DISSERTATION ON

A PROSPECTIVE STUDY OF VARIOUS CNS MANIFESTATIONS ASSOCIATED WITH HIV/AIDS AND TO STUDY A RELATIONSHIP BETWEEN IT AND CD4 COUNTS

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations

for the award of the degree of

M.D. DEGREE IN GENERAL MEDICINE

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THANJAVUR - 613 004

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032

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CERTIFICATE

This is to certify that this dissertation entitled "**A PROSPECTIVE STUDY OF VARIOUS CNS MANIFESTATIONS ASSOCIATED WITH HIV/AIDS AND TO STUDY A RELATIONSHIP BETWEEN IT AND CD4 COUNTS"** is the bonafide original work of **Dr. M.SATHISH KUMAR** in partial fulfillment of the requirements for **M. D. Branch - I (General Medicine)** Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in APRIL - 2013. The period of study was from january- 2012 to September - 2012.

Prof. Dr. P.G.SANKARANARAYANAN,M.D.,
Unit Chief M-II,
Department of Internal Medicine,
Thanjavur Medical College,
Thanjavur - 613004.

Prof. Dr.S.MUTHUKUMARAN,M.D.,
Professor and Head,
Department of Internal Medicine,
Thanjavur Medical College,
Thanjavur - 613 004.

Prof. Dr.M.GUNASEKARAN, M.D.,
DEAN,
Thanjavur Medical College,
Thanjavur - 613 004.

DECLARATION

I, **Dr. SATHISH KUMAR.M**, solemnly declare that dissertation titled **" A PROSPECTIVE STUDY OF VARIOUS CNS MANIFESTATIONS ASSOCIATED WITH HIV/AIDS AND TO STUDY A RELATIONSHIP BETWEEN IT AND CD4 COUNTS "** is a bonafide workdone by me at Thanjavur Medical College, Thanjavur during JAN - 2012 to OCT - 2011 under the guidance and supervision of **Prof.Dr.P.G.Sankaranarayanan, M.D.,** Unit Chief M-II, Thanjavur Medical College, Thanjavur.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University towards partial fulfillment of requirement for the award of **M.D. Degree (Branch - I) in General Medicine**.

Place: Thanjavur.
Date:

(Dr.SATHISH KUMAR.M)
Postgraduate Student,
M.D. in General Medicine,
Thanjavur Medical College,
Thanjavur - 613 004.

A PROSPECTIVE STUDY OF VARIOUS CNS MANIFESTATIONS ASSOCIATED WITH HIV/AIDS AND TO STUDY A RELATIONSHIP BETWEEN IT AND CD4 COUNTS

BACKROUND:

AIDS is a disease caused by human immunodeficiency virus and featured by immunosuppression leading on to opportunistic infection secondary neoplasm's and neurological manifestations. According to WHO HIV is a pandemic. The mortality due to opportunistic infection is more. The opportunistic infection occurred when there was a decrease of cd4 counts.

METHODS:

A prospective study was conducted in Thanjavur medical college thanjavur with an objective to determine the various CNS manifestations associated with HIV and its relation with the CD4 counts. All the seropositive aged more than 14 yrs with CNS manifestations where included in the study. Clinical examinations, CT, MRI, serology, CSF analysis were done and diseases where diagnosed based on respective criteria's. CD4 counts where done and co related with the diagnosis. A total of 40 cases were studied.

RESULTS:

The infection was common among males. The people aged between 30-39 where affected the most. Tuberculosis was the most common infection. Toxoplasma and tuberculoma presented with focal neurological signs. One case of progressive multifocal keukoencephalopathy was observed, he presented with seizures. Seizure was also seen with toxoplamosis and neurocysticercoisis. Most of qall the cases had headache as the commonest symptom.CNS TB had mean CD4 count of 217, cyptococcal meningitis had a mean count of 130, toxoplasmosis with a mean count of 104, PML with 286.Two cases of stoke were observed and it was attributed to direct virus infection and they had a mean count of 323. Three cases of the 22 tb cases had TB lymphadenitis, intestinal TB AND TB pericarditis.

CONCLUSION:

The various cns manifestations studied were TB meningitis, cryptococcal meningitis, tuberculoma, toxoplasmosis, PML, stoke, ATM. TBM was the most common infection observed. TB occurred over a range of CD4 counts so cannot be used as a AIDS defining illness. The mortality for CNS TB was more when it occurred with low CD4 counts. Headache was the most common presentation.

Thanjavur Medical College

THANJAVUR, TAMILNADU, INDIA-613004

(Affiliated to the T.N Dr.MGR Medical University, Chennai)

ETHICAL COMMITTEE

CERTIFICATE

Name of the Candidate	:	Dr. M.SATHISH KUMAR.
Course	:	M.D (GENERAL MEDICINE)
Period of Study	:	JANUARY 2012 – NOVEMBER 2012
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The Ethical Committee, Thanjavur Medical College has decided to inform that your Dissertation Topic is accepted and you are permitted to proceed with the above study.

Thanjavur

Date :

THANJAVUR MEDICAL COLLEGE * THANJAVUR-4 *

Secretary

Ethical Committee

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A special mention of thanks to all the patients who participated in this study for their kind cooperation. I would like to thank my colleagues and friends who have been a constant source of encouragement.

CONTENTS

INTRODUCTION

IT was in 1983, the cause of acquired immunodeficiency syndrome was identified as human immunodeficiency virus type-1. Almost 28 years have elapsed since discovery,and through these years it has been changed from a fatal disease to a treatable chronic diseases. The greatest discovery in the history of medicine was the discovery of Anti retro viral theraphy for AIDS that has made the condition treatable. However still largely many people of the developing and third world countries are inaccessible to ART.

GLOBAL SCENARIO

Antiviral therapy and increased incidence of HIV has increased the number of people living with HIV. According to data in the 2010 AIDS epidemic update (1)because of HAART and population growth more people are living with AIDS and the death rate has come down by 10% saving nearly 2.9 million people. There is a 17% reduction in death during the past 8 years. (2001. United nation declaration of commitment on HIV/AIDS.[1])

SCENARIO IN INDIA

Despite being the world's 3rd biggest population affected by HIV/AIDS (south Africa and Nigeria), the disease prevalence is lower than other countries.1.4-1.6 million have HIV in India and there is a 50% decrease in incidence with the epidemics being stable at the national level(BMJ). Gender disparity, labour,

migration, illetracy largely contribute to the spread of the diseases. Available data shows stable figures at national level.

The estimated adult HIV prevalence was 0.31% in 2009. The states with high HIV prevalence rates include Manipur (1.40%), Andhra Pradesh (0.90%), Mizoram (0.81%), Nagaland (0.78%), Karnataka (0.63%) and Maharashtra (0.55%).The adult HIV prevalence in India is declining from estimated level of 0.41% in 2000 through 0.36% in 2006 to 0.31% in 2009.

