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A Study of C. N. S. Manifestations of 30 HIV Positive Patients

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Abstract: ***Neurological complications of HIV infection cause considerable morbidity and are often associated with high mortality. These complications include not only the more common opportunistic diseases affecting the brain (cerebral toxoplasmosis, primary central nervous system lymphoma, progressive multifocal leucoencephalopathy, and cryptococcal meningitis) but also the AIDS dementia complex, with its characteristic cognitive and motor dysfunction, which is caused by HIV itself. Additionally, the peripheral nervous system is the target of several disorders, including a common painful neuropathy. Because these and other, less common, central and peripheral nervous system complications of HIV can often be specifically treated or effectively palliated, their accurate and timely diagnosis is important***

Keywords: HIV, CNS manifestations, Opportunistic infection

1. Introduction

The human immunodeficiency virus (HIV), the cause of acquired immunodeficiency syndrome (AIDS), has infected an estimated 33 million individuals worldwide. [1] India has the third - largest HIV epidemic in the world, following South Africa and Nigeria [2]. The estimated number of people living with HIV (PLHIV) in India is around 2.1 million HIV is a member of the lentivirus genus, part of the Retroviridae (retrovirus) family. HIV is associated with immunodeficiency, neoplasia, and neurologic disease [3]. The development of an identifiable neurologic syndrome in an HIV - infected person is the culmination of a chain of events, determined by properties of HIV itself, genetic characteristics of the host, and interactions with the environment (including treatment). HIV - associated neurologic syndromes can be classified as primary HIV neurologic disease (in which HIV is both necessary and sufficient to cause the illness), secondary or opportunistic neurologic disease (in which HIV interacts with other pathogens, resulting in opportunistic infections [OI] and tumors), and treatment - related neurologic disease (such as immune reconstitution inflammatory syndrome [IRIS]).

The epidemic is concentrated among key populations such as:

- Sex workers (HIV prevalence: 1.56%)
- Men who have sex with men (HIV prevalence: 2.69%)
- People who inject drugs (HIV prevalence: 6.26%)
- Transgender people (HIV prevalence: 3.14%)

Despite medical advancements, stigma and discrimination remain challenges in effectively addressing the HIV epidemic in India [2].

HIV - Associated Syndromes in Primary Infection

Acute HIV infection is the period from initial infection to complete seroconversion. During this time 40% to 90% of individuals describe physical symptoms, similar to influenza, or mononucleosis. The most common features include a short period of fever, lymphadenopathy, night sweats, headache, or rash. [4, 5]. Early CNS infection is usually asymptomatic, but cerebrospinal fluid (CSF) [6] and imaging studies [7] can detect abnormalities even during the ‘‘asymptomatic’’ period that presage later neurologic events. A minority of seroconverters will experience a neurologic event that brings them to medical attention, such as aseptic meningitis, Bell’s palsy, [8, 9] or inflammatory neuropathy. Individuals with symptomatic neurologic disease tend to have higher CSF HIV levels than those without neurologic symptoms. Neurologic symptoms may occur before an HIV diagnosis is suspected, for example, before there are sufficient HIV antibodies to produce a positive HIV enzyme - linked immunosorbent antibody (ELISA, also called an HIV enzyme immunoassay). In such cases, a polymerase chain reaction (PCR) test for HIV may lead to the diagnosis. Early diagnosis of acute HIV infection is important, as these individuals are at high risk of transmitting the virus. The most common neurologic syndrome associated with primary HIV infection is an acute aseptic (viral) meningitis or meningoencephalitis. The symptoms are similar to other viral meningitides, with fever, headache, stiff neck, and photophobia. CSF shows a mild

lymphocytic pleocytosis, normal or slightly elevated total protein, and normal glucose. [10] HIV may be detectable by p24 antigen or PCR testing. [11] Most individuals will recover with supportive care. A few will have recurrent bouts of septic meningitis. Information on the management of HIV aseptic meningitis is limited to case reports. Initiating treatment with cART, or changing and intensifying the regimen to include more CNS - penetrating drugs, may suppress the symptoms. [12] Others have recurrent meningitis when they stop combined antiretroviral therapy (cART), for example, during structured treatment interruptions. [13]

Conditions primary to HIV:

1) Aseptic meningitis
2) HIV - associated neurocognitive disorders (HAND), including HIV encephalopathy/ AIDS dementia complex
3) Myelopathy
   - Vacuolar myelopathy
   - Pure sensory ataxia
   - Paresthesia/dysesthesia
4) Peripheral neuropathy
5) Acute inflammatory demyelinating polyneuropathy (Guillain - Barre syndrome)
6) Chronic inflammatory demyelinating polyneuropathy (CIDP)
7) Mononeuritis multiplex
8) Distal symmetric polyneuropathy
9) Myopathy

