Management of intracerebral lesions in patients with HIV: a retrospective study with discussion of diagnostic problems

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Summary

A total of 95 patients who presented in 1994 and 1995 with focal brain lesions at a London HIV centre were studied retrospectively. Patients were allocated to ‘definite’ or ‘presumed’ diagnostic categories of toxoplasma encephalitis (TE), primary CNS lymphoma (PCNSL) or progressive multifocal leukoencephalopathy (PML), based on strict criteria. The number in each category was: TE, 20; PCNSL, 9; PML, 7; presumed TE, 12; presumed PCNSL, 8 and presumed PML, 17. There were 20 patients in whom a diagnosis could not be made, and there were three non-HIV diagnoses. Demographic data, features at presentation and routine CSF analysis were not discriminatory in making a diagnosis. Toxoplasma titres in those with TE compared to 1:16 in all other groups (p < 0.001) and those with TE were less likely to be on toxoplasma prophylaxis compared to those with PCNSL (p < 0.002). Survival with TE (median of 446 days) was significantly longer than survival in all other groups. Survival with either confirmed or presumed PML was similar. The problems of diagnosis of focal brain lesions in HIV patients are discussed and a management flow chart for mass lesions is proposed.

Introduction

Neurological involvement in HIV is common. Overall, around 40–60% of patients with AIDS present with a neurological disorder at some stage, and this may be the AIDS-defining diagnosis in 10–20% of HIV patients. At post mortem, nervous system pathology is almost ubiquitous. While HIV encephalitis is probably the most common diffuse CNS disease, the most common focal intracerebral pathologies are TE (50–70% of total intracerebral pathology), PCNSL (20–30%) and PML (10–20%). Other pathologies such as tuberculomas or cryptococcomas are reported, but are very rare in comparison.

The above disorders would head a differential diagnosis for all HIV patients presenting with intracerebral pathology pending further investigations. Information such as CD4 lymphocyte count, toxoplasma serology and prophylactic drug regimen may suggest one diagnosis above others in a given patient. CT or MRI brain scanning provides additional information, and is often the most important tool in determining the immediate management and the possibility of a lumbar puncture. However, making an unequivocal diagnosis is often difficult without recourse to invasive procedures such as brain biopsy, and the approach adopted by this and many other centres is to make a provisional diagnosis (usually TE) while awaiting the results of investigations or a response to treatment. While this is a practical approach, a firm diagnosis may remain elusive and may only be provided by a post-mortem examination. However, the outlook for patients with HIV and focal brain lesions other than TE is poor, and a balance needs to be struck between the need for an accurate diagnosis to enable advice and palliation to be given, and the need to avoid protracted and invasive investigation of dying patients.

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A lumbar puncture is possible in many patients and polymerase chain reaction (PCR) amplification of viral DNA from a sample of CSF may be used to confirm a diagnosis. PCR techniques are available for the detection of DNA from many viruses, including Epstein-Barr virus (EBV) and JC virus (JCV), the agents responsible for PCNSL and PML, respectively. Toxoplasma DNA can also be detected in CSF using PCR. While the sensitivity of some assays is disappointing, the specificity is uniformly high, and a positive result on PCR allows a confident diagnosis.

This study is a review of patients who presented with focal intracerebral lesions in 1994 and 1995 at a large London centre for the treatment of HIV. The presenting clinical features, supportive investigations, the response to treatment and survival are summarized. PCR techniques were in routine use throughout that time, and their contribution to the diagnostic process is addressed. A pragmatic algorithm for the management of intracerebral lesions based on our experience is proposed.

**Methods**

**Patient definitions**

For this study, HIV infection was defined as written documentation in the records of a positive result of an HIV test with appropriate CD4 lymphocyte subset results. AIDS or AIDS-related refers to the subgroup of patients with HIV infection who met the Centers for Disease Control (CDC) diagnostic criteria for AIDS (in the UK this does not include a CD4 count <200/mm³).

**Patient ascertainment**

From January 1994 to January 1996, there were 95 patients with focal intracerebral pathology who attended the Chelsea and Westminster Hospital Kobler Clinic. Since 1993, a computerized summary of HIV-patient activity has been maintained, with all diagnoses on each patient coded by CDC category. This coding database is part of a system which provides routine laboratory results, so all patients who have ever had an investigation in the HIV/GUM department are included. New diagnoses are coded on a weekly basis, on review of all in-patient records.

