Neurological manifestations in people living with Human Immunodeficiency Virus (PLHIV) in Central India with special reference to Neuroimaging: An initial experience

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Abstract:
AIDS is primarily an immune system disorder caused by the human immunodeficiency virus (HIV) which can affect the nervous system. HIV does not directly invade nerve cells but it jeopardizes their function resulting in behavioral abnormalities, headaches, progressive weakness, motor as well as sensory impairment and damage to the peripheral nerves. With the advent of Magnetic resonance imaging and Computed tomography, it has become possible to differentiate most of these disease entities and accordingly the management of the patient. The present study was carried out to correlate neuro-imaging and immune status of patients. It was a cross-sectional study done in diagnosed cases of HIV infection referred for neuroimaging. Total of twenty patients of Neuro-AIDS were underwent neuroimaging i.e. Computed Tomography or Magnetic Resonance Imaging and were categorized in a particular HIV related Neurological disorder. Out of these the commonest neurological disorder was neuropsychiatric followed by cryptococcus meningitis, infarcts, progressive multifocal leukoencephalopathy, viral encephalitis, cerebral atrophy, myelitis, toxoplasmosis, tuberculoma, Pott's spine, and hydrocephalous. Neurological manifestations were also correlated with the Immune status and categorized in four categories. Imaging findings of most of the neurological disorders diagnosed on clinical and laboratory basis were then correlated with neuroimaging. Neuroimaging is important in diagnosing HIV patients presenting with neurological symptoms. Together with CD4 count and clinical manifestations neuroimaging helps in categorizing the HIV patients and planning the treatment.

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Introduction

AIDS (Acquired immuno-deficiency syndrome) is a condition that occurs inmost advanced stages of Human immunodeficiency virus(HIV) infection. Although AIDS is primarily an immune disorder, it also affects the nervous system and can lead to wide range of severe neurological disorders.Among the most common neurological complications are: AIDS dementia complex causing symptoms such as encephalitis, behavioral changes, and a gradual decline in cognitive function; central nervous system lymphomas, cancerous tumors, cryptococcal meningitis; cytomegalovirus infections; herpes virus infections; neuropathy; neurosyphilis; progressive multifocal leukoencepha-lopathy (PML); and psychological and neuropsychiatric disorders(1). Neurological complication among AIDS patient is called as neuro-AIDS. As per current estimate, more than 35 million people in the world have been infected by AIDS (2). Approximately 40%-90% of patients with AIDS will developneurological manifestations during the course of their illnesses (3-5). As a consequence, neuro-imaging has come to play an important role in the diagnosis and treatment of AIDS. Patients with AIDS develop a variety of CNS lesions and the diagnosis of these lesions may require the application of several imaging techniques including Computed tomography and Magnetic resonance imaging (6).

As the sensitivity of Magnetic Resonance Imaging is superior to that of Computed Tomography and MRI allows acquisition of images in multiple planes, it has become the "gold standard" in neuro-imaging. In the differential diagnosis of brain diseases in patients with AIDS, some generalizations about the imaging appearance of CNS lesions are helpful because the clinical presentation of these lesions are often more dependent on their anatomic location than on their aetiology.

The disorders seen in Neuro AIDS are AIDS dementia complex (ADC)-HIV associated dementia (HAD) and HIV associated neuro-cognitivedisorder(HAND), lymphoma, cryptococcal meningitis, cytomegalovirus

(CMV) infection, herpes virus infection, polyneuropathy, progressive multifocal leukoencephalopathy(PML), psychological and neuropsychiatric disorders, toxoplasma encephalitis, vascular myelopathy. The clinical manifestations of CNS disease in patients with AIDS are based on neurological examination and neuro-imaging studies. Further examination such as standard analysis of cerebrospinal fluid may be useful.

Materials and Method

For the purpose of this study, cases with neurological complication of HIV were selected.The subjects were selected from patients who came to our tertiary care center for treatment.Total numbers of patients were 20. Patients of either sex were included in the study irrespective of their age.

Inclusion criteria: Patients with HIV, diagnosed by NACO criteria and reported to our tertiary care center with neuro-AIDS irrespective of whether they were receiving anti-retroviral treatment (ART) or not.

Exclusion criteria: Cases without neurological sign and symptoms.

