Original Article

Study of Neurological Disorders in HIV Positive Patients in a Tertiary Care Hospital

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ABSTRACT

Introduction and Objectives : The varied spectrum of HIV associated neuro-disorders have emerged despite HAART era. The objective was to enumerate opportunistic and non-opportunistic disorders, correlate with CD4 and assess the effect of ART on mortality.

Materials and Methods : A short-term prospective observational study of subjects with HIV positive status (either naive or known) with neuro-manifestations or other symptoms with neuro-deficit on examination. Subjects underwent thorough neurological examination, CSF and radiological investigation and classified as per standard definitions for neuro-diseases.

Results : Of the 219 patients HIV positive patients admitted 100 (45.66%) had neurological manifestation, 83% were neuro-symptomatic, 17% admitted for some other medical illness with subsequent neuro-deficit. Of the 82 known HIV patients, 69 were on ART (84.14%), 13 were not despite known HIV status (15.85%). 18 naive HIV positive patients were started on ART. Of the 69 on ART, 57 on 1st line (82.60%) and 12 were on 2nd line HAART (17.89%). 29 patients had non-opportunistic disorders and 69 patients had OI. 2 patients expired before evaluation. Most common non-opportunistic disorder was HIV neuropathy (Distal Sensory Polyneuropathy or Toxic Neuropathy) (19 patients = 65.51% non-OI) followed by HAD (8 patients = 27.58%), one patient each of GBS and Primary CNS Lymphoma. Most common OI was Tubercular meningitis (37 patients = 53.62% of OI), closely followed by Cryptococcal meningitis (26 patients = 37.68%) 4 had coinfection with both Tubercular and Cryptococcal infection, 2 patients of PML and 1 each of Toxoplasmosis, CMV encephalitis, Herpes Encephalitis and Pyogenic meningitis. Total mortality was 18 patients of which 16.66% were on HAART, 11.11%, on 2nd line regimen and 72.22% not on ART.

Conclusion : Occult neuro-manifestation of cryptococcal and tubercular meningitis and shift of HAD from definite subcortical-slowing to subtle high-cortical cognitive defects requiring neuropsychological testing emphasise the fact that neuro-disorders should be differentials despite apparent neurological paucity.

Conflict of Interest: None.

Keywords : HIV, Neurological disorders, CD4 Counts, HIV Associated Dementia (HAD), Opportunistic Infection (OI).

Introduction :

The incidence of HIV has increased with wide spectrum of CNS manifestations[1]. The later stages of HIV severely hampers the immune system and affects virtually every component of the nervous system[2],causingconsiderable morbidity and mortality[3]. Initially, polyclonal hyper gamma globulinemia caused by the virus results in demyelinating diseases of the CNS and peripheral nervous system (PNS)[4]. As the HIV infection progresses, direct toxic effects of the virus and opportunistic infections ensue[5].

Neurological disease is the initial presenting manifestation in 7-20% of patients, 39-70% detected during subsequent course of the disease and further 80-90% at autopsy[6]. With the continued wide spread use of combination antiretroviral therapy (ART), the incidence of various neurological complications was expected to dwindle but has persisted[7]. CNS manifestations are a surrogate indicator of uncontrolled HIV and immunosuppression reiterating the importance of knowing the varied neurological presentations[8]. This cross-sectional study was conducted to

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document the neurologic events in HIV cases in a tertiary care hospital.

Aims And Objectives :

- To Enumerate the frequency and occurrence of various opportunistic and non-opportunistic CNS manifestations in HIV affected population.
- To correlate the CD4 counts with the possible occurrence of the various neurological disorders in HIV.
- To assess the outcome of ART in modifying occurrence and clinical presentations of these disorder.

Materials and Methods :

This was a short-term prospective observational study of subjects > 13 years of age HIV positive status with neurological manifestations for a period of 2 Years (from November 2016 to October 2018). 100 patients were selected having either neurological symptoms or signs on examination.

Inclusion Criteria :

- All HIV positive patients admitted for any presenting complaint with neurological symptoms or signs on subsequent neurological evaluation.
- Subjects who presented with primary neurological complication / presentations and was detected HIV positive during the evaluation of the same.

