(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 5, Issue 4 , Page No: 791-799
July-August 2022

IJMSCR

Role of Magnetic Resonance Imaging and Spectroscopy in Evaluation of CNS Abnormalities Associated with HIV Infection

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Introduction: Human immunodeficiency virus (HIV) infections of the central nervous system can cause a variety of neurological complications, including opportunistic brain infections and neurocognitive deficits. Characterizing and distinguishing pathological changes in the central nervous system (CNS) helps proper diagnosis and treatment.

Aim of the study: Present study aimed to assess role of MRI and spectroscopy in evaluation of CNS abnormalities associated with HIV infection.

Methods: The study included 54 patients diagnosed as HIV-positive by enzyme-linked immunosorbent assay. Brain magnetic resonance imaging (MRI) and Magnetic resonance spectroscopy (MRS) of all the patients were carried out on 1.5 Tesla BRIVO MR355 whole-body scanner (GE Medical Systems, Milwaukee, WI) equipped with echo-speed gradients. Slice thickness will be 4–5 mm, with an inter-slice gap of 0.5 mm. MR spectroscopy was performed on patients in whom the lesions could not be definitively characterized using basic MRI sequences.

Results: The frontal lobe was the most commonly affected area, with tuberculosis (38.8%) accounting for the majority of cases. Bacterial abscesses showed restriction on diffusion-weighted imaging and amino acid peaks on magnetic resonance spectroscopy. Herpes encephalitis is most specifically diagnosed by MRI and DWI images help locate the pathology. MRI, especially T2W, FLAIR, and diffusion-weighted imaging sequences are more sensitive than CT, and magnetic resonance spectroscopy is useful for early diagnosis of some clinical conditions.

Conclusion: MRI can be used to distinguish and characterize various brain lesions in HIV-infected patients. Contrast-enhanced MRI provided invaluable clues in diagnosing localized lesions and detecting patterns of meningeal and lining enhancement. MRI sequences like DWI and MRS in selected cases proved to be the specific studies of choice when correlating with CSF analysis, CD4 + count, and treatment response.

Keywords: HIV infection, Magnetic resonance imaging, magnetic resonance spectroscopy, CD+4, Tuberculosis

Introduction

Human immunodeficiency virus (HIV) infection can lead to a variety of clinical symptoms. Because HIV belongs lentivirus category, it has the potential to cause chronic neurological damage in animal hosts [1]. According to current statistics of the World

Health Organization (WHO), more than 37.9 million people are currently living with human immunodeficiency virus (HIV). More than 19 million of them are being treated with antiretroviral drugs. [2] Next to Sub-Saharan Africa, India has the second highest HIV-related disease burden, mainly caused due to HIV1 Clade-C infection. [3] Movement of HIV-infected CD4+ cells across the blood-brain barrier induces infection of resident cells of the central nervous system (CNS). [4] HIV-associated CNS abnormalities can manifest primarily as lesions, infections, and cancers. These may include lymphomas, neurocognitive disorders, dementia, psychosis, neuropathy, vacuolar myelopathy, and opportunistic neuroinfections. Opportunistic infections are one of the main causes of exacerbation of HIV-infected patients with high morbidity and mortality. [5] These include toxoplasmosis, tuberculosis, cryptococcal meningitis, leukoencephalopathy, and neurosyphilis. [6]

Imaging technology plays an crucial role in guiding the accurate diagnosis and appropriate treatment of HIV-induced neurological complications. [7] Advanced techniques such as diffusion weighted imaging (DWI) and MR spectroscopy (MRS) have been used to improve sensitivity to characterize type, viability and burden disease severity and host tissue response. Furthermore, newer MR techniques, DWI and MRS provide additional insight into functional and metabolic features, further contributing to the understanding the pathophysiology of CNS infections. [8] The effects of HIV on the CNS can be well assessed by magnetic resonance imaging (MRI). MRI can favorably show the extent and depth of infection and soft tissue necrosis and is more sensitive for detecting new lesions, making it the modality of choice. It helps to understand the disease process and disease progression in a non-invasive way. [9,10]

MR spectroscopy allows non-invasive *in-vivo* quantification of normal and abnormal concentrations of metabolites in the brain. It has been shown to provide valuable complementary data to the classical MRI protocol, which helps in the differential diagnosis of intracranial cystic lesions, granulomas and encephalitis. With this background, present study was designed to assess role of MRI and spectroscopy in evaluation of CNS abnormalities associated with HIV infection.