Patients were subjected to neuroimaging after acquiring permission from Institutional Ethical Committee. Clinical examination was performed as per the proforma. In neuroimaging following imaging protocols were considered:

1. Computerized tomography (CT):
   - NECT-non enhanced computerizes tomography
   - CECT-contract enhanced computerized tomography
2. Magnetic resonance imaging (MRI):
   1. Routine brain sequences-
      - Axial T1 weighted images
      - Axial T2 weighted images
      - Axial T2 FLAIR
      - Saggital T2weighted images
      - Diffusion weighted images(DWI)
      - Post contrast T1 weighted images
   2. Non contrast and contrast MRAngiography
   3. Special brain sequences(if required)-
      - Magnetic resonance spectroscopy(MRS)
      - Susceptibility weighed imaging(SWI)
      - Diffuse tensor imaging(DTI)

MRI was performed in all the patients. In patients where MRI was contraindicated, CT was done.An informed consent was taken from every patient and patient information sheet were explained to the patient in their vernacular language. Data was analyzed using appropriate statistical tools i.e. Epi.info 7 and Microsoft Excel. Frequencies and percentage were computed for the information and was gathered in a tabular form.

Result

A total of 20 cases were studied during the period of 2 months. The distribution of cases is depicted in Table 1 and 2.

Table 1: Distribution of cases

Age group	Frequency
0-14	0
15-29	4
30-49	10
50 and above	6
Total	20

Table 2: Gender wise distribution of cases

Gender	Frequency
Male	13
Female	7
Total	20

Neurological manifestations:

Of these, 20% cases had presented with EFV and neuropsychiatric disorders.15% had presented with cryptococcus meningitis.10% cases had presented with cerebral artery infarcts and PML and viral encephalitis and pneumocystiscarinii pneumonia, cerebral atrophy, myelitis, toxoplasmosis, tuberculoma, Pott's spine with myelopathy, hydrocephalous, cerebral atrophy and infarcts; constituted 5% cases each.5% cases had no neurological manifestation associated with HIV (Table 3).

Table 3: Neurological manifestations

Neurological disorder	Frequency (Number of cases)
EFV and neuropsychiatric disorder	20%(4)
Cryptococcus meningitis	15%(3)
Cerebral artery infarcts	10%(2)
PML	10%(2)
Viral encephalitis	5%(1)
Cerebral atrophy	5%(1)
Myelitis	5%(1)
Toxoplasmosis	5%(1)
Cerebral atrophy and infarct	5%(1)
Tuberculoma	5%(1)
Pott's spine	5%(1)
Hydrocephalous	5%(1)
No manifestation	5%(1)
Total	100%

Neurological manifestations and immune status (CD-4 count):

20 patients were categorized into 4 groups depending on their immune status/CD 4 count i.e.

i. Category 1-----<50.
ii. Category 2-----<200.
iii. Category 3----200-500.
iv. Category4 ---.>500.

In category 1, 42.86% cases were suffering from Cryptococcal meningitis, 14.29% with myelitis, 14.29% with PML, 14.29% with viral encephalitis and 14.29% had no neurological manifestations. All these patients had CD4 count less than 50.In category 2, 37.50% cases were suffering from EFV and neuropsychiatric disorders, 12.50% with tuberculoma, hydrocephalous, PML and cerebral atrophy, cerebral atrophy and infarcts each. These patients had CD4 count less than 200.
In category 3, 66.67% cases were suffering from cerebral infarcts, 50% with EFV and neuropsychiatric disorders and toxoplasmosis each and the 33.33% with Pott'sspine. These patients had their CD4 count 200-500.In category 4, no manifestation were seen (Fig. 1-3).

