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Management of HIV-associated focal brain lesions in developing countries

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Summary

Background: HIV-associated focal brain lesions (HFBL) are caused by opportunistic infections, neoplasms, or cerebrovascular diseases. In developed countries, toxoplasma encephalitis (TE) is the most frequent cause, followed by primary CNS lymphoma (PCNSL). Guidelines based on these causes however are poorly suited to developing countries, where treatable infections predominate as causes of HFBL.
Aim: To determine a practical approach to the management of HFBL in developing countries.
Design: Case series.
Methods: Patients ($n = 32$) were managed based on presumed aetiologies of the focal brain lesions, determined by collating information from CT scans, CSF and blood studies, concurrent non-neurological illness and response to treatment.
Results: The principal presumed cause of HFBL was tuberculosis (69%). The therapeutic response was good in 69% of patients.
Discussion: In developing countries, infections are the predominant cause of HFBL, the principal causes being infections that are endemic to the populations being studied. Empiric treatment based on limited investigations should be directed according to the nature of such infections. A modified algorithm is proposed.

Introduction

Focal brain lesions (FBL) caused by opportunistic infections, neoplasms, or cerebrovascular diseases are common neurological consequences of HIV infection.[1] In developed countries, toxoplasma encephalitis (TE) is the most frequently identified cause of HIV-associated FBL (HFBL), followed by primary CNS lymphoma (PCNSL).[1,2] On this basis, the Quality Standards Subcommittee of the American Academy of Neurology (AAN) proposed that HIV-positive patients presenting with FBL should be empirically treated for toxoplasmosis initially.[1] Failure to improve clinically or radiologically over the succeeding 10–14 days warrants stereotactic brain biopsy, in order to institute specific and appropriate therapy.[1] An alternative non-invasive approach that is otherwise similar, is based on the fact that brain biopsies do not influence survival in these patients.[2] With this approach, diagnosis is determined by the response to anti-toxoplasma treatment.[2] Failed responders are reviewed and presumed to have PCNSL or toxoplasmosis resistant to standard therapy and treated appropriately.[2] These guidelines and approaches to the management of HIV-associated FBL have been effective in developed countries.

In developing countries, however, infections are the main cause of HFBL.[3–10] Studies from African and Central American countries describe

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either tuberculosis (TB) or toxoplasmosis as the two most frequently occurring causes.[3–8] These observations have been corroborated in similar studies from India.[9,10] The relative frequencies with which these infections cause FBL are not well documented. The nature of the HFBL is probably determined by the infection/s that are endemic to the population being studied.[7] As TB is endemic in many developing countries,[11] if the AAN or British guidelines are strictly applied to such regions, large numbers of patients will be inappropriately managed.

We therefore prospectively studied and managed 32 patients with HFBL. Our approach was to presume the most likely cause in our setting, determined by collating information obtained from computer tomography (CT) scans, CSF and blood studies, concurrent non-neurological illness and response to treatment. We did not emphasize the need for accurate histological diagnosis of the FBL.

Methods

We studied 32 HIV-infected patients (aged >18 years) with FBL as diagnosed on computerized tomography (CT) scans. The study was carried out at the Chris Hani Baragwanath Hospital (CHBH) in Soweto, South Africa. Patients were recruited over a 12-month period. The CHBH is a 3300-bed public university hospital that serves a predominantly Black urban population of approximately 3 million people.

The patients were all in-patients, admitted to the medical wards of the CHBH. All patients in the study were Black, heterosexual, did not abuse intravenous drugs, and were anti-retroviral-therapy naive. None of the patients were on prophylactic treatment for *Pneumocystis carinii* or toxoplasma.

Data collected

Demographics

Age, sex, ethnic group, medication/drug use, and associated non-neurological illnesses.

Blood

Full blood count, ESR (erythrocyte sedimentation rate), glucose, urea and electrolytes, serum calcium, phosphate and magnesium, liver function tests, T-cell subsets, HIV viral loads (HIV-1 RNA), serological tests for syphilis (WR, TPHA, FTA-Abs), cysticercosis (ELISA), *Toxoplasma gondii* (CFT), typhoid (TMX), viral studies for hepatitis A, B and C, CMV (cytomegalovirus), HTLV-I and blood cultures.