Exclusion Criteria :

- Subjects with previous neurological diseases like cerebrovascular accidents, epilepsy, parkinsonism etc before the diagnosis of HIV.
- Known case of Psychiatric disorders on or off treatment.
- Alcohol and other drug abusers like narcotics, sedatives and hypnotics were excluded from the study as intoxication and withdrawal symptoms may hinder with the sensitive neurocognitive testing methods used in the study.
- Subjects with diabetes and other immunosuppressive disorders other than HIV AIDS which might be confounding factors were excluded.

Study Method :

- All medical records were reviewed for information regarding demographic variables, sexual behaviour, CD4+ cell counts. Previous access to HIV related medical care prior to hospitalization and antiretroviral regime use in the 6 months prior to the evaluation period were examined.

Plan of Study :

All patients were confirmed for HIV reactivity and CD4 Counts traced with ART registration number from local ART centre. General examination and basic investigations were done and patient was put through thorough neurological examination (along with Fundus, CSF analysis and Neuroimaging as and when required) and Modified IHDS scale for dementia[9] if no other organic cause has been found with definite neurological disease.

Disease Definitions :

PRIMARY:

a) The criteria for HIV-associated dementia were defined according to the Frascati Criteria 2007 consensus[3]. Patients are subjected to Modified HIV Associated Dementia scale after excluding all primary and secondary opportunistic illnesses. A score less than 7.5 is considered significant for HAD[7].

b) Distal symmetrical polyneuropathy and acute inflammatory demyelinating polyneuropathy by EMG-NCV studies[10].

c) Primary cerebral lymphoma was diagnosed in patients with unifocal enhancing mass lesions shown by computerized tomography (CT) and confirmed with MRI[11].

SECONDARY:

a) Toxoplasma encephalitis is defined as the focal neurological signs and symptoms and multifocal ring enhancing lesion on CT Head all associated with initiation of therapy with pyrimethamine and sulfadiazine or clindamycin[12].

b) Cryptococcal meningitis was considered in the presence of typical symptoms and direct identification of cryptococcal organisms by

Indian Ink staining or detection of the cryptococcal antigen[13].

c) Tuberculosis was presumed by typical symptoms of basal meningitis, focal sign and symptoms in addition to predominance of lymphocytes with high protein levels in CSF with ADA positivity (>10U/L)[14,15].

d) Progressive multifocal leukoencephalopathy (PML) was defined in patients with progressive focal signs and symptoms, a decline in cognitive function and multifocal non-enhancing white matter lesions in the MRI[3].

e) Cytomegalovirus (CMV) encephalitis was defined as the presence of diffuse neurological signs and symptoms and CT non-specific findings such as ventriculomegaly and periventricular enhancement on MRI associated with a positive protein chain reaction (PCR) for CMV DNA in CSF[5].

f) Herpes simplex virus (HSV) and varicella zoster virus (VZV) encephalitis were considered in the presence of diffuse or focal signs and symptoms, non-enhancing focal lesions in the CT with typical pox lesions or herpes zoster. The detection of these viruses in CSF by PCR analysis[5].

g) Neurosyphilis diagnosis was based on the combination of reactive serological tests and abnormalities of CFS cell count or protein or a reactive VDRL-CSF with or without manifestations[5].

h) Bacterial meningitis was diagnosed by detection of bacteria in GRAM stain and culture in CSF[5].