Patients with CDC diagnostic codes for presumptive or confirmed TE (4C1: 38, 4C1: 16, respectively), PCNSL (4D: 56, 4D: 50), PML (4C1: 29) or ‘neurological other’ (4E: 109) were identified, and all available medical records and images were reviewed. Data were abstracted on demographics, medical history, risk factors for HIV, initial presentation for each of the diagnostic categories, duration of treatment and patient survival. Selecting patients on diagnostic coding may miss patients with one of the above pathologies who were not coded correctly. However, as all of the above diseases have a rapidly progressive natural history, it is unlikely that any patient would have been missed completely, and the inclusion of the CDC code for undefined neurological conditions was a further safeguard to ensure full acquisition of patients with focal intracerebral lesions. Also, patient records provided the prospective diagnoses, and the information used to obtain each diagnosis, so that miscoding within the above categories could be corrected if necessary. Diagnosis date was defined as the admission date of the in-patient episode in which the diagnosis was made. The date of death was recorded in the notes of in-patients, and for those who died outside of the hospital, it was the date recorded by the community liaison team who were responsible for care of that patient.

**Diagnostic definitions**

Diagnoses were made prospectively by clinicians caring for each patient. Each diagnosis was initially ‘presumed’ until one of the diagnostic criteria (shown below) was met.

On presentation, patients were scanned using CT or MRI, and most patients had both forms of scanning either during the diagnostic period or as part of their clinical follow-up. Scans were reported prospectively by radiologists with experience in HIV neuroradiology who were aware of the clinical picture at the time of presentation. The radiological criteria for the diagnosis of intracerebral pathology in HIV patients have evolved in the course of the epidemic, are well established, and have recently been reviewed. A detailed review of the criteria for each diagnosis is beyond the scope of this paper, although ‘typical’ radiological appearances of TE would include multiple (>5) lesions with ring contrast enhancement, surrounding oedema and mass effect, with basal ganglia and grey/white matter borders as common sites for TE abscesses. On imaging, PCNSL may present with fewer lesions, and may have a more homogenous pattern of contrast enhancement. Extension of a lesion across the corpus callosum or periventricular placement with subependymal spread suggests PCNSL rather than TE. Radiology alone is not specific enough to differentiate TE from PCNSL in every patient at presentation, although this distinction becomes easier in retrospect after a period of specific antitoxoplasma treatment, as a radiological response is an accepted CDC definition of TE. Typically, areas of PML appear on MRI as high signal on T₂-weighted images with corresponding hypointensity on T₁ weighting. The lesions are in the white
matter, rarely have contrast enhancement and have no mass effect.

A confirmed diagnosis was one which met the following diagnostic criteria after appropriate investigations or a trial of treatment (TE). The remaining patients had a presumed diagnosis.

**TE**
Radiological features consistent with a diagnosis of TE, and evidence of radiological resolution or improvement after a period of 2 weeks on antitoxoplasma treatment.

**PCNSL**
Features consistent with PCNSL on brain biopsy or at post-mortem examination or EBV DNA detected in CSF by PCR in a patient with supportive radiology.

**PML**
Features typical of PML on brain biopsy or at post-mortem examination, or the presence of JCV DNA detected in CSF by PCR in a patient with supportive radiology.

**Other diagnoses**
In addition to the above, other diagnoses were: one CNS secondary spread of systemic lymphoma, one infarct and one patient with atrophy following intracerebral trauma. Patients for whom there was inadequate information to allocate them to one of the above groups fell into the ‘undetermined’ category.

**Viral PCR techniques**
All CSF samples for viral PCR, including JCV and EBV were sent from this centre to University College Hospital where viral PCR was performed according to methods detailed elsewhere.\(^{11,16}\)

**Toxoplasma titres**
Blood for toxoplasma titres was routinely taken from all patients, usually at their initial presentation at this centre, and again once CD4 count fell to around 200/mm\(^3\). Thereafter, the titre was rechecked every year or so. If a titre was 1:16 or above on screening with an Eiken toxoplasma reagent test (Japan), a further sample was sent to the toxoplasma reference laboratory for confirmation. Patients with a toxoplasma titre \(\geq 1:16\) were considered to be at risk of reactivation of toxoplasmosis.\(^{17}\)

**TE prophylaxis**
Patients receiving TE prophylaxis were defined as those taking cotrimoxazole, dapsone, fansidar, atovaquone or azithromycin at the time of diagnosis of new intracerebral pathology.

**Statistical analysis**
Descriptive statistics were used to calculate means. Estimations of statistical significance were made using the computer-based SPSS statistical package.

**Results**

**New diagnoses of intracerebral lesions in selected patient population**
A total of 2091 HIV-positive patients attended the clinic in 1994, and 2103 patients in 1995. Of the 95 patients with intracerebral pathology, 35 patients had a confirmed diagnosis, 37 patients had a presumed diagnosis and three had a non-HIV diagnosis. Insufficient data were available in the remaining 20 patients (‘undetermined’ category).

The numbers in each group (% of total) were: TE, 20 (21%); PML, 7 (7%); PCNSL, 8 (8%); presumed TE, 12 (13%); presumed PML, 17 (18%); presumed PCNSL, 8 (8%); and undetermined, 20 (21%).

**Patient risk factors**
All of the patients were white male homosexuals except for one female intravenous drug user. All were Caucasians except for one male of Afro-Caribbean origin.

