

A Correlative Study of Magnetic Resonance Imaging and Biochemical Findings of Neuroinfections in Human Immunodeficiency Virus-infected Patients

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ABSTRACT

Context: Neuroinfections are one of the most common complications in human immunodeficiency virus (HIV)-infected patients. The neurological complications arise from the HIV infection itself or from secondary opportunistic infections and neoplasm. Neurological manifestations cause significant morbidity and mortality in HIV-infected patients. **Aims:** The aims of the study were to assess the magnetic resonance imaging (MRI) features of the central nervous system infections in patients with HIV and to correlate the imaging features with biochemical markers of various neuroinfections in HIV patients to get a better diagnostic probability wherever possible. **Settings and Design:** HIV patients with suspected neuroinfections were included in the study. The CD4 count, the cerebrospinal fluid analysis reports and other serological investigations were taken. The various MRI sequences were then taken and assessed. **Materials and Methods:** All HIV-infected patients who were suspected to have neuroinfection who were referred for MRI imaging to the Department of Radio-diagnosis, Bangalore Medical College and Research Institute, from the attached hospitals were assessed. **Statistical Analysis Used:** Documented observations were compiled using SPSS-16.5 software (IBM). Univariate analysis was carried out for data interpretation. Multiple variables were assessed with Pearson's method. **Results:** In this study, majority were men with a male to female ratio of 5:1 and most falling in the age group of 20–40 years. Out of 50 patients in our study, 48 patients were proven to have some or the other neuroinfections, either purely biochemically or by considering the radiological and clinical criterion and only in 2 patients the exact diagnosis could not be made and were empirically treated with antitubercular treatment. **Conclusion:** This study tried to correlate the various neuroinfections in HIV-infected patients with their respective biochemical markers and CD4 counts. Neuroinfections are common complications in HIV-infected patients with the distribution of infection related to the CD4 count.

Key words: CD4 counts; human immunodeficiency virus; magnetic resonance imaging; neuroinfections

Introduction

According to the Joint United Nations Program on human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), an estimated 35 million people were infected with HIV infections at the end of 2014.^[1] Up to 60% of AIDS patient had neurological disease, and in the era before

the use of antiretroviral therapy, neurological disease was the first manifestation of symptomatic HIV infection in 10–20% of patients.^[2,3] Neurological manifestations cause significant morbidity and mortality in HIV-infected patients. Next to Sub-Saharan Africa, India has the second largest burden of HIV-related pathologies.^[4]

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The neurological complications arise from the HIV infection itself or from secondary opportunistic infections and neoplasm. The opportunistic infections are varied and include central nervous system (CNS) tuberculosis (TB), cryptococcal infection, and other fungal infections such as *Candida*, *Aspergillus*, CNS cytomegalovirus (CMV) infections, CNS toxoplasmosis, neurosyphilis, progressive multifocal leukoencephalopathy (PML), and bacterial intracranial infections. Those arising from the HIV itself are AIDS dementia complex.

Neoplasms includes central nervous system lymphoma

Although there is considerable overlap between the imaging characteristics of different entities, some findings are found to be very suggestive of a particular disease and imaging modalities, mainly magnetic resonance imaging (MRI) play an important role in the diagnosis and follow-up of AIDS patient.^[5] There are various biochemical and radiological tests which can be used to evaluate neuroinfections. However, the serological tests and the cerebrospinal fluid (CSF) analysis results are not helpful many a time, and even the imaging studies are not commonly diagnostic. Hence, empirical management is more often prescribed to patients.

Materials and Methods

Source of data

All HIV-infected patients suspected to have neuroinfection and referred for MRI to the Department of Radio-diagnosis, Bangalore Medical College and Research Institute, from various attached hospitals were included in the study.

Study period

The study was a prospective study conducted over 1 year from January 2015 to December 2015.

Inclusion criteria

- All adult HIV patients with suspected neuroinfections
- All pediatric and obstetric HIV patients with suspected neuroinfections.

Exclusion criteria

- All patients in whom MRI is contraindicated
- All patients who are unstable
- Nonconsenting patients
- All neurological disorders unrelated to HIV.

Methods

The subjects being assessed were serologically diagnosed as having HIV either by enzyme-linked immunosorbent assay, Western blot, or by polymerase chain reaction (PCR) where ever indicated. The CD4 counts of the patients were then taken.