Observations and Results :

A total of 219 patients were examined out of which 100 (45.66%) presented with neurological symptoms or had subclinical neurological signs fulfilling inclusion criteria. Nearly 83% were symptomatic for the neurological disease, either as a primary complaint, or as a neglected symptom. 17% of the patients in the study were admitted for some other medical illness but were not symptomatic. There were a total of 78 male and 22 female patients (male : female ratio of 3.5:1) with a mean age of 46 for males (46.08 ± 14.67) and 50 for females (50.40 ± 10.18). The age distribution of the patients is given in ***Figure 1.***

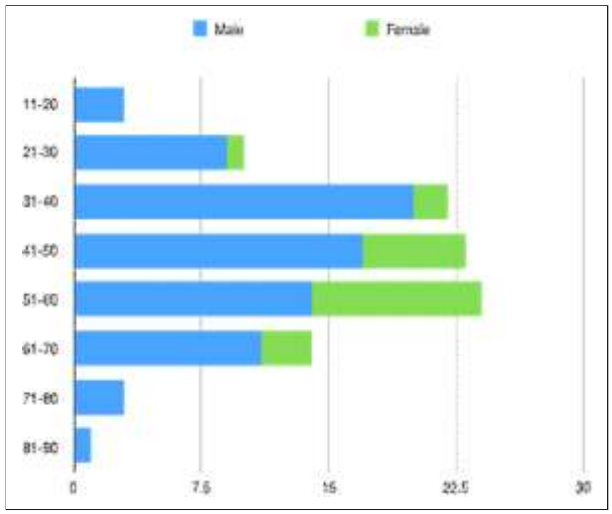

Figure 1. : **Age-wise distribution of Male and female patients who had neurological disease in HIV**

Among 100 patients, 82 patients were already diagnosed cases of HIV who were either on or not on treatment. 18 patients had been admitted for a neurological or non-neurological complaints and subsequently turned out to be HIV positive and were registered for ART and started on treatment. The mean number of years after which the patient developed neurological disease and symptoms was 3.52 ± 4.16 ($p < 0.001$) with the maximum number of patients being in the 1-4 year category. Median (Range) being 2 (0-22) as shown in ***Table 1.***

Table 1 : **Distribution of HIV infected patients according to duration of years since detection after which patient developed neurological disease**

Duration (in year)	Number of patients	Percentage
<1	2	2.40%
1-4	50	60.97%
5-9	22	26.82%
≥10	8	9.75%
Total	82	

Out of the total of 82 patients, 69 were on an ART regimen, either 1st Line or 2nd Line HAART (84.14%) (57 patients were on 1st line HAART (82.60%) therapy and 12 patients were on second

line therapy (17.89%)). 13 patients were not on ART drugs despite of known HIV-1 status (15.85%). Mean CD4 Count was 106.27 ± 58.40 with a median 102 (6 - 281). 3 patients who were known cases of HIV-1 came with neurological complaints and definite signs on physical examination but could not be evaluated due to the poor GC on admission.

Symptomatology of Non-oppurtunistic Diseases :

- The most common non opportunistic neurological disorder detected in the study was ***HIV associated neuropathies,*** both DSP (Distal Sensory Polyneuropathy) and Toxic neuropathy secondary to HAART[16].

  There were a total of 19 patients with DSP/TN out of which 6 were symptomatic(most common being painful neuropathy) and others were subsequently detected on neurological examination; (Most commonly hyperaesthesia of soles (7 patients), followed by absent ankle reflexes (6 patients), and confirmed with nerve conduction studies. All 6 patients had symptoms of painful sensory neuropathy (31.57%), and one patient had sensory ataxia (5.26%).
- The second most common non-opportunistic disorder was ***HAD (HIV associated Dementia)*** with a total of 8 patients out of which 4 were symptomatic for the disease at presentation. Most common symptom was Abnormal Behaviour in all 4 patients in the form of diffuse slowing of movements and irrelevant talk (50%), followed by Abnormal Movements in 1 patient (12.5%), Ataxia in 1 patient(12.5%), and difficulty in speech in 1 patient (12.5%). Others were subsequently diagnosed with subtle neurocognitive defects detected on neuropsychological testing (Modified IHDS score <7.5[9]) which the patient was not aware of but causing significant affection of daily living such as memory loss, reading and concentration difficulties.
- One 15 year old boy, 2 years since detection of HIV came with Motor deficits of all 4 limbs (LL > UL) and Tingling in foot and was subsequently diagnosed with ***GBS (Demyelinating Polyneuropathy)*** on EMG-NCV.
- One 62 year Male, 5 years since detection of HIV not on any ART since last 3 years came with Headache, Vomiting, Convulsions and Altered sensorium and was subsequently diagnosed as ***Primary CNS Lymphoma*** on MRI Brain ***(Figure 4).***