Cerebrospinal fluid (CSF)

Chemistry, cell counts, cytology, and adenosine deaminase (ADA) level. TB ELISA and PCR, syphilis, cysticercosis and toxoplasma serology, HIV viral load (HIV-1 RNA), PCR for herpes simplex, varicella zoster, CMV, EBV and herpes simplex type 6, India ink staining, cryptococcal antigen, bacterial (including mycobacterium tuberculosis) and fungal cultures.

Sputum

Cytology, microscopy, culture and sensitivity, and acid-fast bacilli (AFB).

Radiology

Chest X-rays (CXRs). CT scans without and with contrast enhancement were done prior to treatment and repeated days or weeks later depending on the patients' clinical condition.

Diagnoses

FBL

The accurate and definitive diagnosis of FBL is dependent on histopathology. In this study, as we were unable to obtain histopathological diagnosis, we presumed the diagnosis of the FBL by collating information obtained from the CT scans (at the time of presentation and on empirical treatment), CSF and blood studies, CXR findings, associated non-neurological illness and response to treatment.

Tuberculosis

Presumed diagnosis based on some or all of the following: (i) CT brain scan appearance, i.e. hypodense or isodense rounded lesions with irregular walls of varying thickness, oedema and mass effect, cortical location, ring or nodular enhancement, increased basal meningeal enhancement. (ii) Positive TB culture in the CSF. (iii) Pulmonary TB (PTB) on CXR and/or acid-fast bacilli (AFB) on sputum microscopy. (iv) Increased protein, decreased glucose, pleocytosis (lymphocytes and/or polymorphonuclear cells), positive TB ELISA, PCR in the CSF. (v) Negative toxoplasma CFT. (vi) Response to TB treatment—clinically and radiologically.

Neurosyphilis

Diagnosed on the basis of CSF serology (WR, TPHA, FTA).

Toxoplasmosis

Presumed diagnosis based on some or all of the following: (i) Positive toxoplasma CFT. (ii) CD4+ count

less than 100 cells/mm^3. (iii) Hypodense, multiple (>5) rim-enhancing lesions with oedema, with basal ganglia and grey/white matter zones as common sites. (iv) Response to toxoplasma treatment.

Neurocysticercosis

Diagnosis based on some or all of the following: (i) Regular thin-walled, cystic, ring-enhancing lesions (often with a scolex). (ii) Intracranial calcifications. (iii) Positive blood and/or CSF serology (ELISA).

Cryptococcosis

Diagnosed on CSF studies (India ink, latex agglutination, fungal cultures).

PCNSL

Presumed diagnosis based on some or all of the following: (i) Hyperdense lesion/s, often confluent, with no oedema, homogenous contrast enhancement, periventricular/subependymal in location, corpus callosum involvement. (ii) CD4+ count <100 cells/mm^3. (iii) Atypical lymphocytes in the CSF. (iv) EBV PCR positive in CSF. (v) No response to ant-TB or anti-toxoplasma treatment.

PML

Presumed diagnosis based on some or all of the following: (i) Lesions confined to white matter, hypodense, non-enhancing appearance on CT scan, T2 hyperintense and T1 hypointense signal on MRI scans if performed, no mass effect. (ii) JC virus PCR positive in CSF.

Treatment

Patients were treated with specific medication based on the presumed diagnosis. TB was treated with isoniazid, rifampicin, pyrazinamide and ethambutol, neurosyphilis with IVI penicillin G, toxoplasmosis with sulphadiazine and pyrimethamine, and cysticercosis with albendazole. If response was good, the initial treatment regimen was continued. If response was poor, a new or second presumed diagnosis was entertained, and additional treatment for this diagnosis was instituted. The additional or new treatment was as described above.

A good response was one in which the patient showed ongoing improvement measured radiologically by a reduction in size and/or number of lesions on scan. A poor response was one in which the patient showed no improvement with no change or worsening of the FBL on scan.

Results

Results are summarized in Tables 1–3.

Age and sex

The age range was 18–49 years (mean 33.5 years) with 19 male patients and 13 female patients (male:female 1.5:1).