Conditions secondary to HIV or those related to treatment include:

1) Opportunistic infection
   - Toxoplasmosis
   - Cryptococcosis
   - Progressive multifocal leukoencephalopathy
   - Cytomegalovirus
   - Syphilis
   - Mycobacterium tuberculosis
   - HTLV - 1 infection
   - Amebiasis
2) Neoplasm
   - Primary CNS lymphoma
   - Kaposi sarcoma

Aims and Objectives:

1) To study **clinical profile** of HIV positive patients with neurological manifestations.
2) To know value of **various investigations** in diagnosis of various neurological manifestation of HIV infection.
3) To correlate various **CD4 levels** with various opportunistic infections and to know change in their value with ART.

2. Methods

Study Setting and Patients

We carried out this study at the DR. M. K. Shah Medical College, a tertiary care centre in Ahmedabad. Prior to commencing the study, hospital local institutional ethical clearance was sought and obtained. We included, all adult (age ≥ 18 years) HIV - 1 positive patients were diagnosed with CNS disease (as described subsequently). Patient selection was done using the hospitalisation register of the Internal Medicine Unit of the DR. M. K. Shah Medical College, where the diagnosis and outcome of all hospitalised patients (discharged or dead) are recorded. Being a specialist hospital, the diagnosis of each patient is recorded by the specialist physician catering for patient. For the study subjects, the diagnoses were those of the neurologist. From this register patients diagnosed with HIV - associated CNS disease were sorted, and their files obtained from the archives for the collection of information relevant to the study. All patients with signs and symptoms evocative of HIV associated CNS diseases but who had no clearly stated working diagnosis were excluded from the study. HIV diagnosis is made according to the National AIDS Control Organisation [2], by antibody detection on two successive samples using a third - generation ELISA test BIOREX (Biorex Diagnostics Limited, Antrim, UK), In case of both samples are positive a third sample is collected and tested using Genie III HIV - VH09 - 2 Assay (Bio - Rad Diagnostics, Marnes la Coquette, France) to Specity either HIV 1 or HIV 2. The patient is declared to be positive for HIV if thesé three tests are positive. In case of any discordance, testing is done using western blot (New LAY blot Diagnostics, Pasteur, Marnes la Coquette, France)

Diagnosis of CNS Disease

In this institution, the diagnosis of CNS diseases follows an algorithm. When a patient presents with symptoms of CNS disease with or without focal signs, a computerised tomographic (CT) brain scan is first done to exclude any space occupying lesions and/or signs of raised intracranial pressure (ICP). In the absence of these or any other finding that might contraindicate a lumbar puncture (LP), an LP is done for cerebrospinal fluid (CSF) analysis and culture, CSF analysis comprises doing a differential white blood cell count, measuring protein and glucose levels by standard biochemical methods, gram and Indian ink staining, and culture for pyogenic micro - organisms. The working diagnosis is then made using an association of clinical, radiological, and/or biochemical findings as described subsequently.

The diagnosis of toxoplasma encephalitis (TE) was presumed by clinical presentation of fever, headache, and/or focal signs of sensory or motor deficits and an associated CT scan image of single or multiple intracerebral ring enhancing lesions. In instances where CT scan could not be afforded. this diagnosis was retained when symptoms and clinical signs regress after commencing antitoxoplasma treatment which was usually cotrimoxazole.

Cryptococcal meningoencephalitis was diagnosed based on complaints of fever, headache, signs of meningeal irritation (stiff neck, Kernig or Brudzinski signs), and CSF finding of Cryptococcus on Indian ink stain.

Tuberculous meningitis diagnosis was presumed by the presence of fever, headache, signs of meningeal irritation with or without focal signs, and in CSF: elevated proteins, low glucose levels, negative pyogenic bacterial culture or antigen assay, past or present history of tuberculosis (TB), and/or suggestive chest X - ray findings or brain CT scan features suggestive of TB meningitis (basal meningeal enhancement, hydrocephalus, cerebral infarcts, oedema, and nodular enhancing lesions). However, this diagnosis was also

considered when the patient did not improve on conventional antibiotics for pyogenic meningitis.

AIDS dementia complex (ADC) was diagnosed by exclusion patients with cognitive impairment after ruling out confounding conditions.

Diffuse encephalitis include fever, altered consciousness, seizures and diffuse cereberal edema without focal signs.

Bacterial meningitis was diagnosed by detection of bacteria on gram stain or culture in CSF or positive test for bacterial antigens.

Primary central nervous system lymphoma (PCNSL) was diagnosed if the patient presented with headache, focal signs, altered behaviour, intracerebral lesion with unifocal nodular heterogenous contrast medium enhancement, and mass effect with surrounding oedema. This diagnosis was also made when a patient with suspected toxoplasmosis did not improve on treatment.