**Age, CD4 count at diagnosis and survival after diagnosis**
Table 1 shows the mean age of each patient at diagnosis, the mean CD4 count at diagnosis (most recent count) and the median survival in days following the diagnosis. In the PML group, there was one patient who had a splenectomy some time before the diagnosis of PML, and had elevated CD4 counts. The mean CD4 count excluding this patient was 116/mm\(^3\). There was no significant difference between the CD4 count in any of the patient groups.

There was no significant difference between the ages of the patients in any of the diagnostic groups, with an overall mean age of 38 years.

Survival was significantly longer in the TE group (median 528 days, or 446 if surviving patients are not censored) compared with survival with PML (median 30 days, \(p<0.0001\), PCNSL (median 24 days, \(p<0.0001\), or with any of the unconfirmed diagnoses, including the diagnosis of presumed TE (median 33 days, \(p=0.0005\), all log rank test). Figure 1 shows Kaplan-Meier survival plots for the confirmed diagnostic categories (1a) and for TE and presumed TE (1b).
Table 1  Descriptive statistics for each diagnostic group

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Mean age (years) (range)</th>
<th>Mean CD4 count at diagnosis (l/mm$^3$) (range)</th>
<th>Median survival (days) (95% CI)</th>
<th>Number of patients with toxoplasma titre $&gt;1:16$ (%)</th>
<th>Number (%) of patients on TE prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PML ($n=7$)</td>
<td>39 (30–49)</td>
<td>116** (10–555)</td>
<td>30 (22–38)</td>
<td>1 (14)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>PCNSL ($n=8$)</td>
<td>37 (25–50)</td>
<td>25 (0–70)</td>
<td>24 (11–37)</td>
<td>2 (25)</td>
<td>7 (88)</td>
</tr>
<tr>
<td>TE ($n=20$)</td>
<td>39 (27–59)</td>
<td>52 (0–198)</td>
<td>528 (311–746*)</td>
<td>18 (90)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Presumed PML ($n=17$)</td>
<td>38 (30–55)</td>
<td>43 (4–119)</td>
<td>75 (41–109)</td>
<td>5 (29)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>Presumed PCNSL ($n=8$)</td>
<td>35 (30–46)</td>
<td>20 (0–78)</td>
<td>73 (27–119)</td>
<td>1 (13)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Presumed TE ($n=12$)</td>
<td>39 (28–54)</td>
<td>22 (2–52)</td>
<td>33 (0–67)</td>
<td>5 (42)</td>
<td>7 (58)</td>
</tr>
</tbody>
</table>

* Excludes 7 patients still alive at September 1996. ** Mean excluding CD4 count of 555/mm$^3$ in a patient with prior splenectomy.

![Survival plots](image)

Figure 1. a Kaplan-Meier plots of survival in the three major diagnostic groups. b Comparison of survival of patients with TE and presumed TE.

**Toxoplasma titres**

Toxoplasma titres $<1:16$ were considered ‘negative’ by our laboratory and not further quantified. The number of patients with toxoplasma titres $>1:16$ in each group is shown in Table 1. Eighteen of the 20 TE patients (90%) had elevated titres, compared to five of the 12 presumed TE patients, three of the confirmed PCNSL patients and one of the PML patients. Median toxoplasma titres were $<1:16$ in all diagnostic groups, except the TE group, where it was $1:256$ ($p=0.001$, one-way ANOVA).

**Toxoplasma prophylaxis and maintenance treatment**

Of the 20 patients with definite TE, 17 were first episodes of TE, and three were relapses of TE which
had responded to earlier treatment. Mean survival in the relapsed group was 515 days, which is not significantly different from the overall mean survival of 476 days in the TE group. Seven patients (41%) with a first episode of TE were on some form of primary antitoxoplasma prophylaxis. Table 1 shows the number of patients taking prophylaxis against TE; in the majority of cases in each group the drug was cotrimoxazole, taken primarily as PCP prophylaxis. TE prophylaxis was significantly more likely in the PCNSL group (88%) compared to those with a first diagnosis of TE (43%, \( p < 0.002, \chi^2 \) test).

**CSF values**

Table 2 shows the protein, glucose and white cell counts in the CSF in those patients who had a lumbar puncture at the time of diagnosis. The values in PML patients are within normal limits, and with only a mild elevation of protein in the TE and presumed PML groups. CSF in PCNSL patients occasionally showed a lymphocytic pleocytosis, and tended towards raised protein, but this was not universal. Few lumbar punctures were performed in patients with a diagnosis of TE.

**Clinical features**

Table 3 shows the number of patients in each group who presented with focal signs. All seven PML patients presented with focal deficits, but focal presentation occurred in only 60% of the PCNSL patients and 59% of the TE patients, despite sometimes extensive intracerebral lesions. The most common focal signs in each diagnostic group were: (i) diplopia and hemi- or quadrantopia in the PCNSL group; (ii) motor weakness, especially hemi- or monoparesis or limb incoordination, and aphasia or other speech deficit in the PML group; and (iii) incoordination, either of limbs or gait ataxia, in the TE group.