SCENARIO IN TAMILNADU

TANSACS (TAMILNADU STATE AIDS CONTROL SOCIETY) is a government organization that is responsible for the prevention, treatment and supportive measures in the state. According to the NACO 2011 AIDS STATISTICS of TAMILNADU , HIV prevalence in antenatal clinic is 0.25%,prevalence in STD clinic is 8.00%, prevalence amoung drug users is 16.80%,prevalence amoung sex workers is 4.68%.

HIV AND OPPORTUNISTIC INFECTION

Apart from the virus, opportunistic infections contribute considerably to the mortality amoung AIDS cases. The level of immune suppression and the endemicity of the agent determine the incidence of the infection. Tuberculosis (TB), amoebiasis and leishmanias have higher incidence amoung HIV infected patients.

CNS MANIFESTATION IN HIV/AIDS

Neurological manifestations are seen ail through the course of the illness from the prodromal stage to the terminal stage and any part of the neuroaxis can be involved. Symptomatic illness develops in 50% of cases and pathological lesions are demonstrated in 90% of the pathological specimens at autopsy. CNS manifestations can either be due to the virus or opportunistic infection. IT can also be demylenating or degenerative in nature. The manifestations depend on the prevailing endemic infections, literacy status, accessibility to ART and nutitional status.

There have been only few studies regarding neurological manifestations in PLWHA. Poone medical research foundation (7) have reported crypticoccal meningitis was commoner than TB meningitis.Amongst mass lesions CNS Tuberculoma and toxoplasmosis was the most common cause.Several studies have reports opportunistic infections were the leading cause of mortality and CNS tuberculosis was not A good predictor of advanced STAGE OF ILLNESS. CNS tuberculosis was relatively more in earlier stages of the disease. AIDS-DEMENTIA complex (ADC) and CNS malignancies were very rare.There has been only few studies from our centre and from our state, inspiring us for this study. Our hospital is a tertiary care centre and a large number of patients have been reported as PLWHA.

AIMS AND OBJECTIVES

Keeping in view of above facts a prospective study will be conducted in department of medicine, THANJAVUR MEDICAL COLLEGE. THANJAVUR between JAN 2012- OCT 2012 with an objective to determine the various CNS manifestations associated with HIV/AIDS and to establish a relationship between occurrences of it with the CD4 count.

ACQUIRED IMMUNODEFICIENCY SYNDROME

DEFINITION

AIDS is a disease caused by retrovirus human immunodeficiency virus & characterized by profound immunosuppression that leads to opportunistic infections , secondary neoplasms & neurologic manifestations.

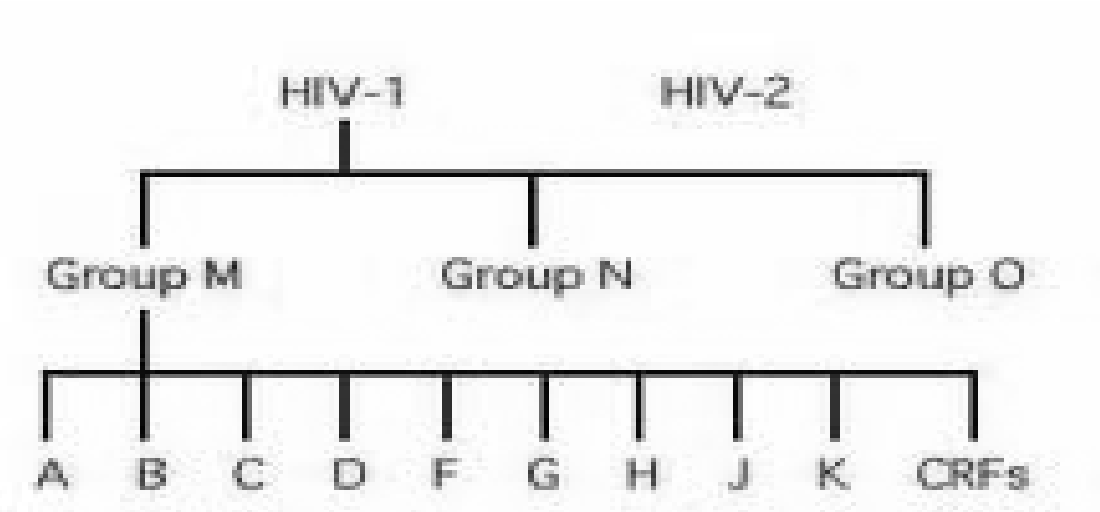
HIV is a pandemic according to WHO. Death toll due to AIDS is 25 million people(1981-2006).[13] HIV infects about 0.6% of the earth population.[13] the prevalence in 2004 was 2.1 million to the present 2.1 million in 2010[14]. A disproportionate number of AIDS deaths(260000 children in 2010 [14]) occurred in Africa, bringing down the GDP and increasing the number people below poverty line.[15] HIV is estimated to infect atleast 90 million people in Africa producing 18 million orphans. Since the detection of HIV in 1984 ,it has been extensively studied,its molecular and cellular biology is now better understood than that of any other virus.

AIDS is caused by Human immunodeficiency virus. It is very small and fragile virus belonging to retro virus family.The virus infects the helper T cells of immune system(mainly CD4 cells, dentritic cells,macrophages). These cells harbor mature viruses in lymph nodes and lymphoid organs and continue to infect other immune cells, in a more vigorous way. There is continuous decrease

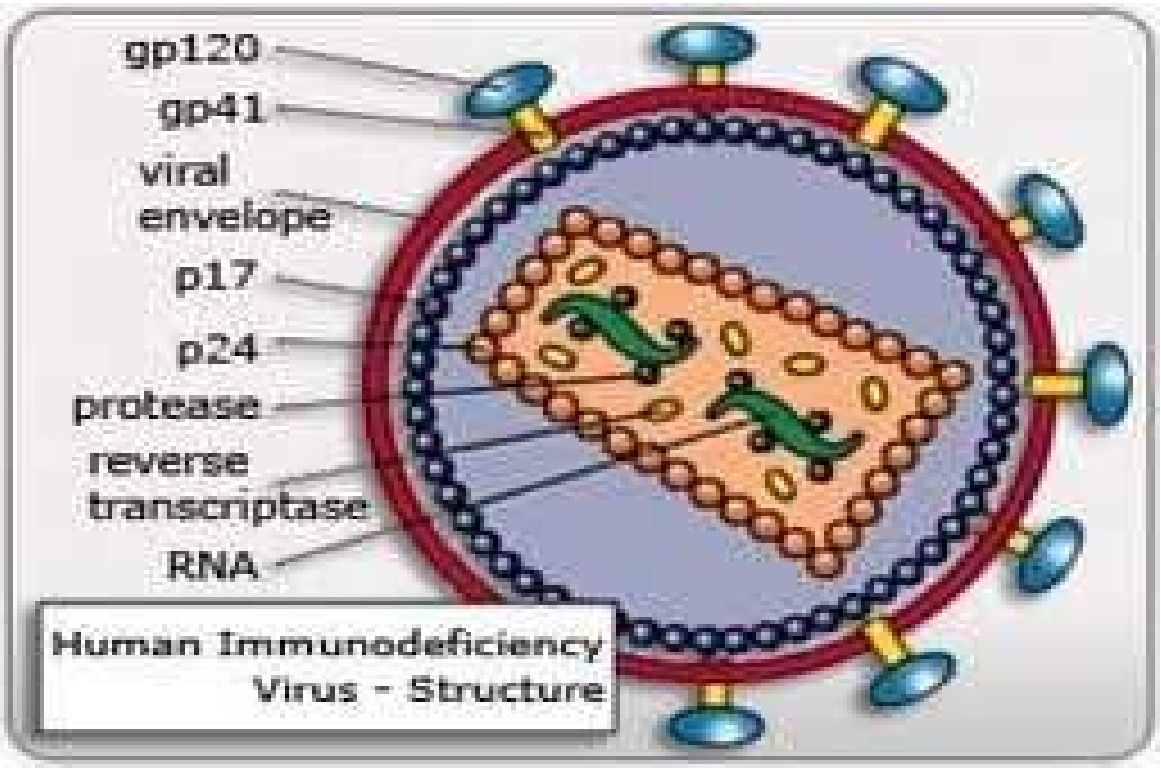
in cell count,with a explosive increase in viral load. After reaching a peak viral concentration,a gradual decrease is observed.