Table 1 Focal brain lesions: clinical and laboratory findings with presumed causes

Overall patient group	Neurological examination	Non-neurological illnesses	CSF results	CD4+ count (cells/mm^3)	Presumed cause
$n=32$ M:F 1.5:1 Mean age 33.5 years	Focal signs 66% Normal 28% Dementia 19% Encephalopathy 6%	PTB 60% PTB+TB breast $n=1$ TB lymphadenitis $n=1$ PCP $n=1$ Syphilis $n=11$	Elevated protein 59% Pleocytosis 9% TB PCR/ELISA +ve 6% Crypto Ag +ve 3% Cysti ELISA +ve 21% Syphilis +ve 3% Toxoplasma +ve 3% Normal 22%	<200 72% 200–500 13% >500 15%	53% TB 19% NCC 3% Toxo 3% PML 3% PCNSL 6% Infarcts 13% Mixed

CSF, cerebrospinal fluid; TB, tuberculous (sis); PTB, pulmonary tuberculosis; PCP, *Pneumocystis carinii* pneumonia; NCC, neurocysticercosis; Toxo, toxoplasmosis; PCNSL, primary central nervous system lymphoma; PML, progressive multifocal leukoencephalopathy; crypto, cryptococcal; cysti, cysticercosis; PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay. Elevated CSF protein (with or without pleocytosis) was found in 23 patients. Cysticercosis was ELISA +ve in 8 patients. TB was ELISA +ve in 1 patient, PCR +ve in 1, and culture +ve in 1. Cryptococcal antigen was +ve in 1 patient. Syphilis serology was +ve in 1 patient. Atypical B-cells were present in 1 patient. Toxoplasma was IgG +ve in 1 patient. Findings were normal in 7 patients (22%). CSF was not performed in two patients for practical reasons.

Table 2 Imaging characteristics of focal brain lesions (FBL) (total of 90 FBL)

Type of lesions	Site of lesions	Wall definition	Density relative to brain	FBL enhancement characteristics	Basal meningeal enhancement
Solitary 38% Multiple 62%	Cortical 79% Subcortical 11% Basal ganglia 7% BS/cerebellar 3%	Regular Thick 0% Thin 100% Irregular Thick 61% Thin 39%	Hyperdense 6% Isodense 9% Hypodense 85%	Ring 63% Nodular 6% Lobular 3% Gyriform 5% Mixed 21% Nil 2%	Present 53% Absent 47%

Table 3 Treatment outcomes of focal brain lesions

Response	*n*	Mean CD4+ count (cells/mm^3)	Presumed cause	CD4+ count range (cells/mm^3)	HIV viral load range (copies/ml)
Good	22 (69%)	188	TB 55%	21–610	76 000–>750 000
			NCC 27%	107–768	10 751–305 123
			TB + Other 18%	63–238	288 281–>750 000
Poor	3 (9%)	80	TB (100%)	1–180	647 696–>750 000
Died	7 (22%)	28	TB 44%	6–40	242 000–>750 000
			Toxo 14%	8	ND
			PCNSL 14%	22	>750 000
			PML 14%	7	>750 000
			Crypto 14%	96	228 668

TB, tuberculosis; NCC, neurocysticercosis; Toxo, toxoplasmosis; PCNSL, primary central nervous system lymphoma; PML, progressive multifocal leucoencephalopathy; Crypto, cryptococcosis; ND, not done.

Clinical presentation

CNS examination: focal signs in 21 patients (66%), normal in 9 (28%), dementia in 6 (19%), encephalopathy in 2 (6%). Patients were examined clinically on admission by GM or AM, who were blinded to the CT scan result. Once patients were recruited into the study, the follow-up examinations (also done by either GM or AM) were not blinded.

Non-neurological illnesses

These were present in 27 patients (84%): active PTB, 19 patients (60%); active PTB and tuberculous breast abscess, 1; tuberculous lymphadenitis, 1 (diagnosed on fine-needle aspirate); *Pneumocystis carinii* pneumonia (PCP), 1 (diagnosed on sputum cytology); positive syphilis blood serology (WR, TPHA), 11.

CD4 counts and staging

Staging was determined using the Centers for Disease Control (CDC) 1993 revised classification system for HIV infection and AIDS defining illnesses.[12] The patients had CD4+ T lymphocyte counts of 1–768 cells/mm^3. Four patients (12%) had counts >500 cells/mm^3, 4 (12%) had counts of 200–500 cells/mm^3, and 24 (76%) had counts of <200 cells/mm^3.

HIV viral loads

HIV blood viral loads were obtained in 29/32 patients. These ranged from 10 750 copies/ml to >750 000 copies/ml.

CSF results

Elevated CSF protein (with or without pleocytosis) was found in 23 patients. Cysticercosis was ELISA-positive in 8 patients. TB was ELISA-positive in 1 patient, PCR-positive in 1, and culture-positive in 1. Cryptococcal antigen was positive in 1 patient. Syphilis serology positive in 1 patient. Atypical B-cells were present in 1 patient. Toxoplasma was IgG-positive in 1 patient. Findings were normal in 7 patients (22%). CSF was not performed in two patients for practical reasons.