Seizures occurred in between 12 and 50% of patients at presentation in all categories except PML, where no patients presented with seizures but two had seizures at some point during the course of their illness. In the PCNSL group, one patient had focal seizures and corresponding focal neurological deficits, whereas the other three had generalized seizures with no signs of focal neurology. One patient was known to be epileptic before his HIV diagnosis.

Of the TE patients, one presented with focal seizures and signs, while the other two had generalized tonic-clonic seizures and no focal neurology. In the remaining diagnostic groups, both of the presumed PCNSL patients had focal seizures and focal signs, and in the presumed PML and presumed TE groups, there was one patient each with focal fitting and focal signs and one with generalized seizures without focal signs.

All patients who presented with seizures had a CT brain scan, which showed focal abnormalities regardless of seizure type.

Headache occurred in between 8% and 38% of patients, and cognitive dysfunction was present in 7% of the TE group, 29% of the PML group and in 63% of the PCNSL group, where it was the most common presenting feature.

**Discussion**

Between 2% and 2.5% of the HIV population attending this centre in 1994 and 1995 had a new diagnosis of focal intracerebral pathology. The majority had TE responsive to treatment (21%), with confirmed diagnoses of PML and PCNSL in 7% and 8%, respectively. It is difficult to make direct comparisons between these figures and those of other studies, as the reference populations are different. However, it is interesting to compare them to those obtained in a retrospective study of 122 patients with AIDS treated at this centre until their death in 1987. Of these, 64 were investigated for neurological disease and 15 had focal neuropathology, which was confirmed as TE in 33%, PCNSL in 20% and PML in 7%. Overall, patients with focal neurological disease formed 25% of those with a neurological complaint.

This study highlights the difficulties in making a confirmed diagnosis in HIV patients with focal intracerebral lesions in clinical practice. Only 35 of the

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Mean CSF protein (g/l) (range)</th>
<th>Mean CSF glucose (mmol/l) (range)</th>
<th>Mean CSF white cell count (/mm³) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PML (n = 7)</td>
<td>(n = 6) 0.41 (0.27–0.52)</td>
<td>(n = 7) 3.0 (2.5–3.3)</td>
<td>(n = 6) 0.8 (0–2)</td>
</tr>
<tr>
<td>PCNSL (n = 8)</td>
<td>(n = 5) 1.5 (0.14–2.72)</td>
<td>(n = 7) 3.1 (0.7–8)</td>
<td>(n = 7) 4.6 (1–12)</td>
</tr>
<tr>
<td>TE (n = 20)</td>
<td>(n = 3) 0.91 (0.27–1.9)</td>
<td>(n = 4) 3.2 (1.4–6)</td>
<td>(n = 4) 3.3 (1–10)</td>
</tr>
<tr>
<td>Presumed PML (n = 17)</td>
<td>(n = 9) 0.59 (0.21–1)</td>
<td>(n = 10) 2.7 (1.9–3.7)</td>
<td>(n = 11) 1.0 (0–5)</td>
</tr>
<tr>
<td>Presumed PCNSL (n = 8)</td>
<td>(n = 2) 1.34 (0.82–1.86)</td>
<td>(n = 2) 1.3 (0.6–2)</td>
<td>(n = 2) 33.5 (2–65)</td>
</tr>
<tr>
<td>Presumed TE (n = 12)</td>
<td>(n = 3) 1.1 (0.78–1.3)</td>
<td>(n = 4) 2.2 (0.4–3.4)</td>
<td>(n = 4) 18.5 (1–63)</td>
</tr>
</tbody>
</table>
Table 3  Clinical features at presentation

<table>
<thead>
<tr>
<th></th>
<th>PML (n = 7)</th>
<th>PCNSL (n = 8)</th>
<th>TE (n = 17)*</th>
<th>Presumed PML (n = 17)</th>
<th>Presumed PCNSL (n = 8)</th>
<th>Presumed TE (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor deficits</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td>3</td>
<td>2</td>
<td>(no field defects)</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Visual defects</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Incoordination</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Speech deficits</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Focal vs. non-focal</td>
<td>7/0</td>
<td>3/5</td>
<td>10/7</td>
<td>11/6</td>
<td>5/3</td>
<td></td>
</tr>
</tbody>
</table>

*Incomplete number of patients with clinical features. Motor deficits include hemiparesis, monoparesis, generalized or unspecified weakness. Visual dysfunction includes hemi-or quadrantanopia, nystagmus, diplopia and unspecified visual defects. Incoordination includes limb incoordination, ataxia and unspecified unsteadiness. Speech deficits include aphasia, dysphasia, dysarthria and unspecified disorders.

