REPORT DOCUMENTATION PAGE

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	1.Sep.05	MAJOR REPORT

4. TITLE AND SUBTITLE
AN ALGORITHMIC APPROACH TO NEUROIMAGING IN AIDS

5. FUNDING NUMBERS

6. AUTHOR(S)
MAJ SHERMAN PAUL M

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
JOHNS HOPKINS HOSPITAL AND HEALTHCARE SYSTEM

8. PERFORMING ORGANIZATION REPORT NUMBER

CI04-1237

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
THE DEPARTMENT OF THE AIR FORCE
AFIT/CIA, BLDG 125
2950 P STREET
WPAFB OH 45433

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION AVAILABILITY STATEMENT
Unlimited distribution
In Accordance With AFI 35-205/AFIT Sup 1

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

14. SUBJECT TERMS

15. NUMBER OF PAGES
13

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT

An Algorithmic Approach to Neuroimaging in AIDS

Introduction

Since the recognition of the human immunodeficiency virus (HIV) in the 1980s, there has been increasing awareness of the neurologic complications of the disease. The increased longevity of patients with the disease, in part secondary to multi-drug regimens, as well as the increased incidence of the disease, has furthered the opportunity for radiologic assistance in the diagnosis and management of neurologic complications from HIV. It is estimated that 7-10% of patients with acquired immune deficiency syndrome (AIDS) present with neurologic symptoms as their initial manifestation of illness and nearly 75% have central nervous system (CNS) involvement on post-mortem examination (1-3).

The clinical diagnosis of neurologic illness in AIDS patients can be a daunting task. Multiple illnesses affecting the CNS have overlapping clinical presentations without specific diagnostic laboratory findings. HIV encephalitis, Progressive Multifocal Leukoencephalopathy (PML), toxoplasmosis, lymphoma, and cryptococcus have clinical presentations ranging from subtle personality and mental status changes, difficulties in concentration, depression and memory loss to profound confusion which progresses to dementia. Headaches, motor and sensory neurologic deficits and new onset seizures are also common findings. Laboratory findings such as cerebrospinal fluid (CSF) leukocytosis may indicate an infectious etiology, but are non-specific, as are measurements of CSF protein and glucose counts (1).

We propose a simple algorithmic approach to the neuroradiologic imaging findings that may assist the clinician and radiologist in the diagnosis of the neurologic complications of HIV+ patients.

Algorithmic Approach (Figure 1)

Neuroimaging findings can be divided into four general categories that are useful in the differential diagnosis of patients with AIDS. These include 1) Normal, 2) Atrophy, 3) Intraaxial lesion without mass or mass effect, and 4) Mass lesion. Normal studies do not, however, preclude a diagnosis of infection or neoplasm (1, 2, 4). Close clinical follow up with periodic re-imaging may be helpful in recognition of initially radiologic occult processes in patients with persistent neurologic symptoms.

Atrophy may be related to normal aging or pathologic processes. After the exclusion of malnutrition, dehydration, and iatrogenic causes such as steroids; HIV encephalopathy/AIDS dementia complex (ADC) must be considered. When abnormal parenchymal attenuation on Computed Tomography (CT) studies or abnormal signal intensity on Magnetic Resonance (MR) imaging studies is seen in the absence of a mass lesion or significant mass effect, PML should be the primary consideration. An intraaxial mass lesion suggests an infectious or neoplastic etiology, most commonly toxoplasmosis or lymphoma (4-6). Since prompt clinical diagnosis is necessary for appropriate

An Algorithmic Approach to Neuroimaging in AIDS

Foster MA[1], Sherman PM[2,3], Tharin BD[3], Smirniotopoulos JG[3]

[1]University of Texas Health Sciences Center
Department of Radiology
7703 Floyd Curl Drive
San Antonio, TX 78229
(210) 567-6482 Phone
(210) 567-6469 Fax

[2]The Johns Hopkins Medical Institutions
Department of Radiology, Division of Neuroradiology
600 North Wolfe Ave, Phipps B-100
Baltimore, MD 21287
(410) 502-0012 Phone
(410) 614-1213 Fax
Corresponding author
Email: paul.sherman@usafa90.com

[3] Uniformed Services University of the Health Sciences
F. Edward Herbert School of Medicine
Department of Radiology
4301 Jones Bridge Road
Room C1071
Bethesda, MD 20814
(301) 295-3145
(301) 295-3893

An Algorithmic Approach to Neuroimaging in AIDS

Introduction

Since the recognition of the human immunodeficiency virus (HIV) in the 1980s, there has been increasing awareness of the neurologic complications of the disease. The increased longevity of patients with the disease, in part secondary to multi-drug regimens, as well as the increased incidence of the disease, has furthered the opportunity for radiologic assistance in the diagnosis and management of neurologic complications from HIV. It is estimated that 7-10% of patients with acquired immune deficiency syndrome (AIDS) present with neurologic symptoms as their initial manifestation of illness and nearly 75% have central nervous system (CNS) involvement on post-mortem examination (1-3).