Radiology

Chest X-rays

Features of PTB were found in 20 patients (63%), bilateral perihilar reticulo-nodular infiltrates in 1 patient. Findings were normal in 11 patients (34%).

CT scans

These were performed on admission and repeated days or weeks later, depending on the patients' clinical condition. Twelve patients had solitary lesions (38%) and 20 patients had multiple lesions (62%).

In the 12 patients with solitary lesions, the CT scans were suggestive of TB in eight patients, neurocysticercosis in three and PCNSL in one. In the 20 patients with multiple lesions, the CT scans were suggestive of TB/toxoplasmosis ($n=12$), neurocysticercosis ($n=3$), PML ($n=1$), TB/toxoplasmosis and neurocysticercosis ($n=2$). Two patients had cerebral infarcts.

Meningeal enhancement (Figure 1) was present in 5/12 patients with solitary lesions and in 12/20 with multiple lesions. None of the patients diagnosed radiologically as neurocysticercosis, PCNSL or PML had meningeal enhancement.

The radiological diagnoses were therefore TB ($n=17$), neurocysticercosis ($n=6$), PML ($n=1$), PCNSL ($n=1$), TB with toxoplasmosis and neurocysticercosis ($n=2$), TB with toxoplasmosis ($n=3$), and cerebral infarcts ($n=2$) (both had basal meningeal enhancement).

Presumed causes

Presumed diagnoses were determined after correlating the radiological diagnosis with blood, CSF and non-neurological manifestations.

The two patients with cerebral infarctions had meningitis. In one patient, TB meningitis (TBM) was confirmed by culture positivity, and in the other cryptococcosis was identified on India ink stains and confirmed by fungal cultures and latex antigen tests.

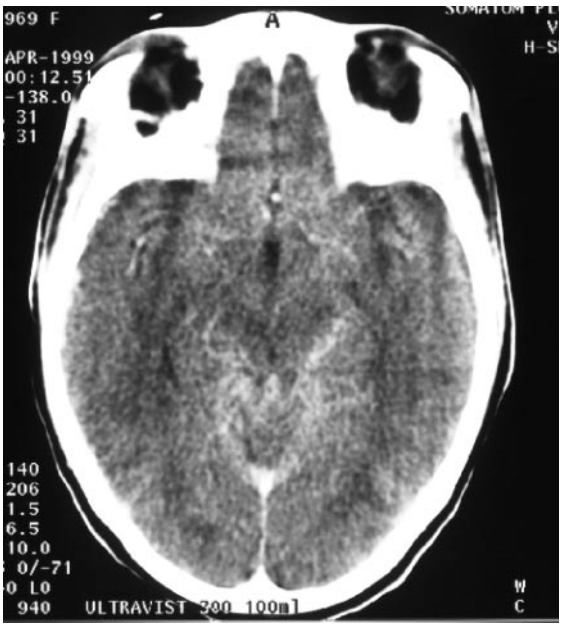

Figure 1. CT scan showing basal meningeal enhancement in a patient with presumed TB.

Of the 17 patients with radiological diagnosis of presumed TB, 14 patients had active PTB (sputum AFB-positive), one patient had histologically confirmed TB adenitis, one had *Pneumocystis carinii* pneumonia, and one had no non-neurological disease. The CSF and blood studies in these patients showed no specific diagnostic abnormalities other than neurosyphilis in one patient. TB cultures were negative in all 17 patients. One patient had a positive TB PCR in the CSF. This patient had PTB and a solitary enhancing FBL. As indicated above, all 17 patients had increased basal meningeal enhancement. In this group correlating the radiological diagnosis with blood, CSF and non-neurological manifestations did not alter the diagnosis. These patients were therefore treated with the four-drug anti-TB regimen as first-line treatment.

Five patients had radiological diagnoses of TB/toxoplasmosis (two of whom had associated neurocysticercosis). Of these five, one had positive toxoplasma serology in the blood and CSF. This patient had multiple enhancing FBL (including lesions suggestive of neurocysticercosis) on CT scan with basal meningeal enhancement. The patient also had PTB. One patient had a positive blood toxoplasma serology, no PTB, and multiple enhancing FBL with no basal meningeal enhancement on CT scan. The other three had PTB, negative toxoplasma serology, multiple enhancing FBL with no basal meningeal enhancement (including lesions suggestive of neurocysticercosis in one) on CT scan. In this group, correlating the radiological diagnosis with blood, CSF and non-neurological manifestations influenced the presumed diagnosis. One of these five was therefore diagnosed with isolated toxoplasmosis and treated with anti-toxoplasmosis treatment as first-line therapy. Of the remainder, two were classed as TB, one as TB with neurocysticercosis, and one as TB with toxoplasmosis and neurocysticercosis, and treated accordingly.

