a** Single right cerebellar lesion on T1-weighted image. **b** A second unsuspected lesion is seen in the left cerebellum after contrast medium

Fig. 2 a, b A 36-year-old homosexual man with a diagnosis of toxoplasmosis based on response to therapy. **a** Meningeal thickening on unenhanced images. **b** Pathological meningeal enhancement

Are enhanced images always normal if the unenhanced images appear so?

The enhanced images were always normal when the unenhanced scan appeared so, except in two cases. The first was a follow-up after treatment for toxoplasmosis. On an earlier examination there had been multiple enhancing lesions. The follow-up unenhanced images were reported as normal, but a single area of contrast enhancement was seen. In retrospect, there was a focal abnormality on the unenhanced T1-weighted images not detected by either viewer (Fig. 3). This new finding increased the specificity of radiological diagnosis but was not of clinical importance. In the second case diffuse ependymal enhancement, with one or possibly two areas of focal enhancement in the posterior cranial fossa were seen only after intravenous contrast medium (Fig. 4). This patient had CMV encephalitis and the findings on the contrast enhanced images were helpful in modifying the suggested diagnosis. Assessment of the new abnormalities seen after contrast medium was the same for the individual as for the consensus readings in these cases.

Did intravenous contrast medium increase the confidence of the radiologist in making a specific diagnosis?

Increase in confidence of the radiologists after intravenous Gd-DTPA records the subjective increase in confidence, without reference to other data (Table 3). Correlation between consensus radiological diagnosis and final diagnosis is not presented for all cases as the radiologists frequently recognised that a specific diagnosis was not possible. However, whenever the radiological consensus was that intravenous contrast medium increased diagnostic specificity, the MRI diagnosis was compared with the final one, showing concurrence in all cases (Table 3). Intravenous contrast medium improved the diagnostic confidence of the radiologist in 14 studies (9%) of 11 patients (11%) (Table 3). Of these, 4 studies (3%) in 4 patients (4%) demonstrated new focal cerebral lesions after intravenous Gd-DTPA. In only two studies (1%) in 2 patients (2%) did new abnormalities after contrast medium help the radiologist make a diagnosis. These were the studies in which contrast medium revealed new abnormalities