Study Methods

We carried out a cross - sectional study on the files of patients admitted during the study period. Sociodemographic information, symptoms, and clinical signs relevant to CNS diseases, CD4 cell counts, and inpatient outcome (death or discharged) were obtained from these files and entered into a data base created using Epi Data version 3.1. Due to unavailability of information on antiretroviral treatment for most patients, it was not included on the data collection form.

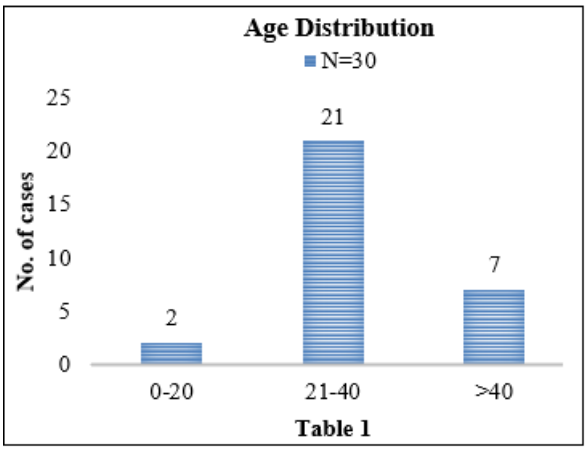


Table 1

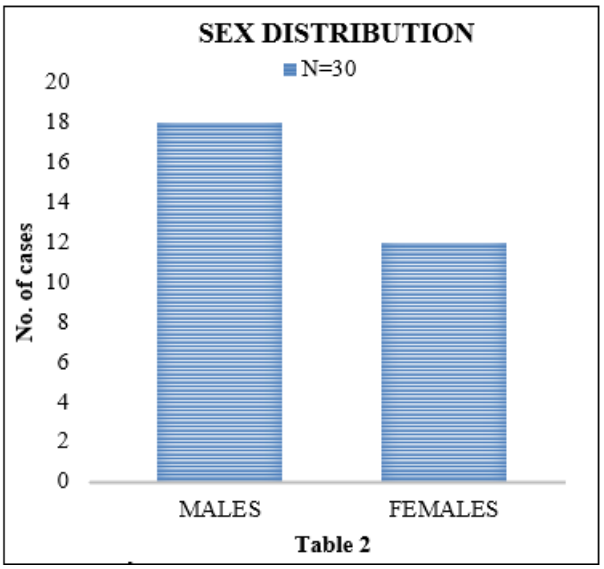


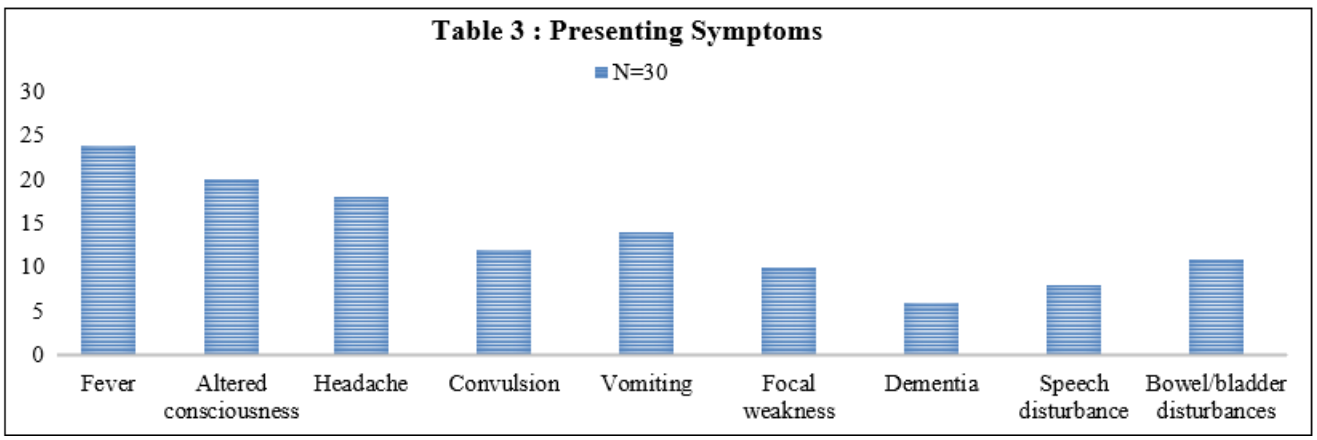
Table 2

Statistical analysis:

Data analysis was done using STATA 11.2 statistical package. Continuous variables were expressed using means and standard deviations where necessary, medians, and interquartile range (IQR). The Chi - square and Fisher's exact tests were used to compare categorical variables. Mantel Haenszel analysis was used to determine the strength of associations between the primary outcome and covariates, a logistic regression model was then built with covariates strongly associated with the outcome. Results of Mantel Haenszel analysis and logistic regression were reported as crude and adjusted odd ratios (OR), respectively, together with their 95% confidence interval (CI). Evidence of association was considered for a two - tailed P value of less than 0.05.