The following presumed diagnoses were thus made: TB, 17 patients (53%); neurocysticercosis, 6 (19%); TB with neurocysticercosis, 2 (6%); multiple infarcts 2 (6%) (1 TBM, 1 cryptococcal meningitis); TB with neurosyphilis, 1; toxoplasmosis, 1; toxoplasmosis with TB and neurocysticercosis, 1; PML, 1; PCNSL, 1.

In the patients with multiple infections as diagnoses, these were based on positive serology in the case of neurosyphilis, positive serology and CT scan features in the case of neurocysticercosis,

basal enhancement on CT scan with non-neurological TB in the case of TB and positive serology in the case of toxoplasmosis. Treatment was instituted for each infection at the outset.

Response to empirical treatment initiated

The following overall responses to treatment were obtained (Table 3): good, 22 patients (69%); poor 3 (9%); death, 7 (22%). Of the patients with a presumed diagnosis of TB and treated only with anti-TB treatment ($n=17$), 12 had a good response (Figure 2) (CD4+ counts 21–610 cells/mm^3), 3 s had a poor response (CD4+ counts 1, 55, and 180 cells/mm^3), and 2 died (CD4+ counts 6, 14 cells/mm^3). The six patients with neurocysticercosis (CD4+ counts 106–768 cells/mm^3) all responded well to treatment. The two patients with infarctions as FBL (CD4+ counts 96 and 240 cells/mm^3) both died, as did the patient treated as isolated toxoplasmosis (CD4+ count 8 cells/mm^3). In the mixed infection group (2 TB with neurocysticercosis, 1 TB with neurosyphilis, 1 TB with toxoplasmosis and neurocysticercosis) response to treatment was good in all four (CD4+ counts of 30–104 cells/mm^3). The patients diagnosed with PCNSL (CD4+ count 22 cells/mm^3) and PML (CD4+ count 7 cells/mm^3) died. The patient with presumed PML had confirmation of this diagnosis at autopsy.

The three poor responders to first-line TB treatment (all presumed TB) received additional anti-toxoplasmosis treatment and broad-spectrum antibiotics. Despite these additional treatments, there was no clinical or radiological change during the follow-up period.

Discussion

The FBL seen in our patients were almost exclusively infectious in nature. Of the 32 patients, only one was presumed to have a non-infectious aetiology (PCNSL). Four (12%) were diagnosed with dual/multiple infections. Dual/multiple CNS infections are not common in HIV, but have been described previously.[13]

The principal presumed cause of FBL in our patients was TB. The key features differentiating suspected TB from other infectious aetiologies were concurrent presence of PTB or other non-neurological TB, and basal meningeal enhancement. The FBL in the patients with presumed TB were predominantly cortical, with thick irregular walls, hypodense centres, and rim enhancement. Despite detailed analysis, of all the parameters used, the only possible differentiating radiological feature was the presence of basal meningeal enhancement in TB (Table 2). Of the 22 patients presumed to have TB (alone or in combination with other infections), basal meningeal enhancement was present in 16 (72%). The patients with presumed toxoplasmosis and neurocysticercosis had no basal meningeal enhancement. Patients with multiple infections who had basal meningeal enhancement all had TB as one of the presumed infections. The only patient with basal meningeal