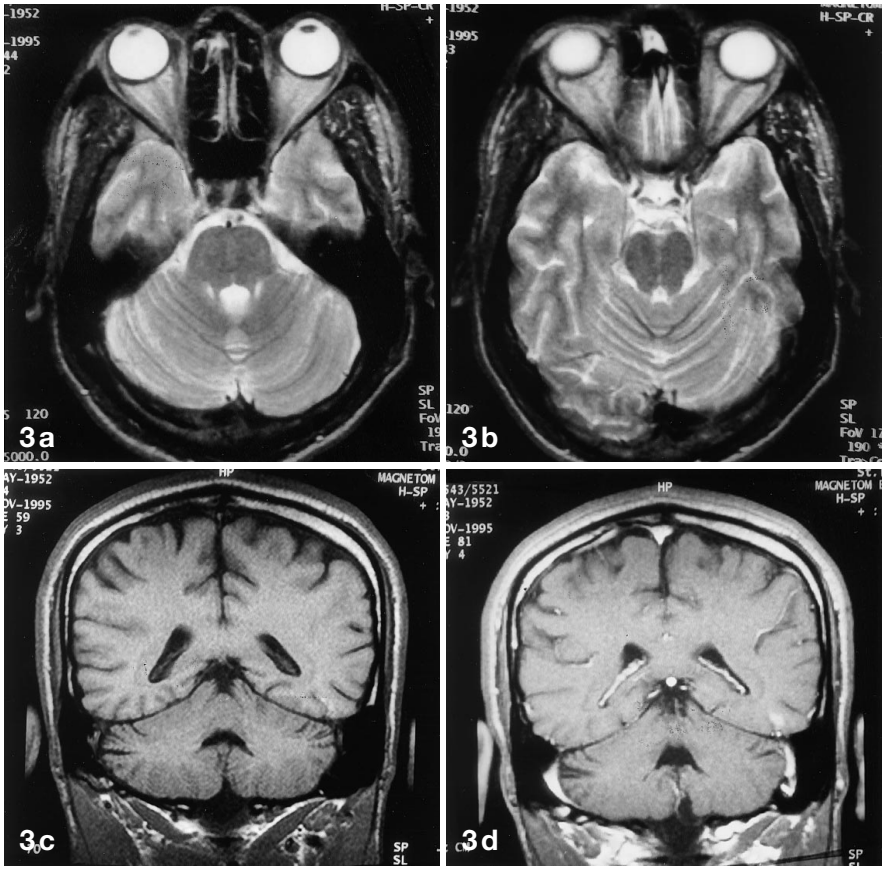

Fig. 3 a–d Follow-up in 45-year-old heterosexual man with toxoplasmosis after therapy. **a, b** Normal T2-weighted images. **c** Unenhanced T1-weighted image reported as normal. **d** Left temporal enhancing lesion reveals to be abnormal. In retrospect the unenhanced image was abnormal at this site

when the unenhanced images had been normal, described above.

In the other twelve cases (8%) where the unenhanced images were abnormal, intravenous contrast medium increased the confidence of the radiologist, because the pattern of enhancement suggested a limited preference for toxoplasmosis (Fig. 5) or lymphoma (Fig. 6), although it was recognised that it was not possible to make either diagnosis with complete confidence. Absence of pathological contrast enhancement helped to characterise white-matter high-signal lesions and progressive multifocal leucoencephalopathy (PML). In one case of the latter (Fig. 7), both readers had interpreted the appearances as representing a mass on the unenhanced images alone, diagnosing PML with confidence after seeing the enhanced study.

When meningeal disease was seen only after intravenous Gd-DTPA, there were focal lesions on all the unenhanced images and in no case did contrast medium increase diagnostic specificity.

Comparison of individual readings

There were disagreements regarding particularly the number of focal high-signal lesions on T2-weighted images and the number of mass lesions on unenhanced and enhanced images. This was usually because of difficulty in distinguishing the number of lesions within an area of abnormality observed by both readers. There was no discordance regarding the number of both unenhanced and enhanced studies which were normal. No disagreement led to significant disparity in diagnosis.

Discussion

Early studies of the value of intravenous Gd-DTPA in cranial MRI of HIV-positive patients, as we have seen, differed in their conclusions. In subsequent correspondence, Elster [14] favoured routine use of contrast medium, drawing attention to the size of the population studied by Jensen and Brandt-Zawadski and emphasising that the pretest likelihood of disease would influence the yield from intravenous Gd-DTPA. Friedman and Rapoport [15] questioned the value of the new findings after intravenous contrast medium in the study