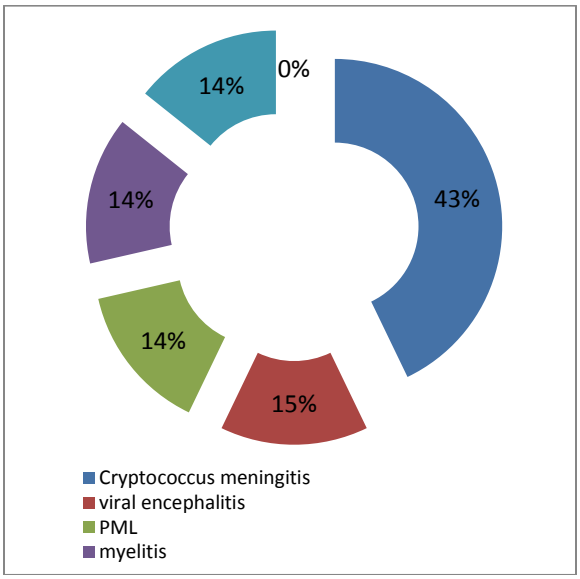

Fig. 1: Neurological manifestations in CD4 count/microliter less than 50

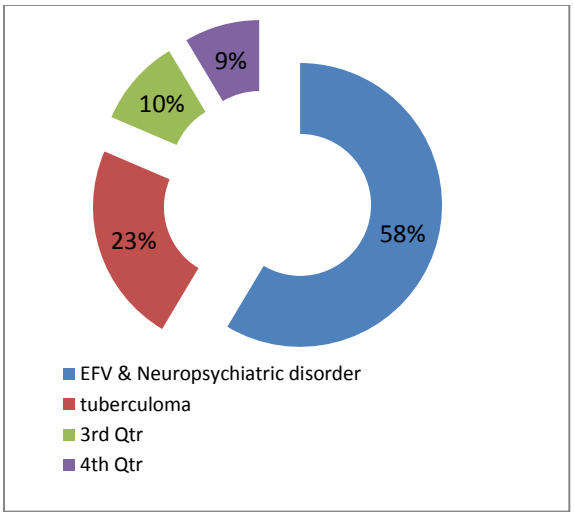

Fig. 2: Neurological manifestations in CD4 count/microliter less than 200

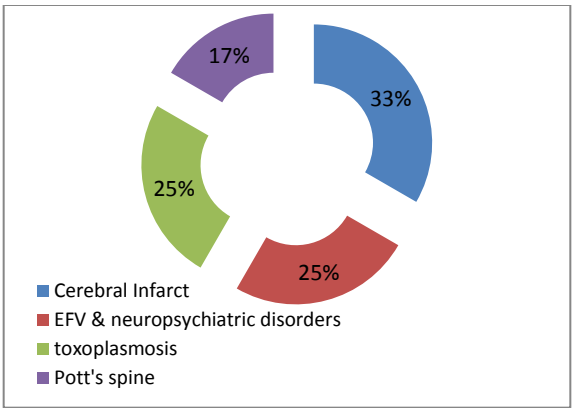

Fig. 3: Neurological manifestations in CD4 count/microliter 200-500

Imaging findings CT/MRI (Table 4):

Table 4: Imaging findings CT/MRI

Disease entity	Imaging findings CT/MRI
Viral encephalitis (one patient)	Hyperintensities scattered or confluent areas on T2WI and isointense or hypointense on T1WI with restriction on DWI.
PML (two patients)	bilateral, asymmetric multifocal areas of T2 hyperintensities, One has left cerebellar involvement with cerebellar atrophy and other has bilateral periventricular demyelinating changes.
Tuberculoma (one patient)	On T2-weighted images, ill definedhyperintense lesion with perilesional oedema and on post contrast study shows peripheral rim enhancement.
Toxoplasmosis (one patient)	The "target" sign is demonstrated when lesions are hypointense or isointense to parenchyma and are surrounded by vasogenic edema and on post contrast shows a ring or nodular enhancement.
Cryptococcus meningitis (three patients)	Multifocal basal ganglia and mid brain hyperintensities on T2 weighted images suggestive of cryptococcoma and dilated perivascular spaces
Pott'sspine (one patient)	Large epidural component compressing the spinal cord
Diffuse cerebral atrophy (four patients)	Dilated ventricles and sulcal spaces.
Hydrocephalous (Three patients)	Enlargement of the ventricular system out of proportion to the subarachnoid space, a prominent periventricular halo and a prominent CSF flow void in the cerebral aqueduct. We got one patient with communicating hydrocephalous.
Infarct (two patients)	A large left middle cerebral artery infarct is seen.

Discussion

AIDS can be defined as clinical diagnosis (presumptive or definitive) of any stage 4 conditions with confirmed HIV infection or immunological diagnosis with confirmed HIV infection and CD4 count < 350/micro liter regardless of presence of symptoms. Stage 4 conditions include HIV wasting syndrome, pneumocystis pneumonia, recurrent severe bacterial infections, chronic herpes simplex infections, oesophageal candidiasis, extra-pulmonary tuberculosis, Kaposi's sarcoma, CMV infection, CNS toxoplasmosis, HIV encephalopathy, Extra pulmonary cryptococcosis including meningitis, Disseminated non-Tuberculous mycobacterial infection, PML, chronic cryptosporidiosis, chronic isosporiasis, disseminated mycosis, recurrent non-typhoidal salmonella bacteraemia, lymphoma, invasive cervical carcinoma, atypical disseminated leishmaniasis(7).