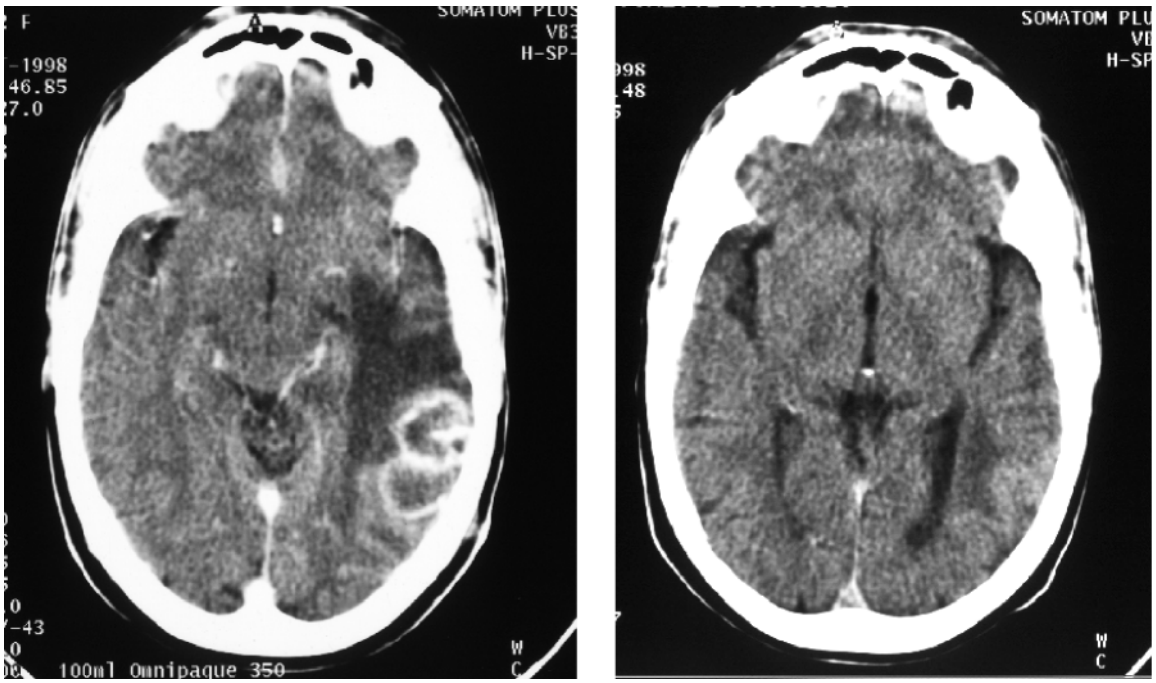

Figure 2. CT scans of a patient with presumed TB at presentation (left) and on anti-TB treatment after 6 weeks (right).

enhancement whose presumed diagnosis was not TB, had cryptococcal meningitis with cortical infarctions as the FBL. TB cultures were not helpful in the acute management of our patients. Only one patient had a positive CSF TB culture. This was the patient with TBM and cortical infarctions as the FBL. CSF TB PCR and ELISA were also of no value in our study, being positive in only one patient each.

In terms of non-neurological TB, this was diagnosed in 21 (66%) of our patients, of whom 19 had active pulmonary TB. TB is endemic in our population.[8,11] In the Gauteng province of South Africa, the incidence of TB in 1999 was 270/100 000 population. In 2001, it was 315/100 000. PTB accounts for 75%, and extra-pulmonary TB for 25%, of cases (Gauteng Department of Health, unpublished data obtained from Dr Riana Louw, with permission). As 63% of our patients had PTB, it is not surprising that our presumed diagnoses showed a bias towards TB.

With regard to toxoplasmosis, only two of our patients had positive serology (1 in serum, 1 in CSF and serum). Prevalence figures for toxoplasmosis in our region and South Africa as a whole have been published. In the Gauteng province, the prevalence among the Black ethnic group is 29%,[14] and in Kwa-Zulu Natal, the prevalence is 46% in Black pregnant females, the highest in the country.[15] It may be, as is widely recognized, that serological tests are falsely negative in patients with advanced immunosuppression. However, active non-neurological toxoplasmosis has not been described in our population. We were unable to find data for toxoplasma retinitis, toxoplasma septicaemia, and toxoplasma pneumonitis in our adult population (with or without HIV). None of our patients had evidence of toxoplasmosis outside the nervous system. The Kwa-Zulu Natal study found toxoplasmosis as the main cause of HFBL.[3] In another South African series of 38 HIV-infected patients with meningitis, toxoplasma IgG was positive in 14 patients (37%).[16] Two of these 14 patients also had FBL, both of which were TB (one confirmed histologically) and responded to TB treatment.[16] The only other study from this country on HFBL concurs with our findings that TB is the commonest cause of HFBL.[4] Further studies are required to clarify this issue. In our patients the presence of positive toxoplasma serology was used as an indication for toxoplasmosis treatment.