Methods

This is a prospective observational study conducted at the Department of Radiodiagnosis, Kakatiya Medical college / MGM Hospital, Warangal, with patients referred from the Departments of General Medicine, Neurology & Neurosurgery.

Ethical approval

Ethical clearance was obtained from the institutional ethics committee, Kakatiya Medical College / MGM Hospital, Warangal, before the commencement of the study.

Participants

The study comprised of 54 patients diagnosed with HIV-positive by enzyme-linked immunosorbent assay (ELISA) referred to the Department of Radio-Diagnosis for brain MRI. Patients who fulfilled the selection criteria were informed about the nature and purpose of the study and were enrolled after obtaining written informed consent. Patients with pre-existing neurological abnormalities with HIV infection, ferromagnetic implants, claustrophobia, pacemakers, and aneurysm clips and those without any visualized MRI pathology, patients with any contraindications to using the contrast drugs, uncooperative and extremely debilitated patients were excluded from the study.

Imaging procedure

Brain MRIs of all patients were performed using a 1.5 Tesla BRIVO MR355 full-body scanner (GE Medical Systems, Milwaukee, WI) equipped with an echo velocity gradient. The thickness of the slices of 4-5 mm, with a distance between the slices of 0.5 mm. Magnetic resonance spectroscopy (MRS) was performed in patients whose lesions could not be clearly identified radiologically using only MRI sequences. If brain MRI shows no lesions, MRI spectroscopy was performed to preserve the voxel in the right frontal lobe.

MRI was performed using a 4-channel head coil, performed a local triaxial single-section scan, followed by Axial T1 (TR 468, TE I), Axial T2 (TR 4500, TE 111), sagittal T2 (TR 4000 TE 110), Coronal T2 (TR 4500, TE). 124), Axial TOUCH (TR 9500 TE 102), Axial DWI (TR 3500, TE117). Axial GRE (TR 779, TE 25) was performed for some patients with hemorrhage and toxoplasmosis.

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Single/multi-voxel MRI spectral sequences were acquired. The radiographic features of the lesions were analyzed and described along with appropriate clinical pathological findings. Magnetic resonance spectroscopy sequences and sensitivity weighted images of the brain were collected as needed. Collected data are expressed as percentages according to suitability.

Results

In the present study, the majority of the study subjects (19) were in the age group between 35-44 years with male predominance (74%) as compared to females (26%). CD4 count was less than 100 in 21 patients. (Table 1) The incidences of various intracranial pathologies in HIV+ patients were represented in Table 2. Results revealed that majority of the patients developed tuberculosis in 21 patients, followed by the toxoplasmosis in 8 patients. Fever is the most common presenting symptoms and was observed in 40 patients followed by headache & seizure in 23 patients each, bilateral involvement in 15, and right-side involvement in 14 patients (Table 3). Among 54 patients, lesions were distributed mainly in the frontal region (31 patients) followed by basal ganglia (18 patients). Ring enhancement pattern was predominant on post-contrast MRI observed in 25 patients (Table 4). Out of 21 cases, 15 were tuberculomas, 3 were CNS miliary tuberculosis, and 3 were TB abscesses. 14 out of 15 cases of tuberculoma were hypointense on T1WI, 1 case was hyperintense on T1WI, and 15 out of 15 cases had hyperintense on T2WI & FLAIR. Of the 15 cases, 3 had central restriction, 7 had peripheral restriction on DWI and 5 cases had no restriction on DWI. 3 cases of tuberculous abscess were hypointense of T1WI, 3 out of 3 cases were hyperintense on T2WI & FLAIR, and all of them had restriction on DWI. 3 out of 3 tuberculous abscesses showed lipid choline peak in MRS. All 3 abscesses showed central restriction on DWI. In this study, 3 cases of CNS Miliary TB were hypointense of T1WI, 3 out of 3 cases were hyperintense on T2WI & FLAIR, 2 had peripheral restriction on DWI, and 1 showed central restriction (Table 5). Out of the 54 cases, only 1 had a bacterial abscess. The abscess was hyperintense on and was associated with the characteristics of otomastoiditis. Definitive MRS results included amino acid peaks in bacterial abscesses and lipid-lactic acid peaks in tuberculous abscesses without choline peaks (Table 6).