HIV SUBTYPES

HIV can be classified into 2 types based on genetics and antigen into HIV-1, the cause of the ongoing pandemic and HIV-2, seen in west Africa but rare otherwise. HIV type 1 is linked to P troglodytes(SIV cpz),while HIV type2 (HIV-2) to the sooty mangabey virus (SIV smm). HIV-1 can be classified based on the env gene in to groups M,O,N and groups M into subtypes A-K(9).Most research is on subtype B, seen in western countries and japan. Africa habours A and AG while INDIA habours C.



HIV STRUCTURE



HIV 1 is made of 2 mRNA copies (positive sensed).Each strand >9700 nucleotides long and is associated with helical nucleocaspid (p9/6). The icosohedral capsid (p24) covers the above complex. This environment contains the reverse transcriptase.The matrix protein surrounds the caspid. The envelope of the virus(go140 &gp41) is derived from the host cell membrane.

The first prototype of its structure designed in 2006 using cryoelectron microscopy showed TRIMER of gp120-gp41 .[15] However later a compact single-stalk "mushroom" prototype was published.[16] Recent evidence however backs the trimer prototype.

THE COURSE OF AIDS:

HIV usually enters the body(most frequiently by sexual route) infects macrophages and dentritic cells invading mucosal tissues as they are primary line of defence. Dendritic cells pileup the viral particles on to their surfaces(by gp140) but fails to internalize them.

Opportunistic infection in hiv/aids HIV poduces the largest number of deaths.Though HIV does not kill, it weakens the human immune system and making the person vulnerable for infection which are rarely seen in those with normal immune system.Such Infections seen in the immuno suppresed are called opportunistic infections.(10)

Opportunistic infections and its complications creates a considerable proportion of mortality. The level of immune suppression decides the infection.(occurring at CD4 counts <200or total lymphocyte count <1200).Tuberculosis,amoebiasis and leishmaniasis occur more frequently in HIV infected patients. Many of these opportunistic infections seen in advanced stages of the diseases are called AIDS defining illness

CNS MANIFESTATIONS OF HIV

The nervous system is a vulnerable target for HIV infection(40% to 70% HIV people). [19] . The CNS complications of AIDS are neurocognitive dysfunction and HIV-associated dementia (HAD; HIV encephalopathy), vasculitis, demylenation[21,22]. Secondary infections due to immunosupresion.

HAD is dreadful CNS complication of HIV infection. [30] Milder form of impairment is called HIV-associated minor cognitive/motor disorder (MCMD).

HIV Dementia

In 1992, 7.3% AIDS cases were said to have HIV Dementia(Centers for Disease Control and Prevention database)[42].One of the difficult to understand sequlae of HIV infection of the brain is HIV dementia . The term *HIV-associated neuro cognitive disorders* (HAND) extends from asymptomatic neuro cognitive dysfunction through minor neurocognitive disorder to clinically severe dementia. Symptoms of HAD can be futher divided into 3 main types: cognitive, motor and behavioral [33]. The primary cognition affected is memory loss with mental and motor retardation and signs being ataxia and weakness. The behavioral symptoms such as apathy and social withdrawal are commonly seen and are often mistaken for depression. ADC develops after many years of latency and is associated with low CD4 counts and

increased viral load. The yearly incidence of HAD in developed countries before HAART was 7%, (cumulative risk = 5-20%).With HAART, the incidence of HAD began to decrease, but it increasing again. Indian based studies show a prevalence of 1-2% as clad C hiv virus is prevalent in india.

Initial presentation may be too elusive to arrive at a clinical diagnosis. Neuropsychological tests to detect milder dysfunction serves as quantitative markers of disease progression [34-35]. As dementia advances, cognitive dysfuntion becomes more manifest(with psychomotor slowing and marked behavioral aberrance).Signs such as paraparesis, incontinence, tremor, and seizures are seen at this stage.

Study by rakendra singh etal in Punjab in 2009 (158) showed HAD to cause significant morbidity(33.65%), CNS infections succeds(21.63%) . Most other Indian studies revealed less prevalence of HIV dementia.

PATHOPHYSIOLOGY

HIV infecting the monocytes and $CD4^+$ cells, enters the brain. Immunohistochemistry revealed dense virus concentration in sudcortical gray matter. Autopsy also proves the predominant subcortical deep gray involvement (basal ganglia, thalamus). The mechanism how HIV infection of the CNS leads to neurocognitive disorders is the subject of intense research.sidits and price [37] deviced a scale for AIDS dementia complex , normal(grade 0) to end

vegetative state (grade 4).The memorial sloan kettering scale for the aids dementia complex is also used.

Diagnostic criteria(9)

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1. Marked acquired impairment of at least two ability domains of cognitive function.
2. Cognitive impairments identified in 1. interfere markedly with day-to-day activities.
3. Cognitive impairments identified in 1. are present for at least one month.
4. Cognitive impairments identified in 1. do not meet the criteria for delirium.
5. No evidence of another, pre-existing aetiology that could explain the dementia. (e.g. a CNS neoplasm, cerebrovascular disease).