Symptomatology of Oppurtunistic Infection :

- Most common opportunistic infection in the study was found to be ***Tubercular meningitis*** in the study (37 patients) followed by ***Cryptococcal meningitis*** (26 patients). 4 Patients were found to have positivity for both Tubercular as well as Cryptococcal meningitis. The Symptomatology profile is compared in ***Table 2.***
- 39 year old male who presented with Fever, Headache and Convulsions and manifested Focal neurological deficit in the form hemiparesis was found to be subsequently Toxoplasma Encephalitis on MRI Brain.
- 2 patients, one 40/m Vomiting, altered sensorium and paucity of movements in the left side, and another 55/m with Fever and convulsions were found to be Progressive multifocal leukoencephalopathy with white matter changes in MRI Brain.
- 49 year old male with Fever, Altered Sensorium and Aphasia and Subsequently unilateral Ptosis and pupillary mydriasis suggestive of 3rd nerve palsy was subsequently confirmed to be CMV encephalitis based on MRI Brain and CSF PCR positivity. Patient had severe respiratory depression and was intubated with suspected Brainstem Encephalitis[17].
- 52 year old male with headache, vomiting and Altered Sensorium suggestive of raised ICT and meningeal symptoms of neck stiffness and photophobia turned out to be Bacterial Meningitis.

All patients with Neurological Disorders was categorised according to their GCS score on presentation. The mean GCS was 12.37 ± 2.81. Range 13 (3 -15).

CT Head was done for all patients as a primary evaluation screening in all patients with

Neurological deficits and was abnormal in only 35.1% of the patients (3 could not be evaluated).

CSF was done in all patients with Neurological deficits and was abnormal in 71.1% of the patients (3 could not be evaluated). The two most common opportunistic infections, TBM and cryptococcal meningitis, had varying presentations in the CSF analysis and were confirmed with CBNAAT and CRAG testing in case of doubtful CSF picture (29 patients with Indian Ink and CRAG Positive, 1 patient with Indian Ink Negative and CRAG positive.

Discussion :

Prevalence of neurological disorders observed in the study was 45.66%. ***Patil et al***[18] study in 2014 which also had a prevalence of 45.25% and a male preponderance and ***Oliviera et al***[11] in their study in Brazilian population in 2006 had a prevalence of 46.5%.

Most common Non-opportunistic infection in HIV-1 infected patients in the study was HIV induced neuropathy either Distal Sensory Polyneuropathy or Toxic Neuropathy(19 patients=65.51% of non-OI). According to ***Cornblath et al***[10] the most common type of peripheral neuropathy associated with HIV infection, predominantly sensory neuropathy, affects 10-30% of patients. Consistent with literature, the study had 19 patients with DSP. ***Price et al***[19] in his study states that pain was the most common presentation among patients with sensory polyneuropathy, consistent with which 6 patients were symptomatic with painful sensory neuropathy and rest diagnosed on examination. The mechanism remains unknown but seems to be dying back neuropathy with distal axonal degeneration[10]. While it remains controversial whether HIV can enter neurons and thus be directly neurotoxic, there is growing evidence supporting the indirect neurotoxicity of HIV through inflammation and viral proteins[20]. ***Schutz et al***[20] states that DSPs originating from HIV or NRTIs are clinically indistinguishable from one another hence both entities were clubbed together. Nonetheless, different pathophysiologic mechanisms have been implicated in the development of the clinical phenotype. One hypothesis is that NRTIs lead to mitochondrial dysfunction through inhibition of mitochondrial DNA polymerase gamma.

Second most common was HAD (8 patients = 27.58%). As per Clifford and Ances[21], severe forms of HAD have been eradicated after the cART era but the subtle inapparent ones remain. The trend was in the shift of presenting features of subcortical slowing in previous HAD patients to indolent cortical defects. This has also been observed in our study with 4 being symptomatic and 4 being detected only on neuropsychological testing with modified IHDS[9]. According to ***Mc Arthur et al***[22] inappropriate and persistent immunological activation seems to play a sole role in HAND, and might explain the incomplete response despite initiation of cART. This is evident by the fact that all 8 patients in our study were known HIV patients already on ART for many years.