The clinical diagnosis of neurologic illness in AIDS patients can be a daunting task. Multiple illnesses affecting the CNS have overlapping clinical presentations without specific diagnostic laboratory findings. HIV encephalitis, Progressive Multifocal Leukoencephalopathy (PML), toxoplasmosis, lymphoma, and cryptococcus have clinical presentations ranging from subtle personality and mental status changes, difficulties in concentration, depression and memory loss to profound confusion which progresses to dementia. Headaches, motor and sensory neurologic deficits and new onset seizures are also common findings. Laboratory findings such as cerebrospinal fluid (CSF) leukocytosis may indicate an infectious etiology, but are non-specific, as are measurements of CSF protein and glucose counts (1).

We propose a simple algorithmic approach to the neuroradiologic imaging findings that may assist the clinician and radiologist in the diagnosis of the neurologic complications of HIV+ patients.

Algorithmic Approach (Figure 1)

Neuroimaging findings can be divided into four general categories that are useful in the differential diagnosis of patients with AIDS. These include 1) Normal, 2) Atrophy, 3) Intraaxial lesion without mass or mass effect, and 4) Mass lesion. Normal studies do not, however, preclude a diagnosis of infection or neoplasm (1, 2, 4). Close clinical follow up with periodic re-imaging may be helpful in recognition of initially radiologic occult processes in patients with persistent neurologic symptoms.

Atrophy may be related to normal aging or pathologic processes. After the exclusion of malnutrition, dehydration, and iatrogenic causes such as steroids; HIV encephalopathy/AIDS dementia complex (ADC) must be considered. When abnormal parenchymal attenuation on Computed Tomography (CT) studies or abnormal signal intensity on Magnetic Resonance (MR) imaging studies is seen in the absence of a mass lesion or significant mass effect, PML should be the primary consideration. An intraaxial mass lesion suggests an infectious or neoplastic etiology, most commonly toxoplasmosis or lymphoma (4-6). Since prompt clinical diagnosis is necessary for appropriate

treatment, the finding of a mass lesion with clinical suspicion for toxoplasmosis is treated empirically, with consideration of biopsy in non-responders for further clarification of diagnosis. Cystic appearing masses in the region of the basal ganglia are pathognomonic for cryptococcal involvement.

This algorithm provides a simple approach to the diagnosis of the most common neurologic complications of AIDS. These entities will be discussed in further detail below.

Discussion

While the CNS complications from AIDS are broad, understanding the most common pathologic processes and opportunistic infections and using our simple algorithmic approach may clarify an otherwise complicated clinical presentation of disease. If the imaging findings cannot be placed within one of the categories of the algorithm, further evaluation should be conducted into an uncommon manifestation of a common process or other less common opportunistic processes.

Pathologic atrophy-AIDS dementia complex (ADC)/HIV Encephalopathy/HIV subacute encephalitis

Subacute encephalitis, clinically referred to as the AIDS dementia complex (ADC), is a common neurologic complication seen in AIDS patients. The prevalence of HIV dementia ranges from 7-27% of patients (1, 7, 8). ADC is characterized by cognitive disturbances that progress to dementia. The etiology is direct infection of HIV-1 in the CNS (8-10). While HIV-1 does not directly damage neurons, it causes indirect injury by infected CNS macrophages that generate neurotoxic factors (7, 10). Two distinct histopathologic patterns have been identified in this disorder: HIV encephalitis (HIVE), which is predominantly perivascular and HIV leukoencephalopathy that is characterized by diffuse myelin loss and infiltration by macrophages. The diagnosis of ADC is made according to clinical, neuropsychological and imaging findings.