95 patients had a firm diagnosis based on strict diagnostic criteria. However, for practical management of HIV patients with intracerebral lesions, a definitive diagnosis may not be important, because median survival was very poor for all patients who failed a trial of anti-toxoplasma therapy. We propose a management algorithm (Figure 2) for mass lesions in HIV patients. It has been kept simple for clarity, and is not intended to be exhaustive. Areas of controversy, or where additional complexity has been left out, will be discussed below. The main diagnostic difficulties arise in trying to distinguish between TE and PCNSL at presentation, and much of this discussion will address this problem. In the algorithm (Figure 2), all patients are started on anti-toxoplasma treatment; but in those in whom TE is less likely at the outset, further investigations are started immediately rather than waiting for clinical or radiological deterioration to occur.

The other main diagnosis, PML, produces lesions with characteristic appearances on MRI scanning which should not cause confusion with the other groups of patients (unless there is multiple pathology—see later). Other pathologies such as tuberculosis, cryptococcomas, and intracerebral atypical mycobacteria are very rare in comparison to TE and PCNSL (none were seen over 2 years at this centre) and are almost always associated with systemic features of the underlying disease, allowing a diagnosis to be made.

Patients with TE

Patients who met the CDC diagnostic definition of TE of a response to specific treatment in the presence of typical radiology had a good outcome compared to other patient groups. Survival was a mean of 476 days (median 446 days, including seven patients still alive at September 1996), significantly longer than in any other diagnostic group including those with presumed TE who had a mean survival of 168 days (median 33 days, see Figure 1, a and b).

The survival of patients who responded to TE treatment at this centre compares favourably with a study of 115 patients with TE between the years 1981 and 1990 in San Francisco, where mean survival after a first episode of TE was 265 ± 212 days, among the 96 patients (83%) who responded to treatment. Median survival of 5 months was seen in a more recent study of patients from 1990 to 1995 in Atlanta. Also, survival was longer in this present study than in an earlier study at this centre in 1988 when survival was a median of 4 months.

Longer survival was reported in a cohort of 25 patients maintained on full treatment doses of pyrimethamine and either sulphadiazine or clindamycin for at least 503 days without relapse. However, there is a high rate of drug toxicity with TE treatment, and most centres reduce drugs to maintenance doses after 6 weeks at higher levels. Treatment at this centre was usually sulphadiazine and pyrimethamine as first choice, with clindamycin substituted for the sulphadiazine in the event of intolerance. Atovaquone was used in those who became intolerant of the above drugs. There were frequent changes of both drugs and doses during the treatment period, so it is not possible to draw any conclusions about the relative efficacy of any particular regimen from this study.

Partial or late responders to TE treatment

Around 80% of patients with TE will respond to one or other of the main drug regimens. but TE may take up to 6 weeks to respond to treatment, although in the majority (95%) this occurs within 2
Figure 2. Flow chart for the management of mass lesions. *The ‘positive’ outcome of investigations takes into account the response to trials of treatment and clinical and radiological progression, or the appearance of new lesions. Toxo, toxoplasmosis.

weeks, and many patients show a response within a few days. Patients with a prompt response to treatment identify themselves readily. Those who show an equivocal response to initial therapy present more of a diagnostic problem. The question is whether these patients have TE, which may be partially responsive to therapy, in which case a more prolonged or different anti-toxoplasma regimen may be tried, or whether they actually have PCNSL.

Recognizing these patients is important because the survival of patients with slowly-responding TE may be prolonged; 54 weeks in a study of biopsy-proven TE in patients with a slow initial response. In the management algorithm (Figure 2), a partial response at 2 weeks may lead to a further scan after a more prolonged period of treatment, the addition or substitution of anti-toxoplasma drugs, or may prompt further investigations (route not shown).

Clinical features
Clinical features at presentation were not discriminatory (Table 3). In those with TE, the overall rate of focal presentation was 59%, usually with signs of limb incoordination, while relatively few patients presented with a focal motor deficit. A high frequency of gait and co-ordination problems has been noted in other studies, but this was usually in combination with focal motor signs such as hemiparesis, and most patients presented with focal deficits which corresponded to the sites of intracerebral lesions. Choreoathetosis has been reported as being pathognomonic for TE, but was not seen in any of our patients. Overall, focal deficits have been found in 70–80% of patients with TE in other studies.

Variable frequencies of non-localizing signs such as cognitive dysfunction (6%), headache (29%) and seizures (18%) were noted in this study. These were also at a low frequency compared to other studies where confusion has been noted in more than 60% of patients.