Neurocysticercosis, alone or in combination with other infections, was found in 9 patients (28%). This may be a chance association of endemic infections.[17] In a case report of four patients from Zimbabwe, the occurrence of neurocysticercosis in HIV-positive patients was likewise suggested to be due to chance association in endemic regions or due to the effect of HIV on the host immune response to cysticercosis.[17] Non-specific host factors (innate resistance), together with acquired immunity, are known to have an effect on the outcome of the primary infection in experimental models of cysticercosis.[17] Host immunity is also an important factor in limiting the occurrence of cysticercosis in humans.[17] The immunodeficient state accompanying HIV infection might therefore increase the frequency and severity of neurocysticercosis.[17] In our series, the mean CD4+ count in patients with neurocysticercosis alone was 509 cells/mm^3. These patients were therefore not immunocompromised. This implies a chance association. Further studies in respect of this association will be needed.

In contrast to the histopathologically-based American guidelines,[1] the initial treatment in the majority of our patients, where diagnosis (presumed) was based on collating clinical information (as described above), was for TB. Only one patient had initial toxoplasmosis treatment alone. Patients with multiple infections were treated for these different infections. Sixty-nine percent of the patients improved clinically and radiologically. These patients had a mean CD4+ count of 188 cells/mm^3. Fifty-five percent of these good responders were diagnosed with TB; 27% them had neurocysticercosis. The remainder had dual/multiple infections associated with TB. There were three poor responders (9%). The mean CD4+ count in these patients was 80 cells/mm^3. All three were diagnosed with TB. Seven of the 32 patients died. These patients had a mean CD4+ count of 28 cells/mm^3. In these patients the diagnoses were TB, toxoplasmosis, PML, PCNSL, and cryptococcosis.

The good responders had higher CD4+ counts than those who responded poorly or died. There was no similar correlation with blood HIV viral loads. This may imply that our diagnoses were more accurate in patients with CD4+ counts in >100 cells/mm^3, but that they were less accurate when the CD4+ counts were <100 cells/mm^3. The patients who died or responded poorly did not improve clinically or radiologically once additional treatments were instituted as described above, and the patients who died deteriorated rapidly with death within a few days of presentation to hospital. This may therefore imply that the poor responses and deaths were due to advanced immune deficiency rather than incorrect diagnosis and treatment of the FBL.

A limitation of our study is the small number of patients and the lack of long-term follow-up.

The patients who improved were discharged and continued treatment as out-patients. After a few consultations, most were lost to further follow-up.

Conclusions

From the data, it is clear that applying the HFBL guidelines for developed nations to a developing region could have a deleterious effect on outcome. This is largely because non-infectious aetiologies such as PCNSL are uncommon, and TE is not necessarily the most frequent infectious aetiology. We agree with the British proposal that brain biopsies are not necessary for treatment. The AAN guidelines are not possible to implement in developing regions, because of financial constraints and the limited availability of neurosurgical and neuropathological resources and services. In developing countries, HIV-positive patients who present with FBL should be treated initially with medication specific to the infections that are endemic to that population. In areas where TB is endemic, our results indicate that anti-TB treatment should be the initial treatment of known or suspected HFBL. Further studies of this nature from other developing regions are needed to validate our approach especially with respect to the role of the endemic infection, which is treatable and would influence outcome and survival.

Perhaps the most important contribution of our study is that we show that detailed laboratory investigations (such as HIV viral loads, viral cultures, TB cultures, TB ELISA, TB PCR, and even CD4 counts) are not necessary to arrive at a reasonable presumed diagnosis of a FBL in HIV-positive patients in order to institute effective treatment. CT scans of the FBL, with the exception of neurocysticercosis and possibly PML, were found to be non-specific. The most useful parameters that assisted us were