Table 1: Distribution of age, gender, and CD4+ count in affected patients

Distribution of age among patients		
Age group	No of patients	
<15	1	
15 – 24	6	
25 - 34	16	
35 – 44	19	
45 – 54	9	
55 – 64	3	
Distribution of gender among patients		
Gender	No. of patients	Frequency (%)
Male	40	73.08
Female	14	25.92
CD4+ count in affected patients		
0-100	21	

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101-200	15
201-300	7
301-400	5
>400	6

Table 2: Incidence of various intracranial pathologies in HIV+ patients

Disease	No. of patients
Tuberculosis	21
Toxoplasmosis	8
Venous hemorrhagic infarct due to CSVT	4
HIVE	3
Arterial infarct	3
PML	2
Primary CNS Lymphoma	2
Non-Specific Hyperintensity	5
Bacterial Abscess	1
HSV	1
7^{th} nerve Palsy	1
GBS with focal demyelination	1
Normal Study	2

Table 3: Clinical features and side distribution among patients

Clinical feature	No. of patient
Seizure	23
Hemiparesis	16
Headache	23
Vomiting	8
Altered Sensorium	16
Fever	40
Involuntary Movements	3
Visual Symptoms	6
Aphasia	3
Side	No. of patients
Right	14

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Left	7
Bilateral	15
Midline	5
Diffuse	10
Facial nerve	1

Table 4: Regional distribution and contrast enhancement of pattern on MRI among patients

Regional distribution of lesions among patients	
Region	**No. of patients**
Frontal	**31**
Parietal	**29**
Temporal	**16**
Occipital	**10**
Corpus callosum	**5**
Periventricular	**4**
Basak ganglia	**18**
Thalamus	**6**
Brainstem	**8**
Cerebellum	**14**
Facial nerve	**1**
Contrast enhancement pattern of lesions among patients on MRI	
Pattern	**No of patients**
Ring	**25**
Nodular	**7**
Meningeal	**4**
Ependymal	**0**
7th nerve	**1**

Table 5: Morphology of tuberculomas, tuberculous abscess on MRI

Morphology of tuberculomas on MRI						
Morphology	**T1WI**	**T2WI**	**FLAIR**	**DWI**		
				Central	**Peripheral**	**Absent**
Hyperintense	**1**	**15**	**15**	**3**	**7**	**5**

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Hypointense	**14**	**0**	**0**	**-**
Morphology of tuberculous abscess on MRI				
Morphology	**T1WI**	**T2WI**	**FLAIR**	**DWI**
Hyperintense	**0**	**3**	**3**	**3**
Hypointense	**3**	**0**	**0**	**0**
Imaging sequence		**Present**		**Absent**
MRS showing Lipid choline+		**3**		**0**
DWI Showing restriction		**3**		**0**
Morphology of CNS miliary TB on MRI				
Morphology	**T1WI**	**T2WI**	**FLAIR**	**DWI**
				Central / **Peripheral**
Hyperintense	**0**	**3**	**3**	**1** / **2**
Hypointense	**3**	**0**	**0**	**-** / **-**

Table 6: Morphology on MRI and comparative evaluation of bacterial and tuberculous