Most common opportunistic infection was Tubercular meningitis (37 patients = 54.41%) and closely followed by Cryptococcal meningitis (30 patients = 44.11%) 4 patients had coinfection with both Tubercular and Cryptococcal infection. ***Oliviera et al***[11] as per the study of Brazilian population had the most common opportunistic infection as toxoplasmosis yet it seems to have a very low prevalence among our developing nation. Consistent with ***Rana et al***[23] in his study of Indian population and ***Bolokadze et al***[24] in his study at Georgia, the most common opportunistic infection in the current study was Tubercular Meningitis with a prevalence of 34%. It was found that the most common symptomatology in both Tubercular Meningitis and Cryptococcal Meningitis was Fever and Headache. But the frequency of patients presenting with convulsions was more in Tubercular meningitis, whereas the patients presenting with altered behaviour was more in Cryptococcal Meningitis. Neck stiffness was a rule in Tubercular Meningitis whereas cryptococcal was lenient on the meningeal irritation unless proteins are highly elevated in CSF ***(Table No. 2).***

The number of patients with normal cells was more in Cryptococcal meningitis whereas patients with

Table 2 : **Symptomatology and Signs of TBM and CM patients**

Symptoms and signs	Number of patients with Tubercular meningitis	Number of patients with Cryptococcal meningitis
Fever	32 (86.48%)	24 (80%)
Headache	26 (70.27%)	21 (70%)
Vomiting	14 (37.83%)	9 (30%)
Altered sensorium	21 (56.75%)	17 (56.66%)
Altered behaviour	3 (8.10%)	9 (30%)
Convulsion	8 (21.62%)	3 (10%)
Abnormal movement	1 (2.70%)	1 (3.33%)
Focal deficit	11 (29.72%)	8 (26.66%)
Ataxia	5 (13.51%)	1 (3.33%)
Dysphasia/Aphasia	20 (54.05%)	9 (30%)
Cranial Nerve deficit	4 (10.81%)	4 (13.33%)
Cerebellar Involvement	2 (5.4%)	1 (3.33%)
Meningeal Signs	25 (67.56%)	18 (60%)

cells > 100 / hpf were more likely to be Tubercular in origin ***(Table 3).*** The number of patients with normal proteins was more in Cryptococcal meningitis whereas patients with proteins > 500 were more likely to be Tubercular in origin ***(Table 4).***

Table 3 : **Cerebrospinal Fluid Cell count in patients of HIV infected with Tubercolosis and cryptococcosis**

CSF Cells	Tuberculosis N = 37	Cryptococcosis N = 26
< 6 (Normal)	1	3
6 - 20	11	13
21 - 50	7	4
51 - 100	7	5
> 100	11	1

Table 4 : **CSF Protein levels in patients of HIV infected with Tuberculosis and cryptococcosis**

SF Protein	Tuberculosis N = 37	Cryptococcosis N = 26
< 40 (Normal)	1	3
41 - 100	13	13
101 - 200	11	7
201 - 500	5	3
> 500	5	0

The in hospital mortality in patients admitted for Tubercular meningitis (9 patients = 30%) was better than cryptococcal meningitis (11 patients = 36.66%) primarily due to the advancement of and easy availability of Anti-Tubercular drugs and instant mortality benefit by initiation of steroids ***(Table 6).*** ***Rana et al***[23] study of outcome of secondary illnesses showed fatal outcome in 9.10% of tubercular meningitis and 32.86% of cryptococcal meningitis. ***Patil et al***[18] states the mortality of TBM as 11.6%, Cryptococcal meningitis 25%.