After getting an informed consent for the investigation and when the patient was stable enough to undergo the

MR procedure, MRI was carried out. The routine T1, T2, fluid-attenuated inversion recovery, gradient recalled echo susceptibility-weighted imaging, and diffusion-weighted imaging sequences were taken. Contrast-enhanced MRI was done where ever possible. Magnetic resonance spectroscopy was also done wherever possible.

The lesions found on MRI were then segregated into intra-axial lesions and extra-axial lesions.

The intra- and extra-axial lesions were again divided into focal or diffuse

The focal lesions included white matter lesions, mass lesions, and others.

The diffuse abnormality included atrophy and white matter lesions.

The extra-axial lesions were divided into meningitis or collections

The MRI findings were assessed by radiologists.

The various microbiological and pathological tests were reviewed, which included:

- CSF analysis – routine, antigen and antibody assays, PCR, and others
- Serological tests – antigen and antibody assays and other markers.

Ethical Committee clearance was obtained.

Results

The results of the study are shown in Tables 1-5.

In this study, majority were men with a male to female ratio of 5:1 and most falling in the age group of 20–40 years. Out of 50 patients, 39 were between the age group of 20 and 40 years, four were between 5 and 20 years, and rest of the

Table 1: Central nervous system tuberculosis - the CD4 count, imaging findings, and biochemical markers

Biochemical markers in TB neuroinfection	MRI lesions in TB neuroinfection	CD4		
		<50	50-200	>200
CSF AFB - positive	(Ring-enhancing lesions). Tuberculomas	4	12	2
	Leptomeningitis		3	1
	Pachymeningitis		1	1
	Infarcts			1
	Hydrocephalus	1		
CSF - culture positive	(Ring enhancing lesions). Tuberculoma	1		
	Meningitis			1
	Infarct		1	
CSF - TB PCR positive	Infarct		1	

TB – Tuberculosis; CSF – Cerebrospinal fluid; PCR – Polymerase chain reaction; MRI – Magnetic resonance imaging; AFB – Acid-fast bacilli

Table 2: Central nervous system toxoplasmosis - the CD4 count, imaging findings, and biochemical markers

Biochemical markers in CNS toxoplasmosis	MRI lesions in CNS toxoplasmosis	CD4		
		<50	50-200	>200
Serum Ig+ (IgM>IgG) assay	Ring enhancing lesions		3	
	Mass lesions-multiple	2		
	Extra-axial			
CSF toxoplasmosis Ag/Ig assay positive	Multiple ring-enhancing lesions	1		
CSF - toxoplasmosis PCR positive	Mass lesion	1		

CSF – Cerebrospinal fluid; PCR – Polymerase chain reaction; MRI – Magnetic resonance imaging; CNS – Central nervous system

Table 3: Progressive multifocal leukoencephalopathy - the CD4 count, imaging findings, and biochemical markers

Biochemical markers	MRI lesions	CD4		
		<50	50-200	>200
CSF JCV + by PCR	Typical white matter changes		1	
CSF JCV – by PCR	Typical white matter changes			
CSF JCV - not done, suspected clinically and excluding others by routine CSF	Typical white matter changes	1	2	

CSF – Cerebrospinal fluid; PCR – Polymerase chain reaction; JCV – John Cunningham virus; MRI – Magnetic resonance imaging

seven patients between 40 and 60 years. None of the patients were above 65 and below 5 years. Out of 50 patients in our study, 48 patients were proven to have some or the other infections, either purely biochemically or by a considering the radiological and clinical criteria and only in two patients, the exact diagnosis could not be made and was empirically treated with antitubercular treatment.

The possible reasons for the disproportionate distribution in sex ration predominating in men could be that men had higher association with other risk factors, especially alcoholism and smoking, and had more incidence of promiscuous behavior in comparison to females.

Of the 48 patients, 29 patients, i.e., 60.4% were diagnosed to have TB, forming the bulk of the neuroinfection diagnosed. The second most common infection was toxoplasmosis, with seven patients being diagnosed with the infection, i.e., 14.6%. Other neuroinfections diagnosed in the study were PML and apparent diffusion coefficient (ADC) with four cases each, i.e., 8.3%, cryptococcosis with two patients, i.e., 4.2% and bacterial meningitis and CMV infections with one patient each.