The most commonly reported imaging finding in HIVE is cerebral atrophy (8, 9, 10). The appearance of atrophy varies from mild (figure 2-1) to severe (figure 2-2), which may include ex vacuo dilatation of the ventricles. Some patients may have subtle white matter hypoattenuation on CT (figure 2-1a, b), or corresponding increased T2 or FLAIR weighted signal intensity of the supratentorial white matter on MR imaging, which does not exhibit mass effect (figure 2-1c, d) (9, 10). The white matter changes are non-specific, occurring as focal or diffuse, symmetric or asymmetric, reversible or non-reversible. Severe HIVE produces significant atrophy and white matter hypoattenuation on CT (figure 2-2e, f) and corresponding FLAIR hyperintensity on MR imaging (figure 2-2g, h). While the findings of atrophy are more specific for HIV encephalopathy, the finding of white matter lesions in addition to atrophy should not exclude the diagnosis. Neuropathologic evaluation suggests that white matter abnormalities in ADC reflect leaky capillaries and a subsequent increased water content, which explains the reversible nature of the findings (10).

Protease inhibitor therapy and highly active antiretroviral therapy (HAART) have been reported to result in regression or stabilization of the periventricular and subcortical white matter signal intensity abnormalities seen in HIV encephalopathy (11). In addition, the treatment may demonstrate positive clinical effects despite progression of the MR imaging findings. There may be significant lag time in the MR imaging findings compared to the clinical symptoms and extended follow up may be necessary to document resolution or improvement in the MR findings (10). Therefore, early follow up imaging should not be the sole factor in evaluation of drug effectiveness.

Parenchymal lesion without mass or mass effect - PML

PML is a white matter demyelinating disease caused by the JC papovavirus, a DNA virus. The virus is named "JC" after the initials of the patient from whom it was cultured in 1971. JC had Hodgkin lymphoma and developed PML as a complication. (12). The virus itself is ubiquitous within the adult population – with an estimated prevalence of 80% for expression of JC antibodies (13). Almost 40% of HIV+ patients may express JC virus in their peripheral blood lymphocytes in the absence of PML (14). An immunocompromised state is theorized to permit reactivation of the virus in the AIDS patient. The JC virus causes lysis of the oligodendrocytes, disrupting the normal repair mechanism resulting in demyelination. Asymmetric involvement of both cerebral hemispheres is typical with involvement of white matter tracts in the cerebellum, brainstem and deep gray matter. Early involvement, however, may present with a single lesion, confusing the diagnosis.

PML affects approximately 4% of all AIDS patients (15). The symptoms associated with PML include altered mental status, speech, motor, and visual disturbances (7). Classic CT imaging findings include single or multiple low attenuation white matter lesions without edema or mass effect (figure 3 a, b, c). MR findings demonstrate hyperintensity of the white matter on T2/FLAIR images (figure 3d, e, f) with corresponding T1 hypointensity. Typically there is no enhancement (figure 3g, h, i) (16, 17). Donovan-Post et al. (18) quantified the pre-treatment MR findings in their study of 48 patients with white matter lesions as bilateral in 91.7%, confluent in 93.8%, and discrete in 66.7%. The lesions were predominantly supratentorial (frontoparietal greater than temporooccipital) within the periventricular region, centrum semiovale, and subcortical white matter. Although patients with HIV encephalopathy demonstrate atrophy on neuroimaging, 68.8% of patients with PML had atrophy with 50% demonstrating ventricular dilatation. Gray matter region lesions, typically in the thalamus and basal ganglia, are also common, likely representing involvement of the traversing white matter tracts. A definitive diagnosis of PML may require biopsy. However, in many cases confirmatory clinical symptoms, CSF polymerase chain reaction (PCR) studies positive for the JC virus and appropriate imaging findings may be sufficient for making a treatment decision and biopsy can be avoided (18).

PML is a progressive disease, typically causing death less within two to five months from diagnosis (18, 19). The standard use of HAART in the United States since 1996 has led

to the recent suggestion that AIDS patients with PML may live longer, although it has yet to be extensively documented (18). Most cases of PML are refractory to treatment. Some studies have attempted to predict prognosis from imaging analysis, however, this has not been analyzed in a large cohort of patients. The presence of mild mass effect has been shown to be a prognostic indicator of decreased survival (18). This finding was, however, contradicted by Thurner et al (20) who reported that the development of mass effect and temporary enhancement on MR images - in the early phase of treatment - might represent positive predictive factors for prolonged survival. Currently, no MR findings have significantly correlated with patient survival. The imaging findings of PML seen in AIDS patients significantly differs compared to other immunocompromised individuals in that AIDS patients may present with a solitary discrete lesion, and lesions that are not confined to the white matter. Thus, PML should not be excluded if it is unifocal and/or appears to involve deep cortical gray matter (4).