Diagnostic Studies

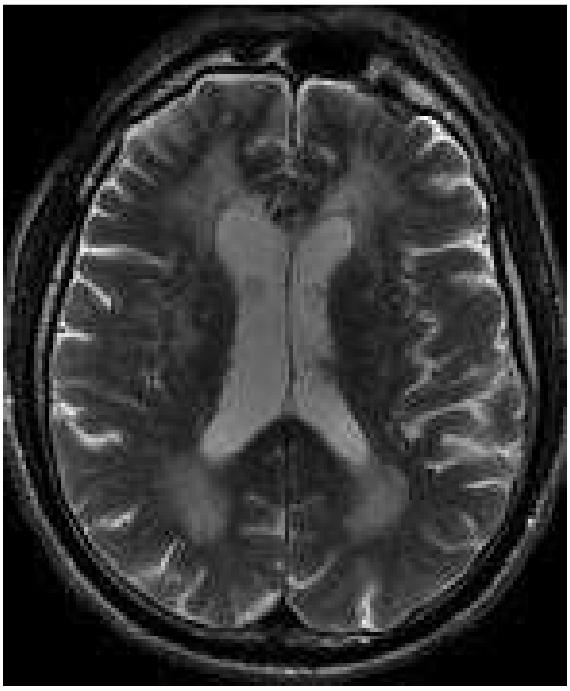
Neuroimaging

Computed tomography (CT) and MRI studies helps to prove ADC and rule out other diagnosis (infections or neoplasms). CT can shows diffuse cortical atrophy, ventricular enlargement, and Basal ganglia calcifications. Neuroimaging results may be normal in early stages.

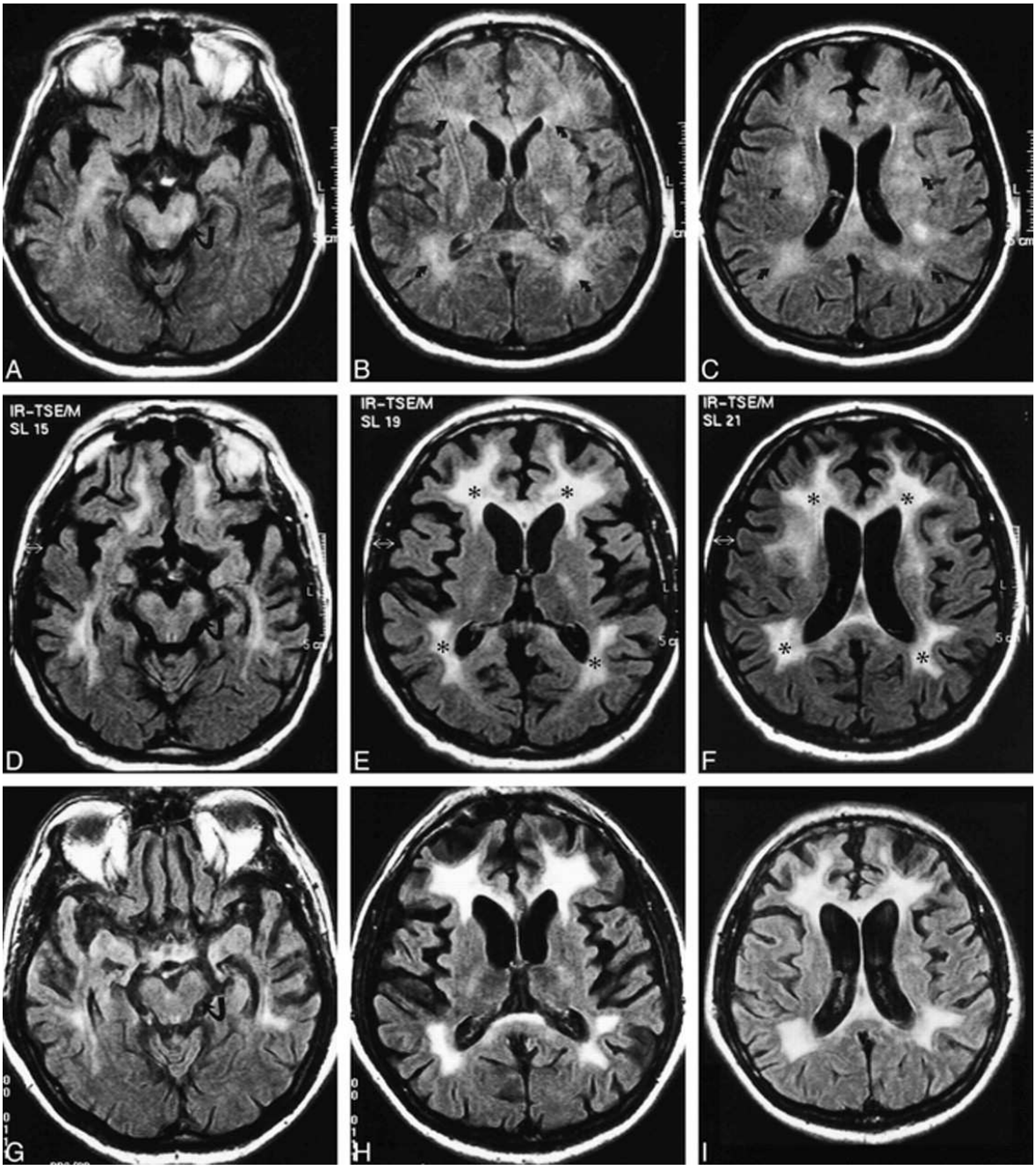
MRI(T2- weighted) shows hyperintense lesions in the periventricular white matter and centrum semiovale. The lesions are patchy initially and spreads as

the pathology advances. Differential diagnosis are multiple sclerosis (MS) and small-vessel disease.(159)