Of the 29 patients with TB, 19 patients were seen to have tuberculomas, i.e., ring-enhancing lesions. Majority of them, i.e., 18 of them had CSF acid-fast bacilli (AFB) positive and

Table 4: AIDS dementia complex/HIV encephalopathy - the CD4 count, imaging findings, and biochemical markers

Biochemical markers	MRI lesions	CD4		
		<50	50-200	>200
CSF routine - normal	Neuroparenchymal atrophy		2	
	Nonspecific			1
CSF routine - mild abnormalities	Neuroparenchymal atrophy		1	

CSF – Cerebrospinal fluid; MRI – Magnetic resonance imaging; HIV – Human immunodeficiency virus; AIDS – Acquired immune deficiency syndrome

Table 5: Others - the CD4 count, imaging findings, and biochemical markers

Biochemical markers	MRI lesions	CD4		
		<50	50-200	>200
CSF - bacterial meningococcal	Ring-enhancing lesion			1
CMV - serology+	Nonspecific findings	1		
Cryptococcal - CSF Ag and India ink positive	Meningitis	1	1	

CSF – Cerebrospinal fluid; MRI – Magnetic resonance imaging; CMV – Cytomegalovirus

17 patients had CD4 counts between 50 and 200 cells/mm³. Six patients had meningitis either patchy or leptomeningitis. Two of the patients had infarcts secondary to vasculitis and one patient had hydrocephalus. Excluding three patients, rest of the patients had CSF-AFB positive while the remaining were diagnosed with CSF culture and TB.

The second most common infection was toxoplasmosis with seven patients, out of which five of them had CD4 counts <50, five of them had serum immunoglobulin positive, and five patients had multiple ring-enhancing lesions. The next most common infections were PML and ADC with four patients each and with typical MRI features and with CD4 counts between 50 and 200 cells/mm³.

Discussion

HIV is a neurotropic virus and enters the CNS early in the course of infection.^[6,7] Neurological manifestations are common in HIV infections. They occur in all stages of HIV infection – early or late. Opportunistic infections constitute 70–80% and the remaining 20–30% are due to direct HIV infection.^[6] The type of neurological involvement depends on the stage of immune dysfunction. Like in late stages, severe disorders such as cryptococcal meningitis, TBM, and CMV encephalitis are common.^[7] The neurological complications arise from the HIV infection itself or from secondary opportunistic infections and neoplasm.

AIDS dementia complex AIDS dementia complex is a neurodegenerative disease characterized by progressive cognitive and motor impairment and atrophic changes involving the brain. Approximately 15–20% of these patients

develop AIDS dementia complex. On MR images, a diffuse cerebral atrophy with symmetric, patchy, or confluent areas of T1 and T2 prolongation is seen within the periventricular and deep white matter. CSF analysis should exclude infectious agents other than HIV. Proton (1H) MR spectroscopy reveals decreased N-acetylaspartate and elevated peaks of in choline and myoinositol.^[8]

CNS-TB is an AIDS-defining illness, can result from reactivation of a previous infection or from a primary, newly acquired infection. Imaging features in one study, hydrocephalus was seen in 51% and meningeal enhancement in 45% of patients with CNS-TB.^[9] The hydrocephalus results primarily from obstruction of the basal cistern by inflammatory exudate. In addition, cerebral abscesses and tuberculomas may be seen.^[9] Tuberculomas occurred in 24% of patients in a study by Whiteman *et al.*^[10] The majority of tuberculomas are supratentorial and may be solitary or multiple; however, they can also be found in subdural,

epidural, and subarachnoid spaces.^[10] Tuberculomas are hypointense on T2-weighted MR images in the early stages; as they mature, they develop a hypointense center surrounded by an isointense capsule, which corresponds to solid caseation necrosis [Figures 1 and 2]. They may further progress to abscess formation with a hyperintense center. At MR spectroscopy, they demonstrate prominent lipid and lactate peaks, but no amino acid peak, unlike bacterial abscesses.^[11]

PML is a progressive demyelinating disorder that results from a viral infection of the myelin-producing oligodendrocyte, caused by John Cunningham virus. Majority of patients with PML are believed to be infected with the John Cunningham virus in childhood or early adolescence; the virus remains latent in the CNS unless reactivated in the setting of immunodeficiency. Imaging features in patients with PML, On MR images, there are typically multifocal, asymmetric areas of T1 and T2 prolongation in the periventricular and subcortical white matter [Figure 3]. In one study, 50% of the long-term survivors had enhancement of PML lesions at MRI, compared



Figure 1: T2 fluid-attenuated inversion recovery axial image showing a ring-enhancing lesion in the right frontal lobe proven to be a tuberculoma