Morphology on MRI				
No. of lesions	Part	T1W	T2W	FLAIR
1	Rim	Isointense Rim	Hypointense Rim	Hypointense Rim
	Centre	Hypointense Centre	Hyperintense Centre	Hyperintense Centre
Comparative evaluation of bacterial and tuberculous				
Abscess		Bacterial abscess		Tuberculous abscess
No. of patients		1		3
Ring Enhancement		1		3
Restriction of DWI		1		3
Conclusive MRS findings*		1		2

Discussion

This is a prospective study of 54 HIV seropositive patients with neurological symptoms referred from various clinical departments at Mahatma Gandhi Memorial Hospital / Kakatiya Medical College for MRI to identify and characterize brain lesions. Diagnosis is based on MRI and MRS findings which were correlated with clinical response to treatment and cerebrospinal fluid (CSF) analysis, with the exception of progressive multifocal leukoencephalopathy.

In our study, 8 out of 21 (38%) showed enhancement of localized lesions and 13 (62%) cases showed enhancement of multiple lesions. 4 (19%) of them showed meningeal / cisterna magna enlargement and 2 (9.5%) showed hydrocephalus. The majority of the patients are in the age group of 35-44 years, and men are mainly affected. Most patients presented with fever, followed by headaches and seizures. Lobar predilection affecting the frontal lobe in 57.40% of cases, followed by the parietal lobe (53.7%).

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Infectious lesions accounted for the majority of cases in our study.

In a study conducted by Morales et al reported that in 13 patients with intracranial tuberculosis, 69% (9/13) indicated peak at 3.8 ppm and 77% (10/13) of peak at 0.9-1.3 ppm. [11] In this study, 71.42% (15/21) of the patients, at 3.3 ppm and 0.9-1.3 ppm respectively. In a study reported by Berenguer et al revealed that in 26 patients with tuberculosis, 23% show meningeal enhancement, which is comparable to current study findings. [12] A study by Whiteman et al delineated that out of 25 patients with tuberculosis, 32% showed hydrocephalus and 44% showed increased parenchymal lesions. [13] In our study, 9.5% had cases of hydrocephalus and 81% showed an increase in parenchymal lesions. In the study carried out by Hussein et al revealed that out of 25 cases of abscess, 16 were reported to be bacterial and 4 were reported to be tuberculous. Of the 16 bacterial abscesses, 15 cases and out of 4 tuberculous abscesses, 3 showed definitive MRS findings. [14] The current study findings are comparable to that of Husain et al findings with the exception of three studies of tuberculous abscess, two showing DWI restriction and three showing conclusive MRS findings. [14]

In a study by Post et al. twenty-two patients showed lesions on MRI and is comparable to the present study [15]. McConnell JR et al. showed clear MRS finding in 10 patients, and is in accordance with our study results. [16] Gilliams et al. reported 13 out of 71 patients had infarcts, 2 of whom were single, 6 of whom were multiple, and 5 of whom were due to opportunistic infections. Multiple lesions are most likely due to vasculitis. [17] Our study showed opportunistic infection-related infarcts comparable to Gillams et al. study. Four patients with hemorrhagic venous infarction with CSVT were presented. All 4 patients were newly proven to be HIV seropositive and were not taking medication. In research study conducted by Sibtain et al revealed toxoplasmosis with features of bleeding, extensive edema, hyperintensity on MRI, with thin ring enhancement, no meningeal / lining enhancement, lipid-lactate peak and choline decrease, NAA decrease on MRS, appeared as multiple lesions, in contrast to primary CNS lymphoma. It manifests as a single lesion less affected by bleeding, edema, and mass, showing hyperintensity on MRI and unstable enhancement on MRS with elevated choline and decreased NAA. [18] The present study findings were comparable to Sibtain et al and was therefore diagnosed with toxoplasmosis. In a study conducted by Bhagavati et al 7 out of 11 patients had haemorrhages, and, in our study, 1 out of 8 patients had haemorrhages. [19]