The mean CD4 Counts give a broad idea of the various possible neurological disorders which the patient may be susceptible to. The range of CD4 counts at which the neurological diseases appeared in our study are given in ***Table No. 5.*** This can be compared to the following studies with similar results : ***Rana et al***[23] states that the mean CD4 Count in Tubercular meningitis was 131.5 +/- 85.75, Cryptococcal meningitis was 47.5 +/- 36.8. ***Ishwar Chouhan et al*** states that the mean CD4 Count in Tubercular Meningitis was 181.44 +/- 83.50, Cryptococcal meningitis was 97.25 =/- 71.27, HAD was 92 =/- 31.63, and Peripheral neuropathy was 159.33 =/- 40.21.

Total in hospital mortality during the study ***(Table 7)*** was 18 patients of which 16.66% were on HAART, 11.11% were on 2nd line regimen and 72.22% were not on any Anti-Retroviral Therapy. The mortality of patients with HAART (5.26%) was relatively less due to the relatively higher immune function on presentation interpreted as CD4 Counts. Mortality of patients on 2nd line drugs (15.38%) was due to the chronicity of the disease and lower CD4 counts in these patients.

Summary and Conclusion :

Thus Neurological Disorders in HIV patients seems to occupy a major role in the morbidity and mortality of the patient and the varied clinical presentation and overlapping symptomatology with paucity of symptoms makes it very necessary to keep a eagles watch for minute signs of neurological affection so that further progression and complications can be prevented.

Table 5 : **Correlation of CD4 count and various opportunistic and non-opportunistic CNS manifestation in patients of HIV infected**

	Number of patients	Mean CD4 CountSD	Cd4 Count	
			<200	>200
Non Opportunistic infection				
HAD	8	169 ± 59.28	6	2
DSP/TN	19	113.63 ± 31.25	19	0
GBS	1	165	1	0
PCL	1	8	1	0
Opportunistic infection				
TBM	37	103.67 ± 58.57	35	2
CM	26	73.8 ± 41.75	26	0
TOX	1	21	1	0
PML	2	73.5 ± 14.84	2	0
NS	0	NA	0	0
CMV	1	42	1	0
HZ/HE	0	NA	0	0
BM	1	281	1	0

Table 6 : **Correlation of Outcome and various opportunistic and non-opportunistic CNS manifestation in patients of HIV infected**

	Number of patients	Outcome		p-value
		Discharge	Deaths	
HAD	8	8	0	0.192,NS
DSP/TN	19	19	0	0.005,HS
GBS	1	1	0	1.000,NS
PCL	1	0	1	0.227,NS
TBM	37	28	9	0.008,HS
CM	26	18	8	0.037, S
TOX	1	0	1	0.227,NS
PML	2	1	1	0.404,NS
NS	0	0	0	-
CMV	1	0	1	0.227,NS
HZ/HE	0	0	0	-
BM	1	1	0	1.000,NS

Key : HAD-HIV associated dementia, DSP/TN-distal sensory polyneuropathy / toxic polyneuropathy, GBS-Guillain barre syndrome, PCL-Primary CNS lymphoma, TBM-Tubercular meningitis, CM-Cryptococcal meningitis, TOX-toxoplasmosis, PML-Progressive Multifocal Leukoencephalopathy, NS-Neuro-cysticercosis, CMV- Cytomegalovirus, HZ/HE-Herpes zoster/Herpes encephalitis, BM-Bacterial meningitis.

Table 7 : **Association of ART taken and patients in-hospital outcome**

ART		Number of patients	Outcome		p-value
			Discharge N=76	Deaths N=18	
Yes	HAART	57	52 (68.42%)	3 (16.66%)	< 0.001, Hs
	2nd line	13	10 (13.15%)	2 (11.11%)	< 0.001, Hs
No		30	14 (18.42%)	13 (72.22%)	< 0.001, Hs

Taking ART but UNKNOWN Regimen-3 patients. Discharge against medical advice-6 patients.