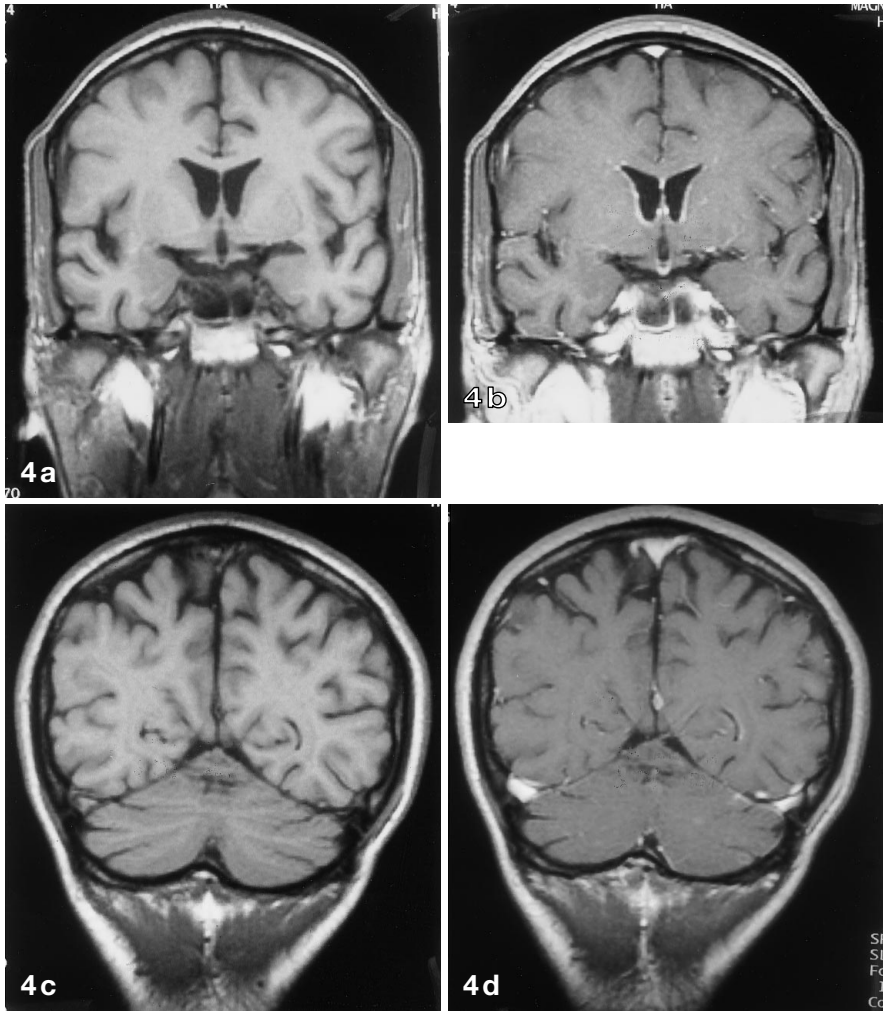

Fig. 4a–d A 38-year-old heterosexual man with CMV encephalitis. **a** Normal unenhanced image. **b** Diffuse ependymal enhancement. **c** Unenhanced image. **d** Enhanced images reveal an unsuspected new lesion in the left cerebellar white matter and a further probable lesion in the left cerebellar cortex (adjacent slices did not suggest that the cortical lesion was a vessel)

by Tuite et al. [12]. Zimmerman [16] preferred routine intravenous Gd-DTPA to avoid recalls for repeat examinations and suggested that intravenous contrast medium should be used in HIV-positive patients in a manner analogous to metastatic disease, making a comparison between the poor prognosis and potential for palliation in these conditions.

The prevalence of abnormalities in this HIV-positive population is probably similar to that in previous studies, although accurate comparison is difficult. However, some features are comparable. In the series of Tuite et al. [12], 15% of patients had mass lesions on unenhanced images, the corresponding proportion being 20% in our series. Jensen and Brandt-Zawadski [13] defined 62% of studies as abnormal (atrophy not being included); our corresponding figure was 64%. The number of examinations in our series is larger than in previous studies and unenhanced images were reviewed independently by two readers without knowledge of findings on enhanced imaging.

In our study, intravenous contrast medium did reveal new focal lesions in some cases, although the value of this information was limited. New lesions were nearly always seen on studies in which multiple lesions were already known to be present, from the unenhanced images. Of 20 studies showing new focal intracerebral lesions after contrast medium, contrast medium was also helpful in making a diagnosis in only 4. In only two of those, with normal unenhanced imaging was the finding of a new intracerebral lesion of extra diagnostic value.