3. Results

During the study period, 30 patients fulfilled eligibility criteria of HIV associated CNS disease (table 1). Among studied patients, 17 patient (56%) were male and rest 13 patients (44%) were female (Table 2). Mean age group was 32+/ - 5 years.



The table 3 shows the distribution of symptoms presented by 30 patients (N = 30). The symptoms are listed along the horizontal axis, while the number of patients with each symptom is shown on the vertical axis. Fever is most common symptom, reported by around 24 patients.20 patients experienced altered consciousness. Headache reported by about 18 patients.12 patients had convulsions. Vomiting was experienced by 14 patients.10 patients showed Focal Neurological weakness. Dementia reported by 6 patients. About 8 patients experienced speech disturbance. Bowel/bladder disturbances was reported by around 11 patients as well. Overall, fever, altered consciousness, and headache are the most common symptoms, while dementia is the least common among the patients in the study.

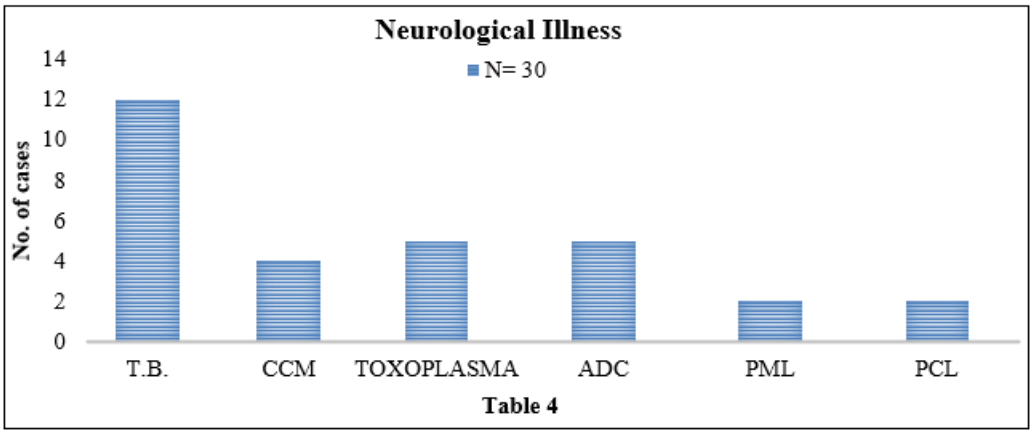
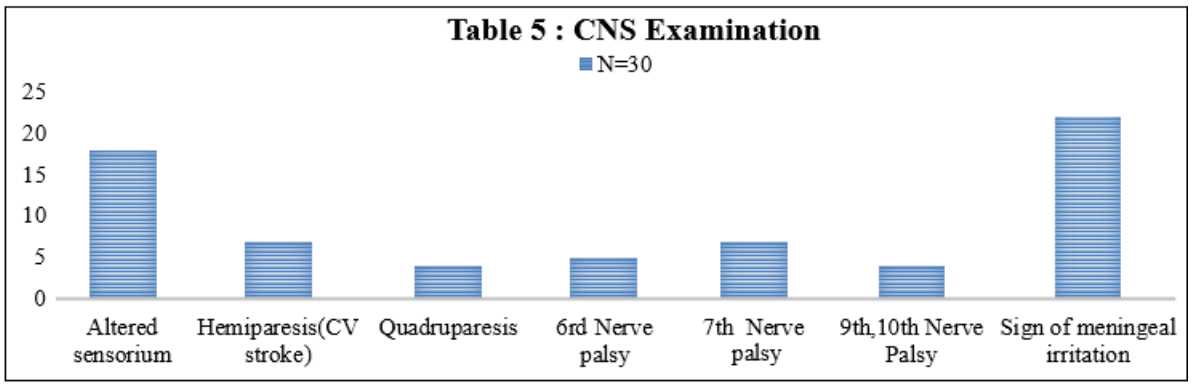
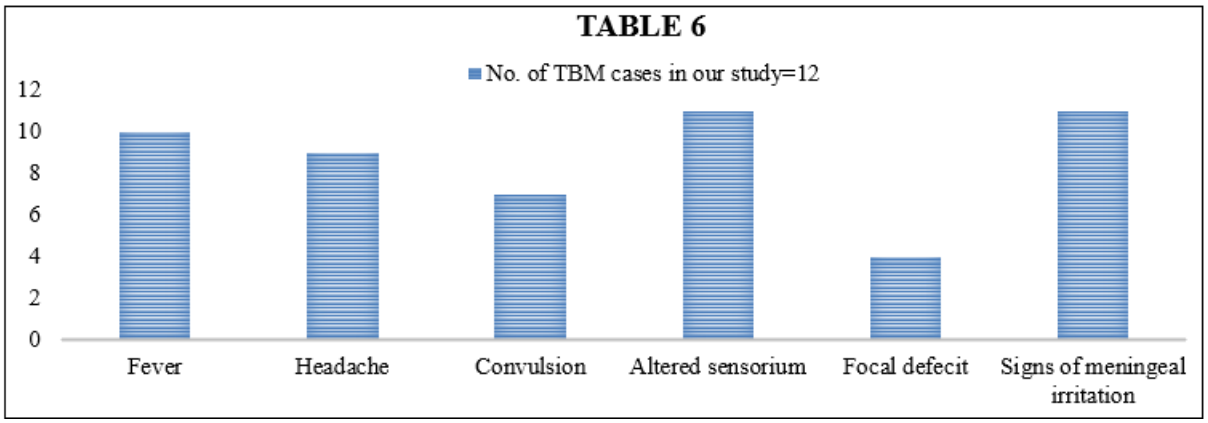