Mass lesion – A. Toxoplasmosis

Toxoplasmosis is the most common cerebral mass lesion in patients with AIDS (7). The infection is caused by an obligate intracellular parasite, *Toxoplasma gondii*, with reservoirs in the house cat (feces) and uncooked meat (e.g. pork and free-range chicken). Approximately (20-70%) of the normal adult population in the US is seropositive for antibodies to toxoplasmosis (2). The incidence ranges between 3-40% of patients with central nervous system complications of AIDS (1, 7, 21). The high frequency of multicentric lesions and evidence of choroid plexus infection with toxoplasmosis suggests hematogenous dissemination of parasites (7). Imaging findings are suggestive, but non-specific. Head CT typically demonstrates multiple, less than 2cm, low attenuation masses with ring enhancement. While the lesions are typically multiple, isolated lesions are also possible (figure 4a). MR images show decreased T1 and increased T2/FLAIR (figure 4b) signal intensity lesions with edema and ring enhancement (figure 4c). Most lesions are within the cerebral hemisphere white matter; however, involvement in any area is possible. The lesions demonstrate restricted diffusion on diffusion weighted imaging (DWI) (figure 4d) and corresponding apparent diffusion coefficient maps (figure 4e), similar to other abscesses.

One of the most significant clinical challenges in AIDS is the differentiation between toxoplasmosis and lymphoma that can both have similar clinical and imaging findings. Since toxoplasmosis occurs two to three times more frequently than lymphoma in AIDS patients in many geographic areas (2), empiric chemotherapy for toxoplasmosis (usually Pyrimethamine and Sulfadiazine for three weeks) has been advocated, with close clinical follow up. Porter et al (22) demonstrated clinical improvement with treatment in 90-95% of patients by day 14. This clinical response to anti-toxoplasma therapy has been the main criterion for diagnosis secondary to low specificity for serologic and PCR tests (23). If response is limited, treatment fails, or there is rapid deterioration, imaging and biopsy should be performed.

Imaging and biopsy should be performed prior to any steroid dosage. Steroids may cause regression of lymphoma and falsely give the impression that there was improvement

secondary to anti-toxoplasmosis medication delaying diagnosis and further treatment for lymphoma. It is important to recognize that lymphoma can progress rapidly. This may be a clinically confusing sign suggesting an infectious process. A fulminant illness should prompt immediate biopsy and earlier follow-up studies during empirical therapy for toxoplasmosis (5).

Mass lesion – B. Lymphoma

Primary CNS lymphoma is a high-grade B-cell non-Hodgkin lymphoma with a strong association with Epstein Barr Virus (EBV) infection (24). Primary lymphoma accounts for 2-10% of brain lesions in AIDS patients (1, 22, 25, 26). It is the second most common cause of a CNS mass lesion in AIDS (27). Histopathologically, this is a small round blue cell tumor, which is often associated with increased attenuation on non-contrast head CT, secondary to a high nuclear to cytoplasmic ratio. However, low attenuation white matter lesions may occur. Lymphoma may be unifocal or multifocal (figure 5) with variable mass effect. There is typically a paucity of edema relative to the tumor size. On MR imaging, these lesions may be isointense or hypointense on T1 weighted images and variable intensity on T2/FLAIR weighted images. However, due to the highly cellular infiltrate of small round blue cells, the lesions may show T2/FLAIR hypointensity (figure 5a, b, c). Most lesions demonstrate homogenous enhancement; but ring enhancement is frequent in AIDS patients (figure 5d, e, f). Steroids may inhibit the visibility of contrast enhancement. Lymphoma is most often periventricular in location but has been described throughout the parenchyma.

Radiologic findings may be helpful in distinguishing between toxoplasmosis and lymphoma. While autopsy studies have shown primary brain lymphoma to be multifocal in 80-100% of AIDS patients, it is important to recognize that when confronted with a solitary mass lesion, lymphoma is more probable than toxoplasmosis and that empirical treatment is not likely to be effective (28). Biopsy should be performed as soon as possible for a non-diagnostic unifocal lesion (4). Lymphoma is most often periventricular in location and may encase the ventricles by subependymal spread, so called "rimphoma." This pattern is highly suggestive of primary CNS lymphoma (PCNSL) and is unusual for other mass lesions. Lymphoma often involves the corpus callosum, whereas edema from infection will not cross this tight white matter tract.