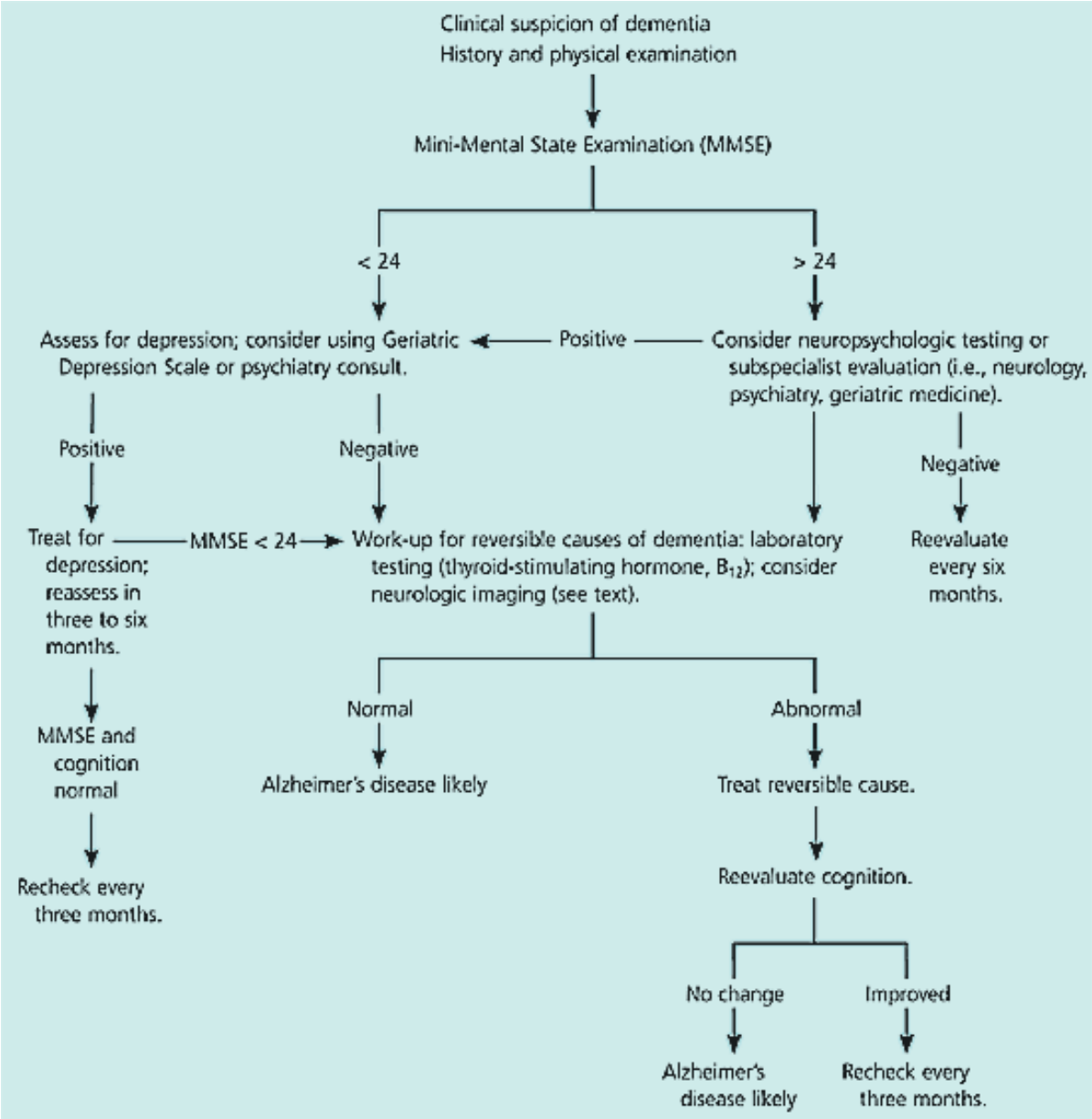
MRI OF PATIENT WITH HIV DEMENTIA



ADC and effect of HAART



Algorithm for Dementia



Treatment

Highly active antiretroviral therapy (HAART) is the basis for the management of HIV-related cognitive disorder. HAART is shown to produce a decline in the rate of dementia from 50% to 10% and partly reverses of neuropsychological deficits.[43]HAART protects from and abates the incidence of AIDS dementia complex and HIV-associated progressive encephalopathy.

Stroke Syndromes

Strokes and TIAs can occur in HIV patients(1.5% of advanced HIV). Though mostly due to opportunistic infection, in more than half there is no attribute apart from the HIV virus itself. A complex mix of effects of anticardiolipin Ab, decreased protein S levels, and dysfunctional heparin cofactor II creates a prothrombotic state and vasculitis produced by the virus itself with significant overlap between the two is attributed as the cause.Uncontroled release of TNF alpha and interleukin-1 in advanced stages appends to the thrombophilia that exist.[46]. Brew and colleagues[44] found the mean CD4+ cell count to be 130 ± 80 cells/mcL, with most having CD4+ cell counts < 50 cells/mcL.

Alaka K Deshpandeand **Mrinal M Patnaik study in Mumbai of 300 hiv infected cases revealed (160)** 67 (22.3%) had CNS manifestations attributable to the direct effects of HIV. The presentations were stroke (29.8%), demyelination(5.9%), HAD (5.9%), and venous thrombosis (4.4%), peripheral

neuropathy (35.8%), spinal cord disease (5.9%), and a case of myopathy. These findings closely co related with their CD4 counts.

MRI with angiograms showed focal segmental narrowing of vessel walls. However, CSF examination are negative for any antibodies, (VARICELLA and CMV , VDRL) thereby concluding vasculitis as a direct effects of HIV.

HIV Myelopathy

Myelopathy was present in ~20% of patients with AIDS, often as part of HIV encephalopathy. This condition is pathologically similar to subacute combined degeneration(pernicious anemia). vitamin B12 deficiency seen in patients with AIDS as a primary complication of HIV infection does not appear to be responsible for the myelopathy . Since the introduction of HAART, there are less than 10% of AIDS patients who develop HIV myelopathy. In Indian studies HIV myelopathy was reported rarely.

CLINICAL PRESENTATION

Characterized by a subacute onset , presents with gait disturbances, predominantly ataxia and spasticity; it may progress to include bladder and bowel dysfunction.(46)

Physical findings include evidence of increased deeptendon reflexes and extensor plantar responses.The second form of spinal cord disease involves the dorsalcolumns and presents as a pure sensory ataxia.The third form is also

sensory in nature and presents with paresthesias and dysesthesias of the lower extremities.

Diagnostic Tests

1. CSF analysis can exclude infection with CMV,VCZ,HSV, HTLV-1, and HTLV-2. CSF results are usually normal in HIVmyelopathy.

2.Serum vitamin B-12 and folic acid levels. (B-12 levels are usually normal in vacuolar myelopathy).

3.A Schilling test, hematologic studies, and $CD4^+$ lymphocyte counts may be indicated.

There can be atrophy of the thoracic or cervical cord segments. T2-weighted MRI shows symmetric nonenhancing high-signal areas, which are present on multiple contiguous slices and are usually symmetrical; these may result from extensive vacuolation.[47, 48,49] Lesions may be confined to the posterior columns, especially the gracile tracts, or may be diffuse.

Treatment & Management

Care for patients with HIV-associated vacuolar myelopathy is primarily supportive. Viral load control with HAART is the main aim however the response is poor.

Secondary Lesions of the Central Nervous System

Toxoplasmosis

Toxoplasmosis is caused by protozoan *Toxoplasma gondii*[.52] .Cats are the primary host. Animals are affected by ingestion of infected meat, or by spread from mother to fetus. Cats are the primary source of for humans. Fecal soiling of extremites is a important risk factor.[53]

Toxoplasma infection is present in a third of world population.[54] The CDC reports a seroprevalence in US of 10.8% (NHANES) (1999-2004).

Seroprevalence of antibodies against T. gondii in HIV patients reflects the rates of seropositivity as of the general population. Those with HIV were more likely to have antibodies to T. gondii if they were ≥50 years of age .Owning a cat or not did not affect the incidence amoung HIV patients.

Toxoplasmosis is mostly asymptomatic. Loss of cellular immunity (esp CD4<100) there is reactivation of the latent infection presenting as cerebral toxoplamosis, however cases amoung seronegative patients are also reported(Renold*et al*, Cohen).

Toxoplasma gondii ,a intracellular protozoan exists in 3 forms: the oocyst, the tissue cyst, and the tachyzoite. Cat is the definitive host. Oocyst excreted by the cat sporulate into tissue cysts(in the muscles if animals).Undercooked meat is the source of infection to humans.The tissue cyst form tachyzoites, which reach the brain heart, muscle, lungs through the blood and remain quiescent. Immunosuppresion cause the disease to manifest. CNS is mostly affected (multifocal necrotizing encephalitis) and cerebral lobes are affected.