Table 4

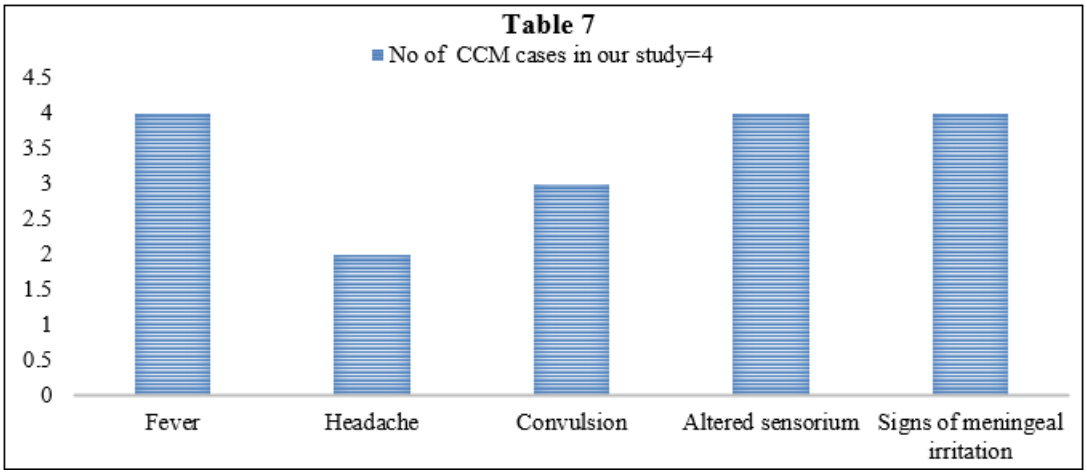
The illnesses are listed in table 4 shows along the horizontal axis, and the number of cases is shown on the vertical axis. T. B. Meningitis has the highest occurrence, with 12 cases followed by CCM (Cerebral Cryptococcal Meningitis has about 4 cases. Toxoplasma are about 5 cases. ADC (AIDS Dementia Complex) 5 cases are recorded. PML (Progressive Multifocal Leukoencephalopathy) is 2 cases. PCL (Primary Central Nervous System Lymphoma) also has 2 cases. This shows that Tuberculosis is the most common neurological illness among the group, while PML and PCL are the least common.



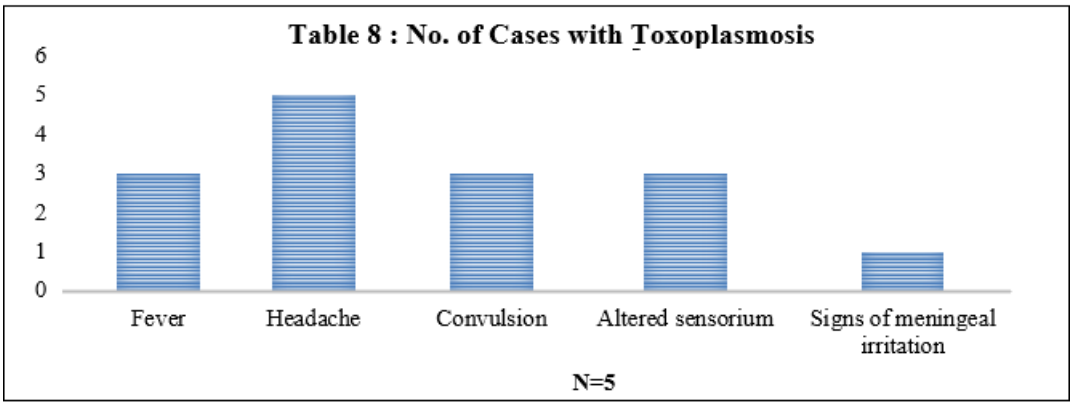
The table 5 details the distribution of various central nervous system (CNS) signs among 30 patients (N = 30). The CNS signs are listed along the horizontal axis, while the vertical axis shows the exact number of patients exhibiting each sign. Altered sensorium present in 16 patients. Hemiparesis (CV stroke) observed in 4 patients. Quadriparesis noted in 4 patients.6th Nerve palsy present in 2 patients.7th Nerve palsy observed in 3 patients.9th and 10th Nerve palsy found in 2 patients. Sign of meningeal irritation is most common sign, occurring in 19 patients. In summary, signs of meningeal irritation and altered sensorium are the most prevalent CNS signs, while 6th nerve palsy and 9th/10th nerve palsy are the least common.