These two cases do indicate that an unenhanced study read as normal does not always predict normal contrast enhanced imaging in HIV-positive patients. In one case, a subtle abnormality on unenhanced T1-weighted images was visible in retrospect after an obvious contrast-enhancing lesion had been detected. This finding, in a patient with resolving toxoplasmosis, did not affect management. The second case showed subtle focal enhancement in the cerebellum and diffuse

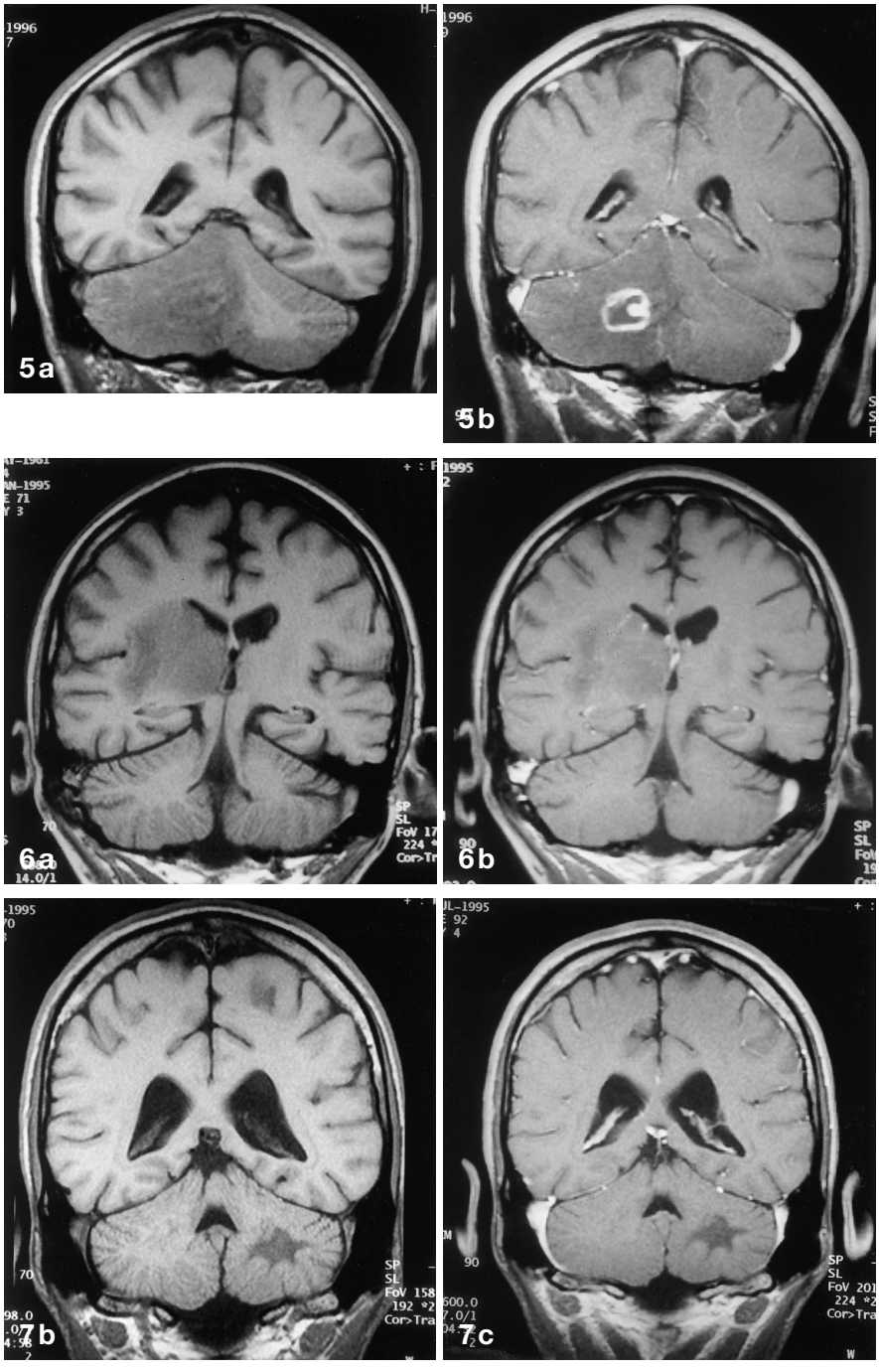

Fig. 5a, b Cerebellar toxoplasmosis in 26-year-old homosexual man confirmed by response to therapy. **a** Indeterminate mass lesion on unenhanced image. **b** Ring-enhancing lesion suggestive of toxoplasma intection