Cerebral toxoplasmosis mostly presents as mass lesion(cerebral cortex)in AIDS patients(3%-40%) [56, 57, 59-61] .It is due to reactivation of latent acquired endogenous infection, as evidenced by the absence of IgM antibodies [61]. It occurs in advanced stages of AIDS[60, 63]. Worldwide, *T. gondii* accounts for most of 'focal brain lesion' in HIV patients.The incidence of infection differs from country to country depending on the prevalence in the general population, genotypes of the organism isolated, racial foactors and ethnicity.

CLINICAL FEATURES

Annals states "Toxoplasma encephalitis can present with focal or generalized CNS manifestations [59-61] , the most frequently as headache (55%)and focal neurologic signs(69%); seizures,fever and altered conciosness are also seen.

[60].Patients develop diffuse encephalopathy as the disease progresses, subacutely over a period of months".

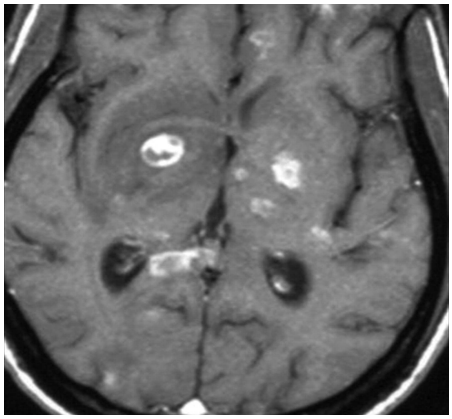
DIAGNOSIS

1.Computed tomography (CT) or MRI." MRI is more sensitive,especially for small posterior fossa lesions. MRI often identifies two or more lesions. Radiological findings can be divided into typical or atypical patterns. 'Typical' patterns is seen in 80% (hypo dense ring or nodular enhanching lesion with perilesional edema). Atypical patterns is seen in around(hypodense lesions in the absence of contrast enhancement and with pressure effect)" .Tuberculoma and primary central nervous system lymphoma (PCNSL) are the closest differncial diagnosis in AIDS patients. PET SCAN and tissue biopsy help in the diagnosis.

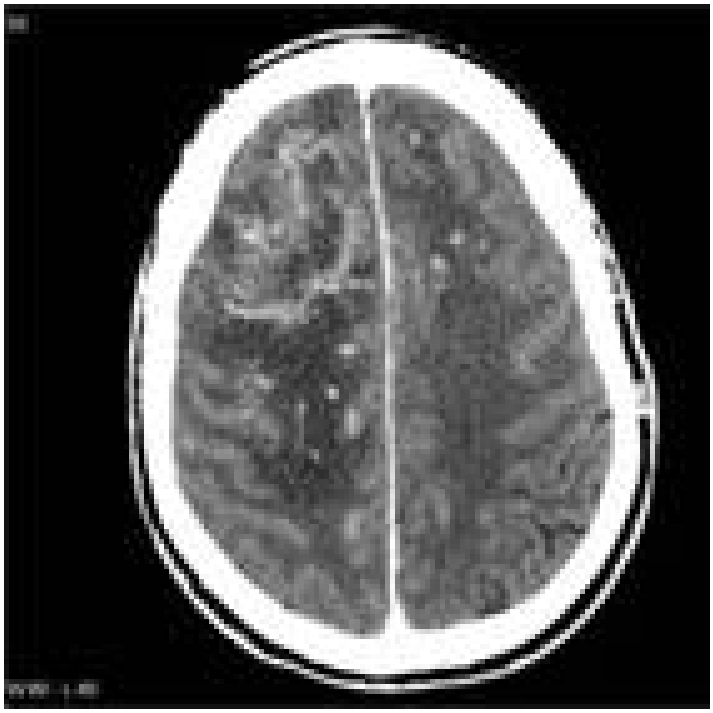
Imaging can be normal in diffuse toxoplasmosis.A journal of radiology states "Single lesions goes in favour of lymphoma than toxoplasmosis, However, multiple lesions are common in toxoplasmosis.MRI is sensitive over CT scan in detecting diffuse lesions"[161]

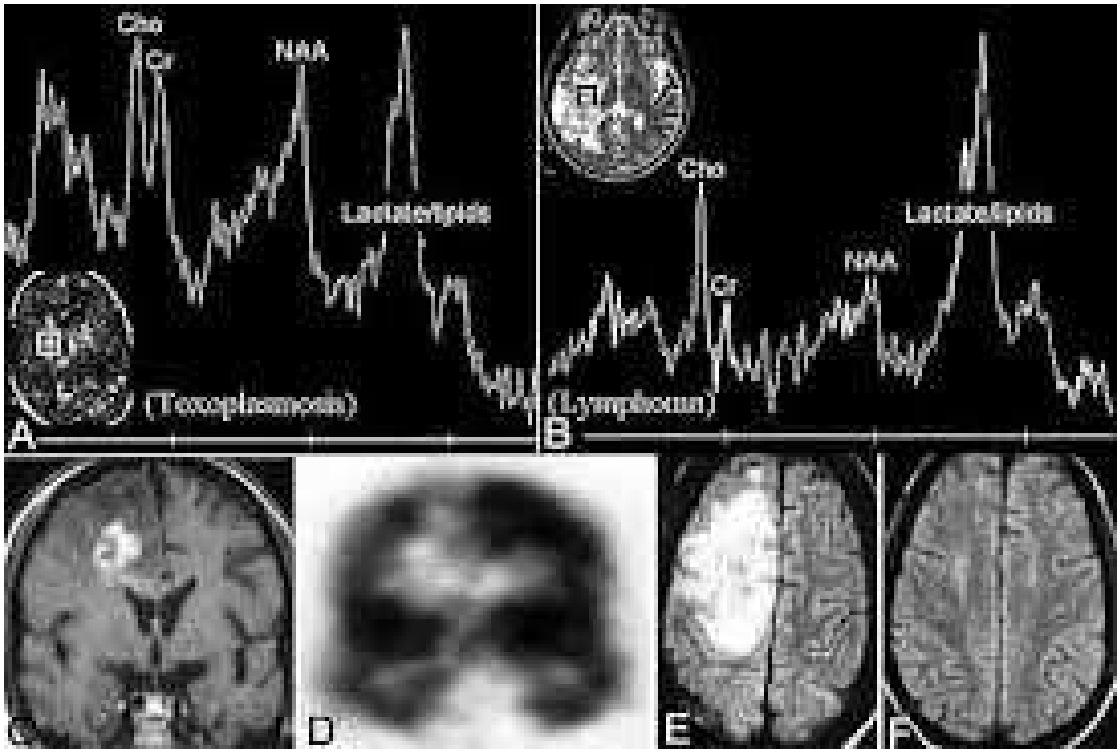
"If the imaging at the beginning of the disease is normal or show focal signal abnormalities (no mass lesion), a diagnosis of meningitis, AIDS dementia ,progressive multifocal leukoencephalopathy should be entertained".