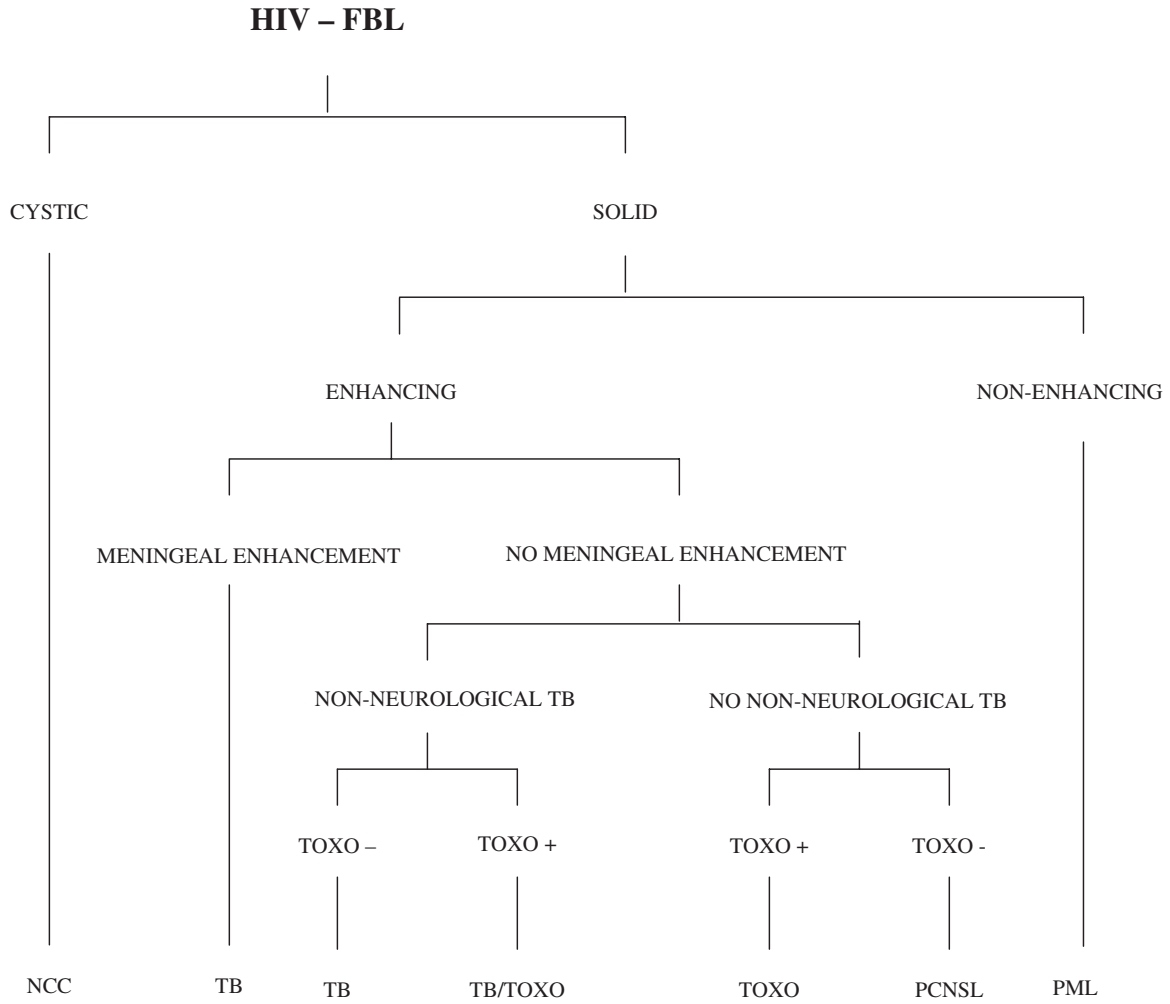

Figure 3. Algorithm for the initial assessment of HIV-associated focal brain lesions (FBL) in developing regions. TB, tuberculosis; NCC, neurocysticercosis; TOXO, toxoplasmosis; PCNSL, primary central nervous system lymphoma; PML, progressive multifocal leukoencephalopathy.

non-neurological illness, toxoplasma serology, and meningeal enhancement on CT scans (Figure 3).

On the basis of our results, we propose the following approach to the presumed diagnosis and thereby initial treatment of HFBL in developing regions. The important parameters (as discussed above) are meningeal enhancement on CT scan, presence of non-neurological TB, and toxoplasma serology.

The FBL are first categorized into solid or cystic. The cystic FBL are indicative of neurocysticercosis (except in rare cases, e.g. hydatid). The solid FBL are subdivided into enhancing or non-enhancing lesions. Lack of enhancement suggests PML. Enhancing FBL are divided into those with and those without increased basal meningeal enhancement. The presence of increased basal meningeal enhancement is suggestive of TB. FBL without increased meningeal enhancement are separated on the basis of accompanying non-neurological TB and toxoplasma serology (see algorithm). Initial treatment is instituted accordingly. Patients are monitored clinically. Good responders are maintained on this treatment. Poor responders are reassessed with CT scans. Presumed diagnosis and treatment is appropriately adjusted, e.g. addition of anti-toxoplasma treatment, antibacterial treatment (pyogenic abscess).

A limitation of this approach is the requirement of a CT scan for evaluation. In developing regions where this is not available, it might be best advised to treat suspected FBL in HIV patients for TB (in endemic areas) and toxoplasmosis.

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