Initial data also suggests that diffusion coefficients may be helpful with toxoplasmosis lesions demonstrating slightly greater diffusion than lymphoma lesions, although further studies need to be done to support this finding (29). Thallium (Thallium 201 [Tl] Thallous Chloride) radiopharmaceutical imaging is often useful as lymphoma is thallium avid while toxoplasmosis is not. Thallium behaves biologically like potassium. It is taken up by anabolic pumps, a process accentuated in actively growing and dividing cells in lymphoma. The sensitivity and specificity of 201 Tl-SPECT in depicting lymphoma has been reported to be as high as 100% and 93%, respectively (30). Diagnostic accuracy may be improved when serum toxoplasma IgG findings are included in the decision tree (31). While these radiologic findings may be suggestive of lymphoma, ideally, brain biopsy is required for diagnosis.

It is important to note that there are imaging differences between the non-AIDS population and the AIDS population. In the non-AIDS population, primary brain lymphoma shows a homogeneous pattern of contrast enhancement on CT and MR with ventricular encasement. In the setting of AIDS, lymphoma is aggressive, often multicentric (figure 5a, b, c) and can grow rapidly, more than doubling in size within 2 weeks (23, 25, 32). The AIDS related lymphomas can look like rings or targets on CT and MR images likely secondary to internal necrosis (figure 5d, e, f).

CNS lymphoma is sensitive to radiation therapy, but is prone to recurrence. Survival usually is less than 1 year despite therapy (23, 32). Whole brain irradiation of 4-5cGY over a period of 3wks is standard treatment (4). There is a four-fold increase in survival rates for those patients who receive treatment over those that do not receive appropriate therapy (30). For this reason, treatment delay or inappropriate diagnosis after chemotherapy for toxoplasmosis and/or steroids prompts more frequent monitoring during therapy, and biopsy for rapidly progressing lesions, or those failing treatment (32).

Cystic mass lesion - Cryptococcus

Cryptococcus is the most common central nervous system fungal infection in patients with AIDS in the United States (33). The overall incidence is approximately 5% of all patients with AIDS (1). Clinical findings are nonspecific and can be subtle. Headache, malaise, fever, nausea and vomiting are common findings (7). The *Cryptococcus neoformans* organism is a common soil fungus that infects the lungs and then spreads hematogenously to the cerebral spinal fluid causing choroid plexitis, meningitis, and encephalitis. The gelatinous polysaccharide coat of the fungus hinders phagocytosis and impairs leukocyte migration (34). CSF is the preferred site secondary to the lack of anticryptococcal factors in the CSF that are usually present in the serum (35). This lack of defense mechanism in the CSF, in addition to the lack of exotoxin from the organism, mitigates the neurologic inflammatory response (34). CT imaging is frequently normal; however when cystic appearing lesions are present within the basal ganglia region, the imaging findings of cryptococcal infection can be quite specific. Cryptococci extend into the parenchyma through the Virchow-Robin spaces and expand these perivascular spaces, filling them with budding cryptococci. These pseudocystic perivascular lesions are characteristic of this disease (34). The signal characteristics follow fluid signal with low T1 signal intensity and high T2 signal intensity on MR imaging (figure 6a, b) typically without enhancement. Leptomeningeal enhancement as well as enhancement extending into the perivascular spaces may also be seen (figure 6c, d, e, f).

Cryptococcomas represent a collection of organisms, inflammatory cells, and mucoid material in the brain parenchyma. Cryptococcomas can develop from extension of organisms from the perivascular spaces into the parenchyma or from direct invasion from other meningeal or ependymal surfaces. Choroid plexitis can result with enlargement and enhancement of the choroid plexus associated with leptomeningeal enhancement (36). Unilateral cystic dilatation of the temporal horn of the lateral ventricle has been described secondary to CSF entrapment by an inflamed choroid plexus. The diagnosis of

Cryptococcus is by detection of cryptococcal antigen in CSF or on identification of the cryptococci by India-ink preparation of the CSF (34). Treatment involves antifungal therapy which may have significant adverse effects. Despite appropriate treatment, recurrence is common and the mortality rates can reach 40% in immunocompromised individuals, with a mean survival of 2 to 3 months (1).