MRI of a Patient with Toxoplasmosis

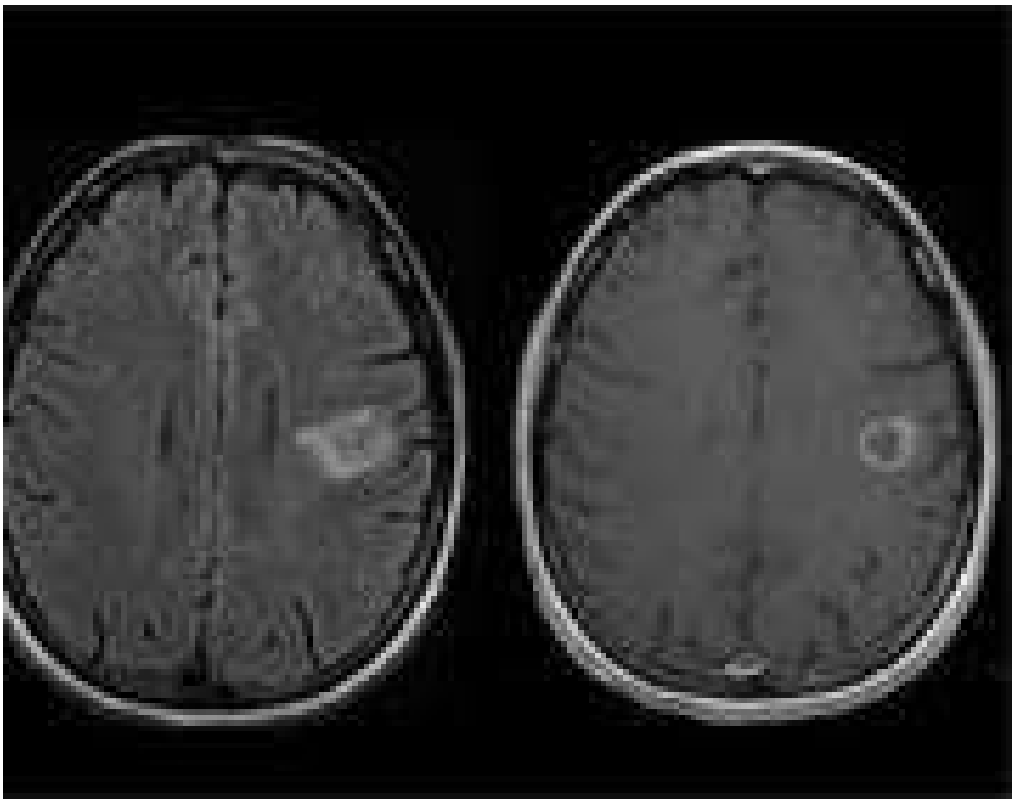


CT of a Patient with Toxoplasmosis (Multiple lesion)

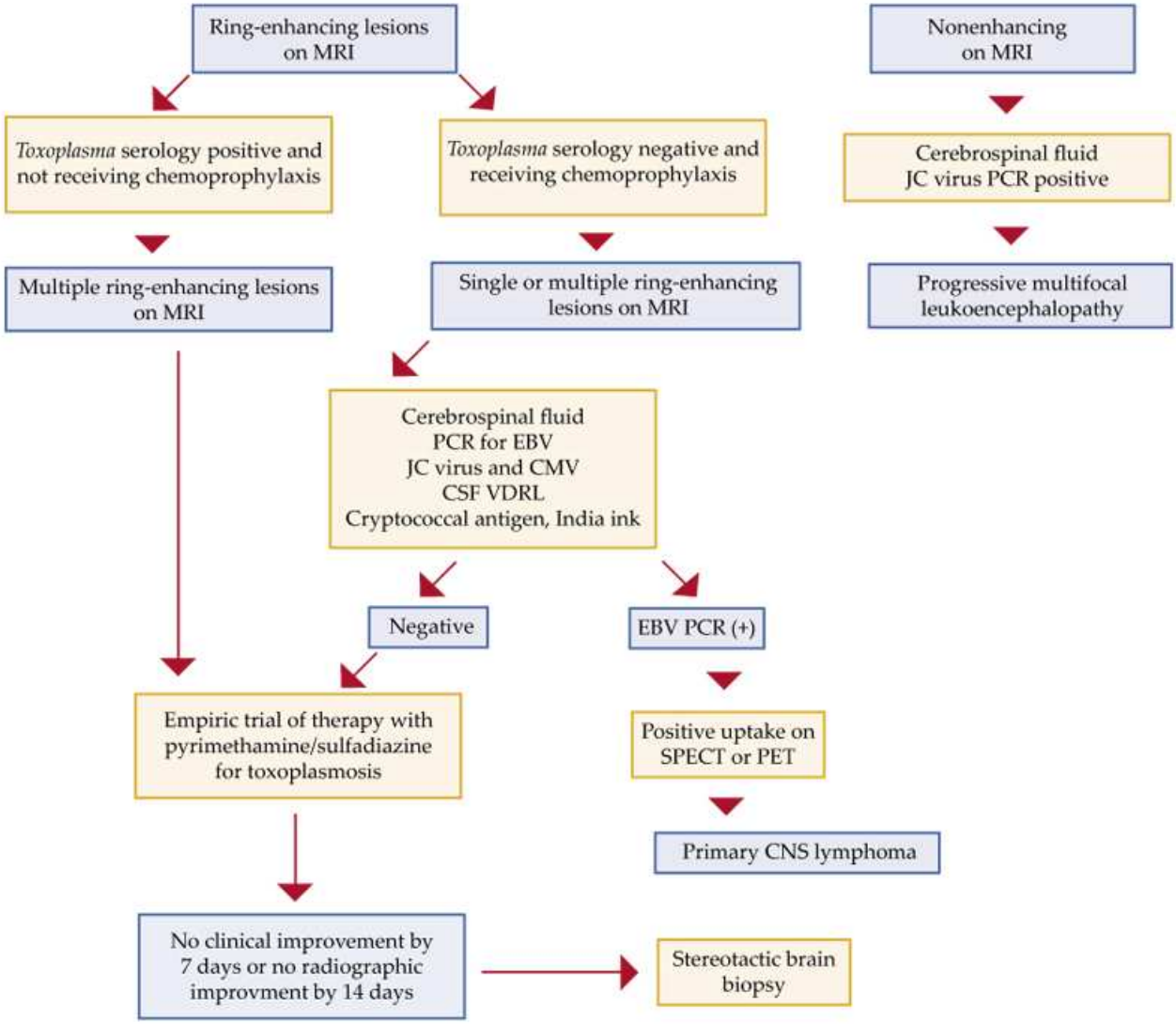




CT of a Patient with Toxoplasmosis (Single Lesion)



Algorithm for evaluation of the AIDS patient presenting with focal neurological disease.



If imaging shows one or more focal mass lesions with ‘impending herniation’, an open biopsy with decompression is indicated. Treatment (infections and neoplasms) is initiated, depending on biopsy results.If there is no evidence of herniation futher investigatios is advised.