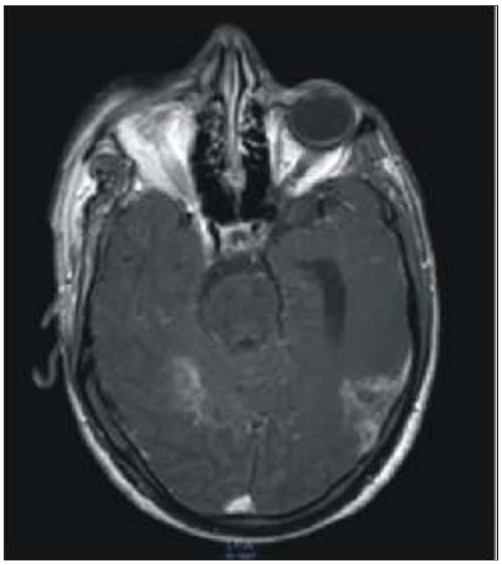

Figure 2 : **Meningeal enhancement in a patient with Tubercular Meningitis with T1 hypo intensity and T2/FLAIR hyperintensity with Acute infarct in pons and midbrain**

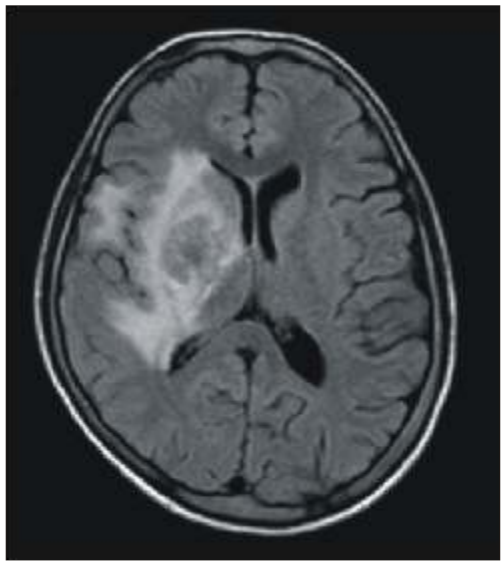

Figure 3 : **Lesion shows peripheral hyperintensity with centrally isointense areas on T2W & FLAIR, disproportionate peri-lesional oedema & mass effect s/o TUBERCULOMA.**

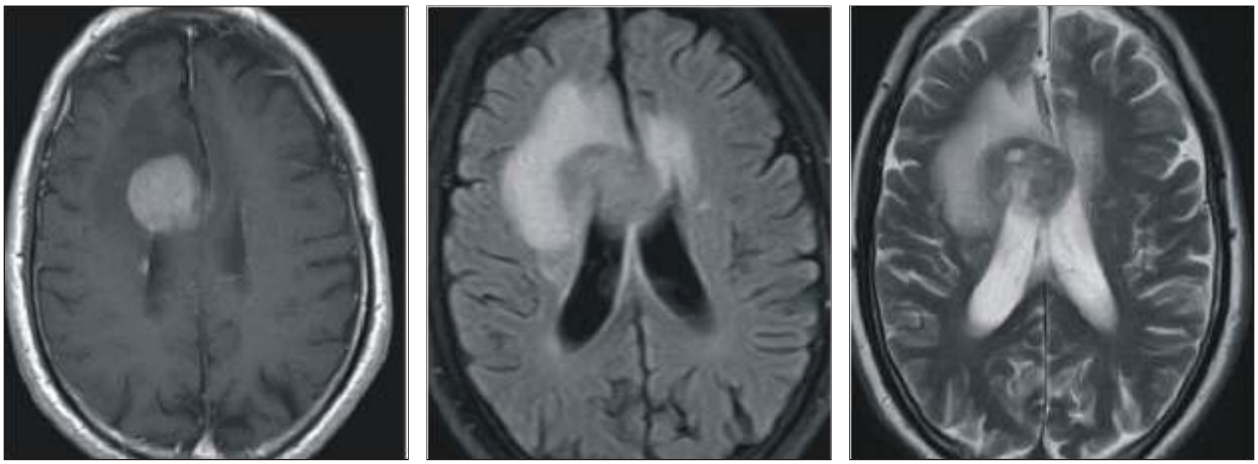

Figure 4 : **Intensely enhancing mass lesion with hypointensity on T1 and T2 isointense on FLAIR with perilesionaledema s/o High Grade CNS Lymphoma**

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