Summary

Imaging studies performed for neurologic illness in AIDS play an important role in diagnosis and management. We describe a simple algorithmic approach based on the imaging findings to guide differential diagnosis for the clinician and radiologist. Four patterns should be recognized: 1) Normal; 2) Atrophy; 3) Intraaxial lesion without mass or mass effect; and 4) Mass lesions. Each pattern provides information helpful in the differential diagnosis of the AIDS patient. Normal studies do not exclude pathology. Frequently cryptococcus and other infectious processes have normal studies in the initial presentation. Normal studies require close clinical follow up with repeat imaging as necessary to assist in the recognition of occult processes in patients with neurologic symptoms. Findings of atrophy may be related to normal aging, or pathologic processes. Pathologic processes, such as HIV encephalopathy/AIDS dementia complex (ADC), should be considered when atrophy is identified. Atrophy can also be seen in PML; however, underlying parenchymal lesions are also present. When encountering a parenchymal lesion without mass or mass effect, PML must be considered. Intraaxial mass lesions represent an ongoing debate related to the fact that 80% of brain masses in patients with AIDS are caused by toxoplasmosis or lymphoma (4-6). Since prompt clinical diagnosis is necessary for proper treatment, the finding of a mass lesion with suspicion for toxoplasmosis is treated empirically, with non-responders receiving biopsy for further clarification of diagnosis. Periventricular masses with thick subependymal spread are highly characteristic of lymphoma. Cystic masses in the region of the basal ganglia are pathognomonic for cryptococcal involvement.

REFERENCES

1. Levy RM, Bredesen DE, Rosenblum ML, et al. Central Nervous System Disorders in AIDS. In: Levy JA ed. AIDS pathogenesis and treatment. New York: Marcel Dekker, 1988: 371-401.

2. Levy RN, Bredesen DE, Rosenblum ML. Neurological Manifestations of the Acquired Immunodeficiency Syndrome (AIDS): Experience at UCSF and Review of the Literature. J Neurosurg 1985; 62: 475-495.

3. Chinn RJS, Wilkinson ID, Hall-Craggs MA, et al. Toxoplasmosis and Primary Central Nervous System Lymphoma in HIV Infection: Diagnosis with MR Spectroscopy. Radiology 1995; 197: 649-654.

4. Ciricillo SF, Rosenblum ML. Use of CT and MR imaging to distinguish intracranial lesions and to define the need for biopsy in AIDS patients. J Neurosurgery 1990; 73: 720-724.

5. Chiang FL, Miller BL, Chang L, McBride D, et al. Fulminant Cerebral Lymphoma in AIDS. AJNR 1996; 17: 157-160.

6. Rosenblum ML, Levy RM, Bredesen DE. Neurosurgical implications of the acquired immunodeficiency syndrome (AIDS). Clin Neurosurg 1988; 34: 419-445.

7. Simpson, DM, Tagliati M. Neurologic Manifestations of HIV Infection. Annals of Internal Medicine 1994; 121(10): 769-785.

8. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. Ann Neurol 1986; 19: 517-524.

9. Donovan-Post MJ, Tate LG, Quencer RM, et al. CT, MR, and pathology in HIV encephalitis and meningitis. AJR Am J Roentgenol 1988; 151: 373-380.

10. Thurnher MM, Schindler EG, Thurnher SA, et al. Highly Active Antiretroviral Therapy for Patients with AIDS Dementia Complex: Effect on MR Imaging Findings and Clinical Course. Am J Neuroradiol April 2000; 21: 670-678.

11. Filippi CG, Sze G, Farber SJ, et al. Regression of HIV Encephalopathy and Basal Ganglia Signal Intensity Abnormality at MR Imaging in Patients with AIDS after the Initiation of Protease Inhibitor Therapy. Radiology 1998; 206: 491-498.

12. Padget BL, Walker DL, ZuRheim GM et al. Cultivation of papova-like virus from human brain with progressive multifocal leukoencephalopathy. Lancet 1971; 1:1257-1260.

13. Greenfield JG. Greenfield's Neuropathology. 4th Ed. New York, NY: Wiley, 1984; 261-288.

14. Tornatore C, Berger JR, Houff SA, et al. Detection of JC Virus DNA in peripheral lymphocytes from patients with and without progressive multifocal leukoencephalopathy. Ann Neurol 1992; 31: 454-462.