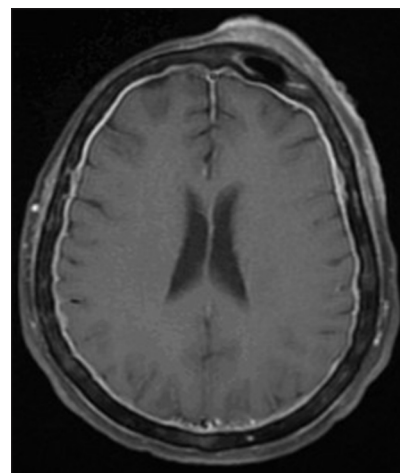


Figure 2: T1 axial image showing dual enhancement proven to be tubercular meningitis

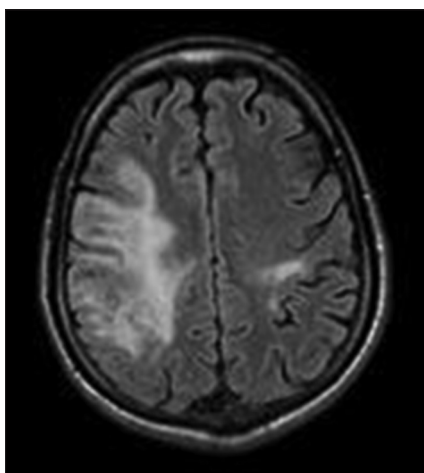


Figure 3: T2 fluid-attenuated inversion recovery axial image showing asymmetric subcortical white matter hyperintensities proven to be progressive multifocal leukoencephalopathy

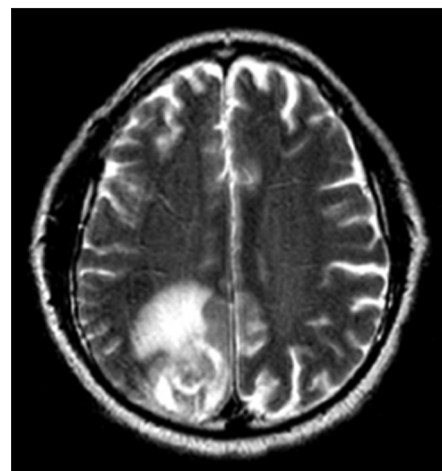


Figure 4: T2 axial image showing a heterogeneous hyperintense lesion in the right occipital lobe proven to toxoplasmosis

with only 8.9% of the short-term survivors. In these cases, the enhancement was described as faint and peripheral.^[12]

Toxoplasmosis, the most common mass lesion in patients with AIDS, is caused by the ubiquitous parasite, *Toxoplasma gondii*.^[13,14] At MRI with T2-weighted sequences, toxoplasmosis lesions are typically hypo- to iso-intense and are surrounded by high-signal-intensity vasogenic edema [Figure 4]. Hemorrhage may be seen occasionally, a finding that can help differentiate toxoplasmosis from lymphoma, which typically does not hemorrhage before treatment.^[15] Postcontrast MRI reveals multiple nodular lesions or ring-enhancing lesions, occasionally, a small eccentric nodule.

CMV is a very common herpes virus that does not produce clinical disease in most people with an intact immune system. Imaging features imaging findings of CNS involvement in patients with CMV infection are frequently nonspecific.

Cryptococcus neoformans is an encapsulated, ubiquitous yeast-like fungus found in soil contaminated by bird excreta. Infection with *C. neoformans* is the most common fungal infection of the CNS.^[16] On imaging features, the radiologic manifestations of cryptococcosis are varied and frequently minimal. The imaging findings may consist of meningoencephalitis, interventricular or intraparenchymal cryptococcomas [Figure 5], gelatinous pseudocysts, or hydrocephalus. Assays for CSF and serum cryptococcal antigen, however, are highly sensitive and specific. India ink test is performed but is less sensitive and specific.

Conclusion

Many of the HIV patients had overlapping clinical symptoms of neuroinfections, who were subjected in biochemical investigations and MRI for narrowing down the differentials. Although routine CSF was helpful in a few, many of the patients required further biochemical investigations and MRI. Many of

the MRI features overlapped which were then differentiated with the biochemical markers. In our study, 25 patients had ring enhancing lesions which were biochemically proven to have TB, toxoplasmosis, or cryptococcosis. In two of the patients in whom the MRI showed nonspecific signal intensity changes, even the initial biochemical markers were inconclusive and further, the patients were noncompliant with further investigations which was the limitation of the study.

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Conflicts of interest

There are no conflicts of interest.