In patients with PCNSL, cognitive dysfunction was the most common presenting feature (63%). Although focal motor deficits were less prominent, they still occurred in 60% of patients, which is a similar finding to that in other studies. None of the clinical features was specific for either TE or PCNSL, and as HIV patients often presented with surprisingly few
signs despite extensive intracerebral pathology, the threshold for brain scanning is low at this centre. This may account for the discrepancy between this study and others in the detection of patients with brain lesions before signs of focal deficit were apparent. Also, if this represents early detection, it may also partly account for the prolonged survival of our patients with TE compared to that seen in some other studies. Furthermore, this reaffirms the value of brain scanning early in the investigation of symptomatic HIV patients.

**Lumbar puncture and routine CSF investigation**

Lumbar puncture is a minimally invasive procedure, but is often not possible in patients with intracerebral mass lesions (e.g., it was performed in less than half of a series of 136 patients with focal brain lesions evaluated using PCR and histology)\(^{13}\). When performed, the main reason was to obtain a sample of CSF for PCR analysis. This is because there are abnormalities on routine investigations of CSF in HIV patients throughout their illness, which makes it a poor tool for identifying patients with secondary infection without specialized tests. Even a sample with all results in the normal range cannot rule out serious infection, as can be seen from the results of this study in patients with PML in particular (Table 2). In one study, 63% of CSF results were abnormal, although 80% of the study population were asymptomatic with CD4 counts above 400/mm\(^3\).\(^{25}\) In a review of several studies, a pattern of abnormalities was described which varied with progression of HIV infection; the CSF pleocytosis commonly found in the early phase of HIV infection fell with time, while CSF protein rose. On the basis of those results, the author suggested that a secondary infection besides HIV need only be considered if a pleocytosis of >100/mm\(^3\) was found.\(^{26}\) That conclusion may have reflected the lack of investigations such as PCR available at the time of publication, and our more recent experience would suggest that in late HIV infection, a pleocytosis of >10 white cells is often significant. There may be a lymphocyte pleocytosis in patients with PCNSL, but even then it is rare for CSF cytology to confirm the diagnosis of PCNSL,\(^{27}\) although it may have a higher diagnostic yield in patients with CNS spread of systemic lymphoma\(^{28}\) (it was diagnostic in the one patient with systemic lymphoma in this study).

**PCR techniques**

The sensitivity of PCR for EBV (which is always associated with PCNSL)\(^{7,29}\) is around 50–100%, with a specificity of 94–100%.\(^{30–33}\) This produces positive and negative predictive values of 90–100% and 97–99%, respectively.\(^{30,32}\) However, there have been reports of the detection of EBV by PCR in the CSF in the absence of visible lesions on scanning. These have been interpreted as being due to microscopic foci of lymphoma, or alternatively as being caused by contamination of the CSF sample by EBV in lymphocytes from the peripheral circulation.\(^{32}\) This study did not include patients without lesions on brain scanning, but caution is still needed, as the visible lesions may not be caused by PCNSL. Multiple pathology is common in HIV patients, with estimates ranging from 13.5% in a series of 1286 patients, to 29% in a series of 69 patients, all of whom had histological confirmation of the various diseases.\(^{33}\) Also, the development of PCNSL in patients who have been successfully treated for TE is well recognized. Usually, the rapid progression of PCNSL will provide swift clarification as these lesions expand, while those around them may shrink in response to anti-toxoplasma treatment. Serial CT or MRI scans are needed throughout treatment. A single scan is not sufficient for a definitive diagnosis, as has been established by several studies.\(^{27,34–37}\) In the proposed management algorithm (Figure 2), a positive PCR for EBV is used as confirmation of a diagnosis of PCNSL and may obviate the need for further investigation. However, it must be emphasized that each diagnosis is based upon several complementary findings. During this study, by the time that a confirmatory PCR was available, each patient with PCNSL had not shown benefit from a period of anti-toxoplasma treatment and showed progression of their lesions on repeat brain scanning.

Further investigations including thallium scanning or brain biopsy (see later) may be considered in some patients in whom lumbar puncture may not be possible, or who have a lesion at a suitable site for biopsy.

PCR techniques are available for the detection of toxoplasma DNA in the CSF, but the problem of multiple pathology is further confounded by the low sensitivity of the test—generally around 50–60% in large studies—although specificity approaches 100%.\(^{12,38}\) Treatment of TE also rapidly reduces the sensitivity of PCR.\(^{12}\)

As a result, toxoplasma PCR is not in routine use at this centre and is limited to the testing of stored samples taken before therapy in those patients who have failed 2 weeks of anti-toxoplasma treatment, who were safe to lumbar puncture, and who had a negative EBV PCR. In these few patients, a positive toxoplasma PCR would strengthen the resolve to continue with anti-toxoplasma treatment, but a negative result may not alter management, due to the poor sensitivity of the test.
Brain biopsy

Brain biopsy was diagnostic in one patient with PML and two pre-mortem diagnoses of PCNSL were confirmed at post-mortem examination. While histological examination is considered the gold standard for diagnosis, 4–36% of biopsies are non-diagnostic, and brain biopsy is perceived as highly invasive. It has a morbidity of up to 12% and mortality of 2%, which is higher than in the non-HIV population and largely made up of excess haemorrhagic complications. Most importantly, biopsy confirmation of a diagnosis has not been shown to improve the survival of HIV patients, except when performed as an early procedure before a trial of empirical anti-toxoplasma treatment in selected patients. This is largely because treatment is ineffective for most HIV-related intracerebral lesions. The survival advantage of early biopsy was an estimated 31 days in one decision-analysis study, which the authors admitted was a poor return for the increased risk involved in the test. Additionally, the possibility of multiple pathology increases the probability that a single biopsy may not identify the most important pathology. It has been suggested that a biopsy should be considered on the appearance of each new pathology, but this is untenable in our patient group.