One case of herpes encephalitis was reported; MRI showed B/L asymmetrical T2 FLAIR hyperintensities showing restriction on DWI, no blooming on GRE was noted in the temporal lobe (hippocampus and uncus), frontal lobe and insular cortex was observed in our study. Chaiklang et al. published a case study in which the initial CT was normal in a case of Herpes encephalitis, but MRI after 1 week helped in the diagnosis. [20] The MRI findings were comparable to the present study. Kannangai R et al, reported 10 cases of opportunistic viral encephalitis, out of which 1 was Herpes encephalitis. [21] However, in the present study, only 3 opportunistic viral infections were encountered due to the prevalence of bacterial infections. Out of 3 viral infections, one was HSV. Sibtain et al reported the classical imaging findings in the diagnosis of Herpes encephalitis, which was correlated with CSF, PCE for HSV, and these studies findings are comparable with our study findings. [22,23]

David Simpson et al examined 65 HIV+ patients with progressive multifocal leucoencephalopathy (PML) and described the imaging findings. [22] Sibtain et al summarized differentiation criteria between PML & HIVE. The present study was comparable to studies reported in the literature in terms of radiological features, and hence a diagnosis of PML was made. [23] In our study, two cases of PML were reported based on classical MR findings. Out of 21 cases of tuberculosis, 7 out of 15 tuberculomas showed ring enhancement, 4 showed mixed nodular, and ring enhancement and 4 showed no enhancement in our study. All CNS Miliary Tuberculosis cases (3) showed mixed nodular and ring enhancement. All tuberculous abscesses (3) showed ring enhancement. Out of 21 cases of tuberculosis, 4 cases showed meningeal enhancement on MRI. Three patients presented with arterial infarcts and 4 patients presented with haemorrhagic venous infarcts with CSVT. All four patients proved to be HIV sera positive denovo and were not on medication.

In our study, 2 cases of Primary CNS lymphoma were reported based on classical MRI findings. In the

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Chinn RJ et al. study, 9 patients showed lesions on MRI, and 3 patients showed conclusive MRS findings, which is comparable to the present study. [24] In our study, 1 patient presented with right 7th nerve palsy. The patient was identified as HIV seropositive by de novo and was not taking any medication. MRI showed thickening of the cisternal and canalicular segments of the right facial nerve, showing a slight increase on contrast. There are no studies available comparing the incidence of Herpes zoster oticus in HIV and non-HIV sera-positive patients. Four out of 5 patients had complicated headaches, fever, and impaired consciousness, 1 patient showed seizures and dementia and one patient was newly diagnosed with HIV. Other patients were on irregular treatment. MRI showed nonspecific T2/FLAIR hyperintensity predominantly in frontoparietal lobes.

One case showed DWI-restricted T2 / Flair hyperintensity in the splenium of corpus callosum (CLOCCS). There are no studies comparing the incidence of shingles in HIV and non-HIV sera-positive patients. One patient in our study showed numbness in the legs and arms, gait disturbance, and enteritis. MRI showed T1 isointense, T2 / FLAIR hyperintensity focus on the frontal parietal white matter without DWI restriction. Albumin cytological dissociation was measured by cerebrospinal fluid (CSF) analysis and the patient was diagnosed with GBS. No studies are available comparing the incidence of Guillain-Barré syndrome in HIV serum-positive patients. 8 patients were diagnosed with intracranial toxoplasmosis. 1 out of 8 patients had haemorrhages.

Conclusion

HIV has distinct clinical symptoms with clear overlap. Most important are CD4 counts and CSF analysis. Along with them, imaging findings help narrow down the differential diagnosis. MRI provides very detailed anatomical information and, given its excellent specificity, is central to the diagnosis of HIV-related brain lesions. Contrast-enhanced MRI provided invaluable clues in diagnosing localized lesions and detecting patterns of meningeal and lining enhancement. DWI and MRS provide additional information about the type of lesion and improve the accuracy of the diagnosis. We conclude that even though CT can be used as best screening tool, MRI along with DWI and MRS, when correlated with CSF analysis, CD4+ count, and treatment response have proven to be the particular study of choice in the selected cases.

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