Fig. 6a, b Non-Hodgkin's lymphoma in a 33-year-old homosexual man, shown on brain biopsy. **a** Indeterminate subependymal mass on unenhanced image. **b** Minimal patchy enhancement

Fig. 7a–c A 39-year old homosexual man. Diagnosis of PML based on MRI findings, particularly lack of enhancement. **a, b** Mass suspected on T1- and T2-weighted images. **c** Enhanced image shows no change

ependymal enhancement in a patient with CMV encephalitis. This was the only case in the series in which new findings after Gd-DTPA were unequivocally useful after a normal unenhanced scan. However, even in this instance the definitive diagnosis was made on routine CSF PCR. In neither of these cases could the new lesions be identified on the T2-weighted axial images alone, even in retrospect, and there was 100% concordance between the two readers as to which unenhanced images were normal.

Meningeal disease was uncommon. Although on 3 studies unsuspected meningeal disease was demonstrated after intravenous Gd-DTPA, this was not helpful in making a specific diagnosis. This is consistent with previous observations that meningeal enhancement is uncommon in toxoplasmosis in HIV disease [17, 18],

Table 4 Concordance of radiologists' observations

Feature observed	Concordant readings	Discordant readings
Diffuse white matter disease (unenhanced)	151	3
Number of focal high signal lesions (T2 weighting)	147	7
Presence of mass lesions (unenhanced)	152	2
Presence of mass lesions (enhanced)	152	2
Number of mass lesions (unenhanced)	147	7
Number of mass lesions (enhanced)	146	8
Meningeal disease (unenhanced)	152	2
Meningeal disease (enhanced)	152	2
Ependymal disease (unenhanced)	154	0
Ependymal disease (enhanced)	154	0
Presence of previously unseen focal lesions after contrast medium (enhanced)	151	3
Absence of focal lesion (unenhanced)	154	0
Absence of focal lesion (enhanced)	154	0

and limits the value of intravenous contrast medium for this purpose.

Contrast medium was sometimes useful, but nearly always because it improved specificity of lesion characterisation, for example by the pattern of enhancement or by confirming lack of enhancement in PML, rather than because new lesions were seen. In all cases with abnormal unenhanced images in which contrast improved diagnostic specificity of the radiologist, reference to the final diagnosis showed agreement with the diagnosis proposed based on MRI. Increased radiological confidence has limited clinical impact, because radiologists and clinicians making management decisions recognise the limitations of specificity of MRI, particularly in distinguishing toxoplasma and lymphoma. Clinical data, CSF examination and response to treatment or biopsy will be necessary to make a final diagnosis.

There are other problems this study does not address. The argument that routine contrast enhancement can avoid recalls is beyond the scope of the studies performed to date. However this study suggests that a very low rate of important new abnormalities is detected in the presence of a normal unenhanced scan, diminishing this consideration. This study is also limited by the absence of newer techniques such as fluid attenuation by an inversion pulse. It is possible that these will increase the sensitivity of unenhanced MRI still further.

A recent prospective study of decision-making analysis in diagnosis of AIDS-related focal brain lesions again revealed the lack of specificity of MRI in distinguishing toxoplasma and lymphoma [19]. It emphasised the importance of the feature of mass effect of focal brain lesions, toxoplasma serology, response to therapy and CSF PCR for EBV-DNA and JCV-DNA in decision making, particularly with regard to biopsy. It is difficult to define precise indications for the use of intravenous Gd-DTPA because algorithms for management of cranial lesions continue to evolve. However, the sensitivity and specificity conferred by intravenous contrast medium are limited and do not make an important contribution in the great majority of cases. It is suggested that, in the light of current diagnostic algorithms, the findings in this series do not justify the recommendation of routine intravenous contrast medium in all cranial MRI studies of HIV-positive patients.

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