In a departure from some earlier management schemes, brain biopsy is not included in our algorithm (Figure 2). A combination of clinical and serological findings, serial scans, CSF PCR or thallium scan results (see below) and a response to a trial of anti-toxoplasma treatment, should remove the need for this investigation in the majority of patients. The emphasis of our algorithm is to optimize survival, rather than to make a diagnosis. While treatment for PCNSL remains ineffective, the hope of prolonged survival in HIV patients with intracerebral disease lies in a response to anti-toxoplasma therapy. Provided that every effort is made to ensure that an adequate trial of these drugs is given, it is unlikely that survival would be improved by a tissue diagnosis.

Thallium scanning

Where initial investigations have been unable to suggest a likely diagnosis, such as in toxoplasma seronegative and EBV-PCR-negative patients, we have recently tried thallium SPECT scanning to distinguish between infective and neoplastic lesions. Thallium localizes in tumour cells, because it behaves like potassium and is transported into metabolically active cells, although some of its distribution may depend upon passive blood flow and tissue permeability. While patient numbers have been small, several reports have shown a sensitivity and specificity of between 80–100%, comparing thallium scan results with those of brain biopsy or post-mortem examinations. In our recent experience of five patients who underwent a thallium scan, two were ‘positive’ for PCNSL, one of whom was also EBV-PCR-positive in a sample of CSF. The other had a posterior fossa mass which prevented lumbar puncture. Both patients deteriorated rapidly. Of the three who were thallium scan ‘negative’ for PCNSL, two were also EBV-PCR-negative, and both eventually made a good response to a prolonged trial of anti-toxoplasma therapy. The remaining patient was positive for EBV on CSF PCR, and initially responded to antitoxoplasma treatment with radiological resolution of his lesions, but within a month he deteriorated clinically and further brain scanning revealed a new periventricular lesion radiologically typical of PCNSL. This last lesion was below the resolution of both MRI and thallium scanning at presentation. An early biopsy in this latter patient may have provided false reassurance.

Toxoplasma serology

The diagnostic value of toxoplasma titres has been a source of much debate. Eighteen of the 20 patients with TE had serum toxoplasma titres >1:16, showing past infection with toxoplasmosis and risk of reactivation. The TE group had proportionately more patients with elevated titres than any other group, and the median titre was also higher at 1:256, compared to 1:16 for all other groups. The rate of positive toxoplasma serology in a population varies geographically, and its value in discriminating between TE and other CNS lesions diminishes with increasing prevalence. Even so, in a study from France, where 60–80% of HIV patients have serological evidence of toxoplasma exposure, anti-toxoplasma antibodies were more frequently seen in those with TE than those without it (87% vs 71%, p<0.001). A recent study estimated the rate of positive serology in a mixed population of HIV patients in South London to be 23%. Using this figure, the only diagnostic groups with more than the expected number of patients with positive serology are the proven and presumed TE groups. Of those with raised toxoplasma titres, 20–47% will eventually develop TE, although this risk may be reduced by 50% with appropriate prophylaxis. In those with latent toxoplasma infection, many studies have shown that changes in toxoplasma titres are unreliable in determining acute reactivation, or for following the course of TE. However, there may be some evidence to suggest that patients with high titres may be at increased risk of TE compared to those with lower titres. Several
studies assert that TE is very unlikely in patients with low titres (<1:16) or negative toxoplasma serology, although this assertion may be biased by studies which exclude patients with negative toxoplasma serology. Studies have documented TE in patients with low toxoplasma titres, however, and one reported 'negative' toxoplasma serology (<1:16) in 22% of 18 patients with biopsy-proven TE, and the French study noted above found that 3/24 (12.5%) patients with TE were antibody-negative. In the present study, 10% of the patients with TE had a blood titre <1:16.

Titres below 1:16 may be significant in the context of advanced immunosuppression. We have seen positive toxoplasma serology become ‘negative’ in patients with advanced HIV and remain so despite an episode of fully-responsive TE. The two titre-negative patients in this study survived for 610 and 153 days from diagnosis. The first patient died of an unrelated opportunistic infection, and the patient with the shorter survival was left with significant neurological deficit despite complete radiological resolution of the TE lesions, and elected to discontinue all treatment one month before his death.