Soon after exposure, HIV, a neurotropic organism enters the CNS. Serologic tests have demonstrated HIV positivity in 73% of adults and children with AIDS. HIV causes neuronal injury leading to cognitive impairment. In the absence of superimposed opportunistic infection or neoplasm, the neurologic manifestations of HIV infection, include encephalopathy, myelopathy and peripheral neuropathy. MR imaging is more sensitive and specific than CT in depicting and diagnosing neurological conditions in HIV-positive individuals. In most of the situations MRI without contrast is able to demonstrate the underlying disease process which is not a case with CT. Moreover, CT as it uses the ionizing radiation is contraindicated in pregnant women. A special sequence in MRI that is spectroscopy is a supportive in most of the instances. However for calcification CT is preferred over MRI (8).

Viral encephalitis:

On MRI, the pathologic changes resulting from viral encephalitis appear as hyper intensities scattered or confluent areas on T2-weighted images and are isointense or hypointense on T1-weighted images, with variable mass effect. On both T1- and T2-weighted images foci of sub acute hemorrhage (extracellular met hemoglobin) demonstrate increased signal intensity. Contrast enhancement may or may not be present. Diffusion-weighted imaging characteristically shows patchy restricted diffusion. In our study 1 patient shows clinical features of viral encephalitis and the above mentioned imaging features are seen in our patient (Fig. 4).On follow-up, although these general features apply to most of the viral encephalitides, certain infections demonstrate particular features that may be characteristic and are thus helpful in the differential diagnosis(9).

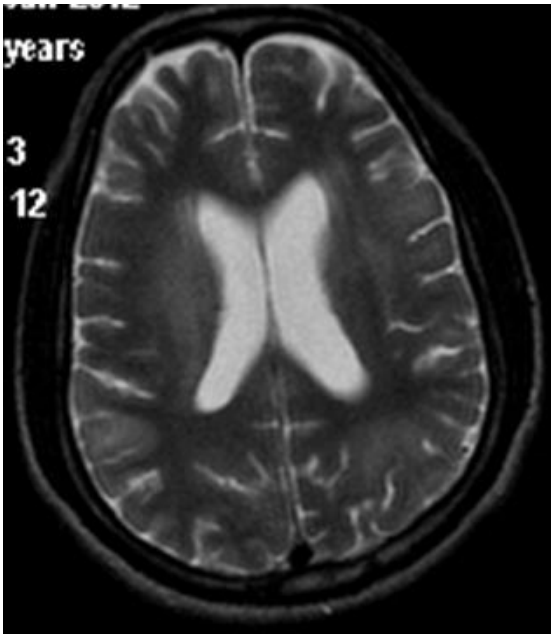

Fig. 4: Axial T2 weighted images shows periventricular hyper intense areas

Progressive multifocalLeukoencephalopathy (PML):

On MRI, PML appears hypointense on T1-weighted images and hyperintense on T2-weighted images. Sites of involvement are periventricular and subcortical white matter. The distribution of the lesions may be bilateral, asymmetric and multifocal. Enhancement is seen in 10% of the patients with PML suggestive of intense inflammatory reaction. In our study two patients were diagnosed as PML. One has left cerebellar involvement with cerebellar atrophy and other has bilateral periventricular demyelinating changes (Fig. 5(a) and (b)). In an untreated AIDS patient with PML, it has been suggested that mass effect, increased atrophy, confluence of lesions, and increased hypointensity on follow-up T1-weighted MR studies can be regarded as indicators of a poor prognosis. However, in a recent report, only the mass effect was related to predicting the risk of death in patients with PML. Frontal and occipital locations are usually involved however any lobe may be affected by PML. In HIV-infected patients the parietal lobe is most commonly involved by PML thus, the lesion location correlates well with the symptoms of homonymous hemianopsia, focal neurologic deficit, and altered mentation(10).