The table 6 presents data related to tuberculosis meningitis (TBM) cases observed in a study. It consists of Column A lists various neurological symptoms associated with TB Meningitis and Column B displays the number of TBM cases corresponding to each symptom. Neurological Symptoms are 10 cases. Elevated body temperature often accompanying infections are 9 cases. Patients presented with headache are 7 cases. Convulsion indicating abnormal brain activity seen in 11 patients. Altered sensorium present in 4 patients.11 patients showed Focal Neurological weakness. Signs of Meningeal Irritation were seen in 11 cases.



The table 7 shows a bar chart representing the symptoms presented by patients with CCM (Cryptococcal Meningitis) in a study involving four cases. The symptoms and their corresponding frequencies are as all 4 cases (100%) presented with fever.2 cases (50%) presented with headaches.3 cases (75%) experienced convulsions. All 4 cases (100%) showed altered sensorium.3 cases (75%) exhibited signs of meningeal irritation. The chart indicates that fever and altered sensorium were the most common symptoms, present in all cases studied.



The table 7 shows a bar chart representing the symptoms presented by patients with Toxoplasmosis in a study involving five cases. The symptoms and their corresponding frequencies are as 2 out of 5 cases (40%) presented with fever.5 out of 5 cases (100%) presented with headaches.2 out of 5 cases (40%) experienced convulsions.3 out of 5 cases (60%) showed altered sensorium.1 out of 5 cases (20%) exhibited signs of meningeal irritation. This indicates that headache was the most common symptom, present in all cases

studied. Fever and convulsions were less common, each appearing in only 2 cases.

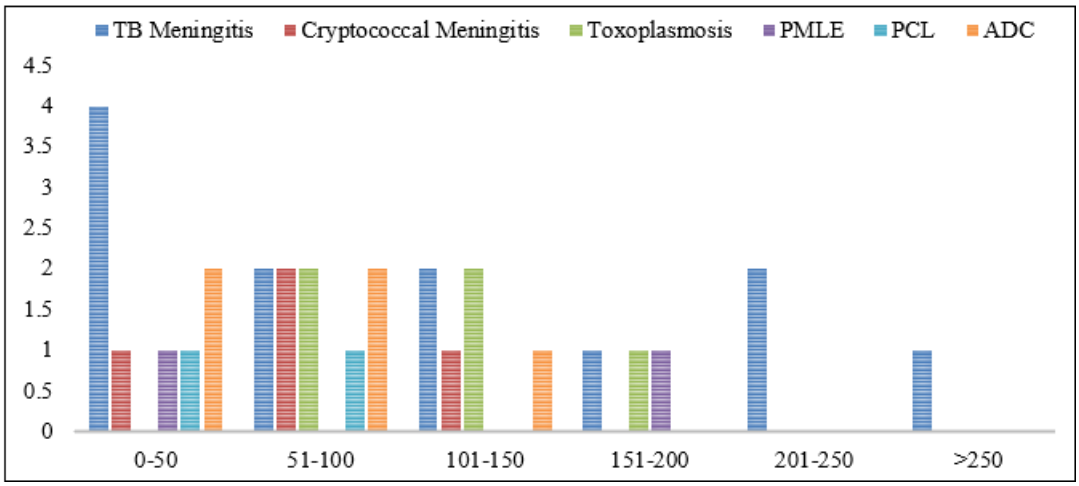


Table 8

The table 8 summarizes the occurrence of various clinical manifestations (TB Meningitis, Cryptococcal Meningitis, Toxoplasmosis, PMLE, PCL, and ADC) at different CD4 count levels. CD4 count levels indicate the severity of immune suppression in individuals, often used in the context of HIV/AIDS. Here's a breakdown:

1) **CD4 Level 0 - 50:**
   a) TB Meningitis: 4 cases
   b) Cryptococcal Meningitis: 4 cases
   c) Toxoplasmosis: 1 case
   d) PMLE: 1 case
   e) PCL: 1 case
   f) ADC: 2 cases
2) **CD4 Level 51 - 100:**
   a) TB Meningitis: 2 cases
   b) Cryptococcal Meningitis: 2 cases
   c) Toxoplasmosis: 2 cases
   d) PMLE: 2 cases
   e) PCL: No cases
   f) ADC: 2 cases
3) **CD4 Level 101 - 150:**
   a) TB Meningitis: 2 cases
   b) Cryptococcal Meningitis: 1 case
   c) Toxoplasmosis: 2 cases
   d) PMLE: 2 cases
   e) PCL: No cases
   f) ADC: 1 case
4) **CD4 Level 151 - 200:**
   a) TB Meningitis: 1 case
   b) Cryptococcal Meningitis: No cases
   c) Toxoplasmosis: 1 case
   d) PMLE: 1 case
   e) PCL: 1 case
   f) ADC: No cases
5) **CD4 Level 201 - 250:**
   a) TB Meningitis: 2 cases
   b) No other conditions are reported at this level.
   c) CD4 Level >250:
   d) TB Meningitis: 1 case.
   e) No other conditions are reported at this level.

Table 9: Cerebrospinal Fluid Analysis

CSF Findings	TB Meningitis	Cryptococcal Meningitis
Protein	230	34
Sugar	32.3	56.12
TC	121.91	17.37
Neu. (%)	22.17	5
LYM (%)	76.96	95

Summarizing that TB Meningitis is seen across all CD4 levels, with a higher occurrence in lower CD4 counts. Cryptococcal Meningitis and ADC are most common at very low CD4 levels (0 - 50). Toxoplasmosis and PMLE are seen across a range of low CD4 counts, particularly in the 51 - 150 range. PCL is seen only at very low CD4 levels (0 - 50) and a moderate level (151 - 200). No clinical manifestations (besides TB Meningitis) are reported at CD4 levels above 250. This table 8 suggests that as the CD4 count decreases, the likelihood of severe opportunistic infections and neurological complications increases.

The table 9 provides a cerebrospinal fluid (CSF) analysis comparing findings in patients with Tuberculosis (TB) meningitis and Cryptococcal meningitis. Here's a summary of the key differences: TB Meningitis: Typically characterized by higher protein levels, lower glucose, higher total cell count with a predominance of lymphocytes, and a moderate percentage of neutrophils and Cryptococcal Meningitis: Shows lower protein and cell counts, higher glucose levels, with a predominance of lymphocytes and very few neutrophils. This analysis helps differentiate between TB meningitis and cryptococcal meningitis based on CSF findings.

Table 10: Radiological findings observed in various cases

Radiological findings	No. of Cases
Meningeal and basal cistern enhancement	12
Meningeal enhancement + granulomatous lesion s/o tuberculoma	10
Meningeal enhancement with infarction	4
Hydrocephalus	3
Multiple Non enhancing lesions in parieto - occipital/periventricular/cerebellum/basal ganglia. s/o PML	2
Multiple Ring enhancing lesions distributed in whole brain	4
Single ring enhancing lesion	1
Cerebral cortical atrophy	4

The table 10 provides a summary of radiological findings observed in various cases, focusing on the number of cases that presented each specific finding. Here's a detailed breakdown

a) Meningeal and Basal Cistern Enhancement:
- Number of Cases: 12
- This finding suggests inflammation or infection, commonly seen in conditions like meningitis, where the meninges and basal cisterns are enhanced on imaging.

b) Meningeal Enhancement + Granulomatous Lesion:
- Number of Cases: 10
- The combination of meningeal enhancement and granulomatous lesions is indicative of a tuberculoma, which is a form of tuberculosis infection that forms a granuloma in the brain.

c) Meningeal Enhancement with Infarction:
- Number of Cases: 4
- This finding indicates that alongside meningeal enhancement, there is also infarction (tissue death due to lack of blood supply) in the brain.

d) Hydrocephalus:
- Number of Cases: 3
- Hydrocephalus refers to the accumulation of cerebrospinal fluid (CSF) in the brain, leading to increased intracranial pressure.

e) Multiple Non - enhancing Lesions in Parieto - Occipital/Periventricular/Cerebellum/Basal Ganglia
- Number of Cases: 2
- The presence of multiple non - enhancing lesions in these regions of the brain can suggest PML, a viral infection that causes demyelination of the white matter in the brain.

f) Multiple Ring Enhancing Lesions Distributed in Whole Brain:
- Number of Cases: 4
- Multiple ring - enhancing lesions are often indicative of abscesses, metastasis, or other infectious or inflammatory conditions affecting various regions of the brain.

g) Single Ring Enhancing Lesion:
- Number of Cases: 1
- A single ring - enhancing lesion could suggest an abscess, tumor, or tuberculoma localized to one area in the brain.

h) Cerebral Cortical Atrophy:
- Number of Cases: 4
- This finding indicates the loss of neurons and the shrinkage of the cerebral cortex, which is commonly associated with neurodegenerative conditions.