15. Berger J, Kashovitz B, Donovan-Post J, et al. Progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection: a review of the literature and report of sixteen cases. Ann Intern Med 1987; 107: 78-87.

16. Whiteman MLH, Post MJD, Berger JR, et al. Progressive Multifocal Leukoencephalopathy in 47 HIV seropositive patients: Neuroimaging with clinical and pathologic correlation. Radiology 1993; 187: 233-240.

17. Mark AS, Atlas SW. Progressive Multifocal Leukoencephalopathy in Patients with AIDS: Appearance on MR Images. Radiology 1989; 173: 517-520.

18. Donovan-Post MJ, Yiannoutsos C, Simpson D et al. Progressive Multifocal Leukoencephalopathy in AIDS: Are There Any MR Findings Useful to Patient Management and Predictive of Patient Survival? Am J Neuroradiol 1999; 20: 1896-1906.

19. Holman R, Janssen R, Buehler J, et al. Epidemiology of Progressive Multifocal Leukoencephalopathy in the United States: Analysis of National Mortality and AIDS Surveillance Data. Neurology 1991; 41: 1733-1736.

20. Thurnher MM, Post JD, Rieger A, et al. Initial and Follow-up MR Imaging Findings in AIDS-Related Progressive Multifocal Leukoencephalopathy Treated with Highly Active Antiretroviral Therapy. AJNR Am J Neuroradiol 2001; 22: 977-984.

21. Anders KH, Guerra WF, Tomiyasu U, et al. The neuropathology of AIDS: UCLA experience and review. Am J Pathol 1986; 124: 537-557.

22. Porter SB, Sande MA. Toxoplasmosis of the cerebral nervous system in the acquired immunodeficiency syndrome. N Engl J Med 1992; 327: 1643-1648.

23. Chang L, Cornford ME, Chiang FL, et al. Radiologic-Pathologic Correlation Cerebral Toxoplasmosis and Lymphoma in AIDS. AJNR 1995; 16: 1653-1663.

24. MacMahon EME, Glass JD, Hayward SD et al. Epstein Barr Virus (EBV) in acquired immune deficiency syndrome-related primary central nervous system lymphoma. Lancet 1991; 338: 969-973.

25. So YT, Beckstead JH, Davis RL. Primary central nervous system lymphoma in acquired immune deficiency syndrome: clinical and pathologic study. Ann Neurol 1986; 20: 566-572.

26. Rosenblum ML, Levy RM, Bredesen DE, et al. Primary central nervous system lymphomas in patients with AIDS. Ann Neurol 1988; 23: S13-16.

27. Lee VW, Antonacci V, Tilak S. Intracranial Mass Lesions: Sequential Thallium and Gallium Scintigraphy in Patients with AIDS. Radiology 1999; 211: 507-512.

28. Morgello S, Petito CK, Mouradian JA. Central nervous system lymphoma in the acquired immune deficiency syndrome. Clin Neuropathol 1990; 9: 205-215.

29. Camacho DLA, Smith JK, Castillo M. Differentiation of toxoplasmosis and lymphoma in AIDS patients by using apparent diffusion coefficients. AJNR 2003; 24:633-637.

30. Kessler LS, Ruiz A, Post JD, et al. Thallium-201 Brain SPECT of Lymphoma in AIDS patients: Pitfalls and Technique Optimization. AJNR 1998; 19: 1105-1109.

31. Skiest DJ, Erdman W, Chang WE, et al. SPECT Thallium-201 Combined with Toxoplasmosis Serology for the presumptive diagnosis of Focal Central Nervous System Mass Lesions in Patients with AIDS. Journal of Infection 2000; 40: 274-281.

32. Cordoliani Y, Derosier C, Pharaboz C, et al. Primary cerebral lymphoma in patients with AIDS: MR findings in 17 cases. AJR Am J Roentgenol 1992; 159: 841-847.

33. Dismukes WE. Cryptococcal meningitis in patients with AIDS. J Infect Dis. 1988; 157: 624-628.

34. Kovoor JME, Mahadevan A, Narayan JP, et al. Cryptococcal Choroid Plexitis as a Mass Lesion: MR Imaging and Histopathologic Correlation. AJNR Am J Neuroradiol 2002; 23: 273-276.

35. Igel HJ, Bolande RP. Humeral defense mechanisms in Cryptococcosis: substances in normal human serum, saliva and CSF affecting the growth of Cryptococcus Neoformans. J. Infect Dis 1966; 116: 75.