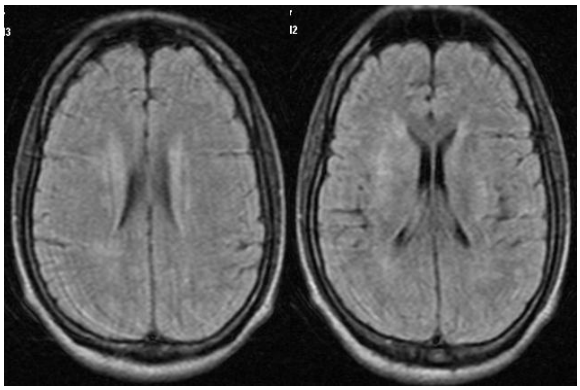

Fig. 5(a) & (b): FLAIR axial images showing bilateral periventricular hyperintensities s/o demyelination

Tuberculoma:
10% to 34% patients of parenchymal tuberculoma have multiple lesions. These appear as circumscribed areas of low attenuation that demonstrate a small post contrast ring enhancement. One third patients may display the "target sign". IT appears as a central calcification or punctate enhancement surrounded by a region of hypodensity with surrounding rim enhancement. This sign is suggestive of TB, but it is not pathognomonic. On Non-contrast MR Studies, non-caseating granuloma appearshypointense on T1-weighted images and hyperintense on T2-weighted images to brain parenchyma. A caseating granuloma is hypointense to isointense to gray matter on T1-weighted images and may have a slightly hyperintense rim .On T2-weighted images, caseoustuberculoma are often isointense or hypointense to brain parenchyma, and it is postulated that this relative hypointensity is related to T2 shortening by paramagnetic free radicals produced by macrophages heterogeneously distributed throughout the caseous granuloma. Alternatively, the diminished signal on T2-weighted images may be attributed to the mature tuberculoma being of greater cellular density than the brain. Granulomas may also be hyperintense to brain on T2-weighted images, and this is likely due to a greater degree of central liquefactive necrosis in these lesions.There is usually an associated mass effect. Surrounding oedema may be minimal in small lesions, and there is generally less oedema than that surrounding a pyogenic abscess of comparable size, based on CT studies. Oedema surrounding the tuberculoma is relatively more prominent in the early stages of granuloma formation. Diffusion-weighted images may reveal hyperintense signal intensity within the tuberculoma(11). In our seriesone patient had tuberculoma showing characteristic MR imaging features (Fig. 6).

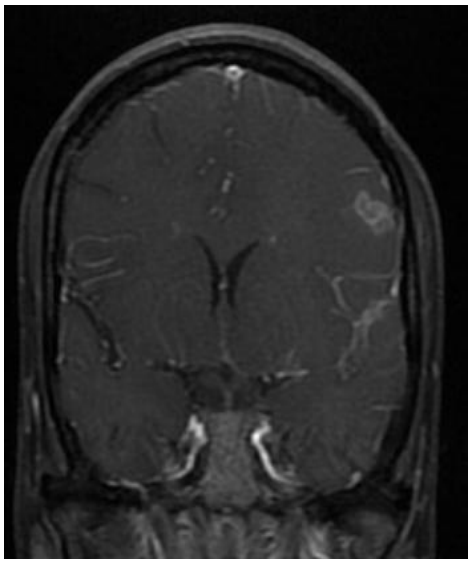

Fig. 6: Post contrast T1 coronal image shows ring enhancing conglomerated lesion in left fronto-parietal region

Toxoplasmosis:
Toxoplasma encephalitis lesions are better demonstrated by MR imaging with and without enhancement. The "target" sign is demonstrated when lesions are hypointense or isointense to parenchyma and are surrounded by vasogenic edema. Sometimes hemorrhage within these lesions is also seen .After post gadolinium injection, Lesions are isointense to hypointense on Noncontrast T1-weighted images, indicating a ring or nodular enhancement in active lesions (12).In our study one patient with Toxoplasma showing characteristic clinical feature was encountered.

Cryptococcus meningitis:
It is a fungal infection seen in HIV and involves CNS by hematogenous spread, cryptococcosis causes meningitis dilated perivascular spaces and cryptococcoma. On imaging the common finding is multifocal basal ganglia and mid brain hyperintensities on T2 weighted images suggestive of cryptococcoma and dilated perivascular spaces. In our study three patients with Cryptococcal meningitis were encountered showing characteristic imaging finding(13).

EFV and neuropsychiatric disorders:
A maximum of 20% cases showed signs of EFV and neuropsychiatric disorders.

Pott's spine:
One patient with imaging finding suggestive of Pott's spine is seen in our study with large epidural component compressing the spinal cord.

Diffuse cerebral atrophy:
In our study we got 4 patients of diffuse cerebral atrophy are seen, out of which two are less than 50years of age and two are more than 50(Fig.7).