The table categorizes various radiological findings in terms of their frequency across cases, indicating that meningeal enhancement, with or without granulomatous lesions, is the most common finding. There are also significant instances of ring - enhancing lesions and cerebral atrophy, with fewer cases of hydrocephalus and non - enhancing lesions suggestive of PML.

4. Discussion

With available evidence that neurological complications in HIV are common and increase in frequency with severity of immune depression [14] the disparity in prevalence across similar settings might portray differences in HIV/AIDS disease burden and the challenges in the diagnosis of HIV - associated CNS disease. Though we found a high prevalence of CNS disease during our study period when HIV treatment scale - up was still at the primary stage, we speculate that present prevalence of HIV - associated CNS disease may still be high, because present national HAART scale - up barely approaches 60% [15], and present CNS disease diagnostic ability across the country has improved recently by the installation of CT scan machines in many regions. Nevertheless, we need more studies to depict this.

Clinically, the most common presenting complaint in our study population was fever (80%) followed by altered sensorium (66%) and headache (56%) while dementia (20%) is the least common among the patients in the study. Headache being a symptom present in overt brain dysfunction and meningitis [16] should always be properly investigated in HIV - infected patients most especially, as it could be the only symptoms in life threatening CNS disease. Other studies found headache to be common in 60 - 90% of patients with HIV - associated CNS disease. [17, 18].

Meningeal signs which were very common in bacterial, tuberculous, and cryptococcal meningitis. This is worth considering in resource limited settings where most diagnoses rely on patients' complaints and clinical findings. Therefore in areas where minimal CSF analysis is possible, clinicians should not hesitate to perform LPs in patients who present with these symptoms and signs. In HIV, CNS diseases have diverse nonclassical presentations, such that the presence of classical clinical signs might be a sign of severity as shown by the high mortality associated with meningeal signs in our study. CNS disease should therefore be suspected in the presence of any nervous system symptom in HIV - infected patients. Focal signs were also common and this could be explained by the etiologic factors of which space occupying lesions were the most prevalent. Our findings are consistent with others. [17, 18]

Tuberculosis meningitis was the most common aetiology of CNS disease in our study (40%). Evidence shows that about a third of the world's population is chronically infected with TB. [19] TB meningitis which is a reactivation of quiescent

chronic infection increases in frequency with severity of immune depression. Tuberculous (TB) meningitis is observed across all CD4 levels, with an increased prevalence at lower CD4 counts. Cryptococcal meningitis and AIDS dementia complex (ADC) are most frequently seen in individuals with very low CD4 counts (0 - 50). Toxoplasmosis and progressive multifocal leukoencephalopathy (PML) occur within a broader range of low CD4 counts, particularly in the 51 - 150 range. Primary central nervous system lymphoma (PCL) is primarily observed in patients with very low CD4 levels (0 - 50) and at a moderate level (151 - 200). Notably, apart from TB meningitis, no clinical manifestations are reported at CD4 counts above 250. This study underscores that as CD4 counts decrease, the likelihood of severe opportunistic infections and neurological complications significantly increases.

Though we showed that CNS disease prevalence is high among HIV patients in Ahmedabad, our study had certain limitations. The use of clinical case files for abstracting data for the study that rendered it difficultly for us to include other confounding causes of death in our analysis and missing data was a major flaw given that the clinical notes of all the patients are not reported the same way. More so, the exclusion of patients who might have had the disease conditions studied, but who did not have a working diagnosis, might have led to over or underestimation of causes of CNS disease in HIV. Furthermore, being a hospital - based study in an urban area, it may not capture the real picture of the burden of CNS disease in Ahmedabad. Finally, the absence of data on HAART during the study period when HAART availability was starting in southeast Asia might have heavily confounded mortality. However, our study has improved our knowledge on CNS disease in HIV patients and sets a template for further prospective studies in the field.

5. Conclusion

HIV - associated CNS disease is common among HIV patients admitted to Dr. M. K. Shah medical college and research Hospital. CNS symptoms in HIV patients require urgent investigation, as they might be associated with diseases that have high case fatality. In view of the high proportion of patients who still present in severe immune depression, more efforts are needed to reinforce guidelines pertaining to timely prophylaxis against opportunistic infections, early diagnosis, and treatment of CNS diseases, and commencement of HAART, as these would help reduce morbidity and mortality

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