References

1. World Health Organization, Joint United Nations Programme on HIV/AIDS. AIDS Epidemic Update: July 2014. Geneva, Switzerland: World Health Organization; 2014.
2. Levy RM, Bredesen DE, Rosenblum ML. Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): Experience at UCSF and review of the literature. *J Neurosurg* 1985;62:475-95.
3. de la Monte SM, Ho DD, Schooley RT, Hirsch MS, Richardson EP Jr. Subacute encephalomyelitis of AIDS and its relation to HTLV-III infection. *Neurology* 1987;37:562-9.
4. Shankar SK, Mahadevan A, Satishchandra P, Kumar RU, Yasha TC, Santosh V, et al. Neuropathology of HIV/AIDS with an overview of the Indian scene. *Indian J Med Res* 2005;121:468-88.
5. Thurnher MM, Thurnher SA, Schindler E. CNS involvement in AIDS: Spectrum of CT and MR findings. *Eur Radiol* 1997;7:1091-7.
6. Gray F, Scaravilli F, Everall I, Chretien F, An S, Boche D, et al. Neuropathology of early HIV-1 infection. *Brain Pathol* 1996;6:1-15.
7. An SF, Giometto B, Scaravilli F. HIV-1 DNA in brains in AIDS and pre-AIDS: Correlation with the stage of disease. *Ann Neurol* 1996;40:611-7.
8. Laubenberger J, Häussinger D, Bayer S, Thielemann S, Schneider B, Mundinger A, et al. HIV-related metabolic abnormalities in the brain: Depiction with proton MR spectroscopy with short echo times. *Radiology* 1996;199:805-10.
9. Villoria MF, de la Torre J, Fortea F, Munoz L, Hernandez T, Alarcón JJ. Intracranial tuberculosis in AIDS: CT and MRI findings. *Neuroradiology* 1992;34:11-4.
10. Whiteman M, Espinoza L, Post MJ, Bell MD, Falcone S. Central nervous system tuberculosis in HIV-infected patients: Clinical and radiographic findings. *AJNR Am J Neuroradiol* 1995;16:1319-27.
11. Gupta RK, Vatsal DK, Husain N, Chawla S, Prasad KN, Roy R, et al. Differentiation of tuberculous from pyogenic brain abscesses with *in vivo* proton MR spectroscopy and magnetization transfer MR imaging. *AJNR Am J Neuroradiol* 2001;22:1503-9.
12. Berger JR, Levy RM, Flomenhoft D, Dobbs M. Predictive factors for prolonged survival in acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy. *Ann Neurol* 1998;44:341-9.

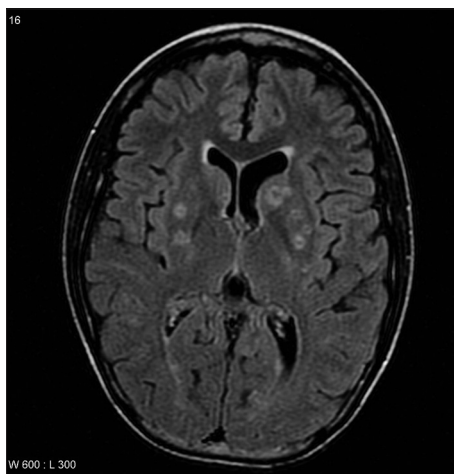


Figure 5: T2 fluid-attenuated inversion recovery axial images showing multiple ring-enhancing lesions in bilateral cerebral hemispheres proven to be cryptococcosis

13. Levy RM, Mills CM, Posin JP, Moore SG, Rosenblum ML, Bredesen DE. The efficacy and clinical impact of brain imaging in neurologically symptomatic AIDS patients: A prospective CT/MRI study. *J Acquir Immune Defic Syndr* 1990;3:461-71.
14. Cornford ME, Holden JK, Boyd MC, Berry K, Vinters HV. Neuropathology of the acquired immune deficiency syndrome (AIDS): Report of 39 autopsies from Vancouver, British Columbia. *Can J Neurol Sci* 1992;19:442-52.
15. Trenkwalder P, Trenkwalder C, Feiden W, Vogl TJ, Einhüpl KM, Lydtin H. Toxoplasmosis with early intracerebral hemorrhage in a patient with the acquired immunodeficiency syndrome. *Neurology* 1992;42:436-8.
16. Sabetta JR, Andriole VT. Cryptococcal infection of the central nervous system. *Med Clin North Am* 1985;69:333-44.

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