A positive toxoplasma titre remains a strong predictor of TE as the final diagnosis in the UK. In one decision analysis study, it was calculated that positive toxoplasma serology (>1:64) and ring-enhancing lesions on CT was 81% predictive of TE. A more recent prospective study of 136 consecutive HIV patients with focal brain lesions used Bayesian analysis to produce a probability of TE of 0.87 in patients with positive toxoplasma serology and who were not taking prophylaxis (the probability reduced to 0.78 for those on prophylaxis). In those who were toxoplasma-seronegative, the probability of TE was 0.22 (0.06 if TE prophylaxis was taken) while the probability of PCNSL was 0.74 (rising to 0.96 if EBV DNA was detected in a sample of CSF). The authors used these probability figures to recommend a course of investigations, i.e. no lumbar puncture in toxoplasma-seronegative patients on TE prophylaxis, even though a positive toxoplasma PCR in this group would increase the probability that they had TE to 0.96. However, survival figures were not given for the various diagnostic groups. In this study, the difference between the survival in the TE and PCNSL groups is so great that a 6% chance of a diagnosis of TE is important, and may warrant an investigation such as toxoplasma PCR, even if the expected yield was low.

**Toxoplasma prophylaxis**

In this study, 43% of those with TE were taking prophylaxis compared to 88% of those with PCNSL ($p<0.002$, $\chi^2$ test). Other studies have shown the value of prophylaxis in preventing TE in those with evidence of previous exposure to toxoplasmosis, and in areas where the prevalence of antitoxoplasma antibodies is high, a prophylaxis history is the most important discriminator in determining who has TE rather than PCNSL.

**PML**

PML produces lesions that appear on MRI brain scans as areas of white matter/high signal on T2-weighted images with corresponding areas of low signal on T1-weighted images. Gadolinium enhancement may occur in around 10% of lesions, but there is no mass effect. These scan appearances are sufficient, in the absence of confounding multiple pathology, to avoid confusion with the previous diagnoses.

At presentation, focal signs were universal in the confirmed PML group, with limb incoordination or hemiparesis predominating. Focal neurological deficit corresponding to the sites maximal involvement on brain imaging was the usual presentation of PML in many other studies. Weakness, visual deficits and cognitive abnormalities are reported in one third of patients and motor weakness of some sort is present in up to 80% at diagnosis. Although they are commonly seen in patients with PML, none of the patients in this study had seizures at presentation, but two developed seizures during the course of their illness.

Confirmation of the diagnosis of PML relied upon detection of JCV DNA in the CSF of patients with lesions typical of PML on brain scanning. The detection limit of most PCR techniques for JCV DNA is in the order of 10–100 viral genomes, but CSF concentration of free DNA is thought to be low because JCV is largely intracellular and found deep in white matter. Accordingly, test sensitivities of around 75–80% have been reported (and may be lower in routine clinical practice), although specificity is better at 92–100%. With a false negative rate of 20–30%, JCV PCR on CSF is only useful if positive. Patients with a negative result may be retested as the disease progresses, which has been shown to increase sensitivity, undergo a brain biopsy, or accept an unconfirmed diagnosis. Other studies have found that in patients with focal brain lesions without mass effect, PML remained the most likely diagnosis whether or not a CSF sample was positive for JCV on PCR. Although JCV PCR may be more likely to be positive later in the course of the disease, studies have failed to show correlation between the radiological extent of PML lesions and the likelihood of a positive PCR. There was a trend towards longer survival in the presumed PML (negative JCV PCR) group: median 75 days vs. 30 days in...
this study, which lends support to the above, although this did not reach significance. Interestingly, the biopsy-proven PML patient in this study had a negative PCR for JCV prior to biopsy. The poor sensitivity of JCV PCR in clinical usage may have important implications for any trial of treatment, and would support the use of clinical and radiological criteria for determining entry into a trial of treatment with diagnostic confirmation established via post-mortem examination.

Conclusions

Survival is poor for HIV patients with intracerebral pathology other than TE. The main diagnostic difficulty is separating patients with a poor initial response to anti-toxoplasma treatment from those with PCNSL. A history of anti-toxoplasma prophylaxis, a brain scan and the presence of anti-toxoplasma antibodies may help to decide the likelihood of TE before treatment. CSF PCR and a thallium brain scan may be of further assistance, but the most important step in making a diagnosis of TE remains a 2-week trial of anti-toxoplasma treatment. A prompt response predicts a prolonged survival. Patients who make a lesser response may require a more prolonged trial of treatment. Brain biopsy is rarely required, and does not alter survival. A diagnosis of PML may be made on the MRI appearance of the lesions in an appropriate clinical setting. A positive JCV PCR confirms a diagnosis, and may identify those patients with a particularly short survival, but the clinical course with or without a positive PCR is similar.

References