36. Andreula CF, Burdi N, Carella A. CNS Cryptococcus in AIDS: Spectrum of MR findings. J Comput Assist Tomogr 1993; 17: 438-441.

FIGURE LEGEND

Figure 2-1. 37 year old African American male with a CD4 count of 15 who presented to the emergency department for worsening lethargy and was found to be encephalopathic. Noncontrast CT images (a, b) show volume loss more than expected for age and periventricular and deep white matter hypoattenuation predominantly involving the frontal lobes. FLAIR images (c, d) nicely demonstrate the white matter changes and absence of mass effect. There was no abnormal enhancement or restricted diffusion.

Figure 2-2. 42 year old African American female with a CD4 count of 19 who was transferred to the emergency department after witnessed tonic-clonic seizures. CSF evaluation was negative as was a JC virus test. Noncontrast CT (e, f) and FLAIR (g, h) images demonstrate atrophy and severe, diffuse white matter hypoattenuation, including involvement of the deep white matter tracts. There is no mass effect. There was no abnormal enhancement or diffusion restriction.

Figure 3. 46 year old African American male who discontinued HAART therapy four years prior who presented to the clinic with ataxia and vertigo. Noncontrast CT images demonstrate foci of low attenuation in the left middle cerebellar peduncle (a), the splenium of the corpus callosum (b), and the posterior left frontal subcortical white matter (c), without mass effect. Axial T2-weighted images (d, e, f) at the corresponding locations to the CT images demonstrate abnormal white matter hyperintensity without mass effect and the T1-weighted post contrast images (g, h, i) show no evidence of abnormal enhancement. The ventricles are mildly enlarged for age which is commonly seen with PML.

Figure 4. 18 year African American female with a CD4 count of 35 who presented with mental status change, high fevers, and 2 weeks of watery diarrhea. Noncontrast CT (a) shows a low attenuation mass centered in the left thalamus with a peripheral rim of hyperattenuation. There is surrounding low attenuation extending into the basal ganglia and deep white matter compatible with vasogenic edema. There is mass effect upon the lateral and third ventricles with mild left to right midline shift. There is also volume loss more than expected for age. The FLAIR image (b) demonstrates the mass to be hypointense (relatively isointense to white matter) and the post contrast T1-weighted image (c) demonstrates rim-enhancement with central necrosis. The diffusion weighted image (d) and corresponding apparent diffusion coefficient map (e) demonstrate characteristic diffusion restriction seen with most abscesses. While lymphoma could have this appearance, the magnetic resonance spectroscopy demonstrated normal choline levels with decreased N-acetyl aspartate levels, compatible with infection and not neoplasm. Thallium SPECT imaging was also negative. Lumbar puncture was not performed. The patient responded to toxoplasmosis therapy in addition to steroids and HAART.

Figure 5. 71 year old African American male with a CD4 count of 25 who presented with gait instability. FLAIR images demonstrate multiple mass lesions in the right middle cerebellar peduncle extending into the right cerebellar hemisphere (a), in the left insula

(b) and left thalamus (c) with surrounding hyperintensity compatible with vasogenic edema. There is mild mass effect and rightward midline shift secondary to the left thalamic lesion. There is mild parenchymal volume loss. The T1-weighted post gadolinium images corresponding to the CT images (d, e, f) show rim enhancement with central necrosis, which is common in CNS lymphoma of AIDS patients. CSF protein was elevated and glucose was normal. Empiric treatment for toxoplasmosis was unsuccessful and follow up MR imaging demonstrated two new lesions. A stereotactic biopsy confirmed CNS lymphoma and the patient was treated with steroids, radiation therapy, and subsequent intrathecal methotrexate.

Figure 6. 40 year old African American male with a CD4 count of 149 with a prior history of cryptococcal meningitis who presented with a one week history of progressively worsening fatigue and somnolence. Serum and CSF cryptococcal antigens were positive. Axial T2-weighted images (a, b) demonstrate mildly dilated Virchow-Robin spaces in the right greater than left basal ganglia. There is no mass lesion or mass effect. Axial (c), coronal (d), and sagittal (e, f) T1-weighted post-gadolinium images demonstrate multiple punctate regions of abnormal enhancement with the right greater than left basal ganglia, right caudate, and cerebellar folia, compatible with cryptococcal meningitis. There was no evidence of restricted diffusion and no ring enhancing mass lesion.