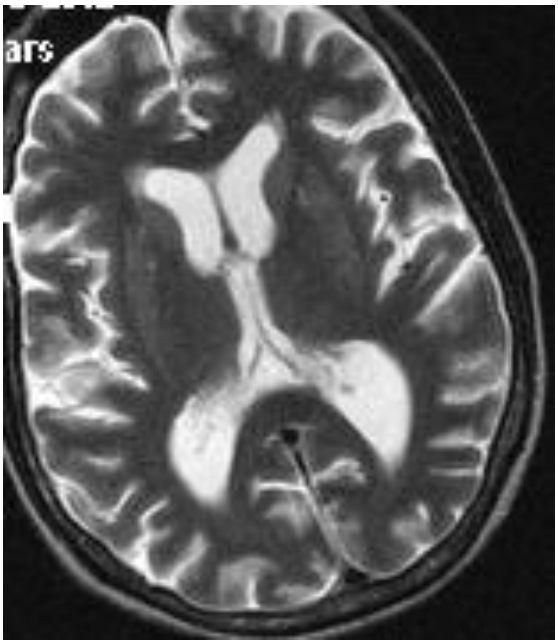

Fig. 7: Axial T2 image is showing dilated lateral ventricles and prominent sulcal spaces

Hydrocephalous:
Three primary MRI findings have been described in hydrocephalous: (a) enlargement of the ventricular system out of proportion to the subarachnoid space, (b) a prominent periventricular halo, (c) and a prominent CSF flow void in the cerebral aqueduct (13). We got one patient with communicating hydrocephalous.

Infarct:
Small vessel ischemic lesions are seen in two patients in our study. A large left middle cerebral artery infarct is seen in one patient. This may be secondary to vasculitis in HIV positive patients.

Conclusion
Neuroimaging plays pivotal role in establishing the diagnosis in a HIV positive patient presenting with neurological manifestations. MRI because of its excellent soft tissue resolution and multiplanner imaging is the modality of choice in these patients. Correlation with clinical and laboratory findings (especially CD4 count) along with neuroimaging help in diagnosing the particular disease entity in HIV positive patients. Most of the time, MRI will not demonstrate any abnormality in the early stages of infection. The main stay of doing MR imaging in these patients is to determine the extentof disease process and response to treatment.

References:

1. Power C. Neuro AIDS: An evolving epidemic. J Neurosci 2009; 36:285-95.
2. Comford ME. Neuropathology of the acquired immune deficiency syndrome (AIDS): Report of 39 autopsies from Vancouver, British Columbia. Can J Neurol Sci 1992; 19:442-52.
3. Anders KH. The neuropathology of AIDS: UCLA experience and review. Am J Pathol 1986 124:537-57.
4. Levy RM. Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): Experience at UCSF and review of the literature. J Neurosurg 1985; 62:475-95.
5. Levy RM. 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.
6. Scott WAtlas. Intracranial infection. In: Atlas, Scott W.MagneticResonance Imagingof the brain and spine. 4th ed. Philadelphia: Lippincott Williams& Wilkins 2009; 942-3.
7. MathewK George, AggarwalPraveen.Immunological factors in diseases. In: Shabina Nasim, Richashrivastava. Medicineprep manual for undergraduates. 4th ed.New Delhi, Gurgaon: ELSEVIER; 2012: 223.
8. Scott WAtlas. Viral Infection. In: Atlas, Scott W.MagneticResonance Imagingof the Brain and spine. 4th ed. Philadelphia: Lippincott Williams& Wilkins 2009; p930.
9. Scott WAtlas. Progressive multifocalleukoencephalo-pathy. In: Atlas, Scott W.MagneticResonance Imagingof the Brain and spine. 4th ed. Philadelphia: Lippincott Williams & Wilkins 2009; p950.
10. Scott WAtlas. Mycobacterium Tuberculosis. In: Atlas, Scott W.MagneticResonance Imagingof the Brain and spine. 4th ed. Philadelphia: Lippincott Williams & Wilkins 2009: p986.
11. Scott WAtlas. Toxoplasmosis. In: Atlas, Scott W.MagneticResonance Imagingof the Brain and spine. 4th ed. Philadelphia: Lippincott Williams & Wilkins 2009; p1000.
12. OsbornAnneG. Infections of brain and its lining. In: Anne.G.Osborn. DiagnosticNeurology. St. Louis Missourui: Mosby 1994; P699-700.
13. Scott W Atlas. Normal Pressure Hydrocephalous. In: Atlas, Scott W.Magnetic Resonance Imaging of the Brain and spine. 4th ed. Philadelphia: Lippincott Williams & Wilkins 2009; p1047.