Immunological Diagnosis

There is a high prevalence of sero positivity amoung the healthy people making serology a less useful test for diagnosis of cerebral toxoplammosis. In Brazil,(8)” Serology was positive in most AIDS cases with focal lesions”. Dhumni and sengupta study of national prevalence of toxoplasmosis in India (162) in 23,094 serum samples with the use of a solid-phase immune capture ELISA.Antibodies (IgG) were found in 24.3%; IgM antibodies were detected in 2% of the samples. The lowest sero prevalences were in the northern parts of India, with the highest in the south. Sero prevalence was 31.5% in Maharashtra,21.5% in tamil nadu, 21.2 % in Orissa,15.8% cases in delhi. These data probably reflect the effects of significantly drier conditions and, therefore, a negative impact on the survivability of T. gondii oocys. A negative serology does not rule out a diagnosis of cerebral toxoplasmosis and the treatment plan should not be altered.

Brain Biopsy

Indications for brain biopsy include either of the following (161)

- 'Single mass lesion and negative serologic results'
- 'No response to 14 days of empiric therapy'

TREATMENT

Radiologic findings and detectable antitoxoplasma antibody is an indication to initiate empirical therapy [63]. Oral pyrimethamine (loading dose of 50 to 200 mg/d followed by maintenance doses of 25 to 75 mg/d) and sulfadiazine (4 to 8 g/d) for 2 to 6 weeks after treatment produces good results [67 68], as both the drugs cross the blood-brain barrier [69]. Therapy with clindamycin and pyrimethamine is an also effective treatment for toxoplasma encephalitis with similar results [72, 74]. A RCT found that the percentage of favorable clinical responses at 3 weeks in patients treated with pyrimethamine and sulfadiazine (79%) was same as the percentage in those given pyrimethamine and clindamycin (77%) [72). If clinical or radiologic improvement does not occur within 1 to 2 weeks of begining empirical therapy, an alternative diagnosis should be sought using stereotactic brain biopsy.

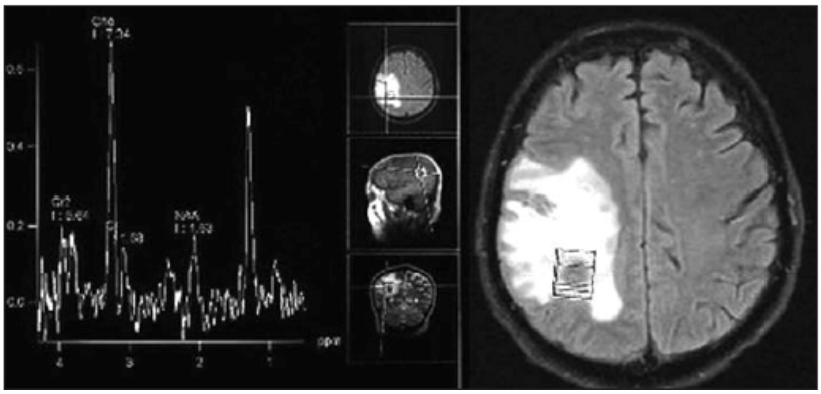
Primary Central Nervous System Lymphoma

Primary CNS lymphoma once considered to be rare is on the rise ,presenting in the late stage when the CD4 counts fall below 100. [84, 85[86, 87]. Many

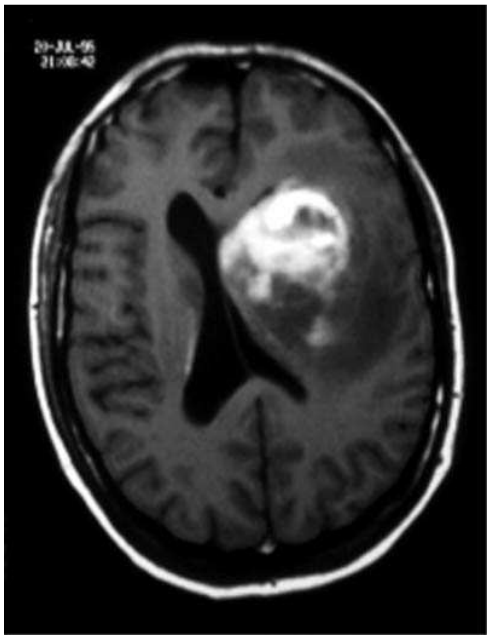
investigators have shown 100% association with EBV [88-92]. Cinque and associates [93] reported the diagnostic value of EBV DNA in CSF.

SIMPSON AND TAGLITI, ANNALS,showed “Patients presented with confusion, memory disturbance ,headache and focal neurologic deficits [84, 94-96]. Radiology may show ‘single / multiple homogeneously contrastenhancing lesions’. It is difficult to differentiate lymphoma from toxoplasmosis with clinical and radiologic evidence [85.], The evidence of a single lesion on MRI, especially when sera is negative toxoplasma antibodies, favors the diagnosis of lymphoma [90].’ Thallium-201 single-proton emission computed tomography [91] and positron emission tomography’ [92] are help to differentiate. Stereotactic biopsy gives definitive diagnoses[85-87].

MR SPECTROSCOPY OF CNS LYMPHOMA IN A HIV PATIENT



CT BRAIN OF CNS LYMPHOMA (SINGLE LESSION)



Primary CNS lymphoma occurring in AIDS carries a poor prognosis in untreated cases(median survival of < 1 month) [86, 87].However Radiation therapy improves neurologic outcome & quality of life in significant number of people [87, 88, 96] increasing the median survival by 4 to 6 months [77, 96].Radiation therapy with chemotherapy have shown positive results in prospective clinical studies.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leuko encephalopathy (PML) is caused by reactivation of the JC (ie, polyomavirus)[97] and as many as 90% of healthy people are seropositive but only <10% have evidence of disease activity. In cases associated with the initiation of HAART and the immune recovery, pre-existing subclinical PML starts to manifest.

Berger and colleagues [98] noted “PML in 4% of patients with AIDS and was the initial manifestation of AIDS in 29% “.The area where the virus replicates is a matter of arguement, however it is proposed to be bonemarrow and reticoloendothelial ststem. Whether the virus in the CNS gets reactivated or the virus on entering the CNS is activated is a matter of dispute.

Clinical Presentation

Patients with progressive multifocal leukoencephalopathy (PML) presents as insidious onset and steady progression(over several weeks) with symptoms like behavioral, speech, cognitive, motor and visual distrubance.[(163)] However, PML demonstrates relatively rapid progression compared to AIDS dementia complex (ADC).

As individual lesions expand, either concentrically or along white matter tracts, manifestations may worsen and involve a larger territory . Although seizures have been considered a rare manifestation of PML. Lima et al found that seizures occurred in 18% of PML and many had demyelinating lesions immediately adjacent to the cortex. Seizures usually responded well to treatment and did not affect survival.In PML related to immune reconstitution, onset may occur weeks to months after the initiation of antiretroviral therapy.

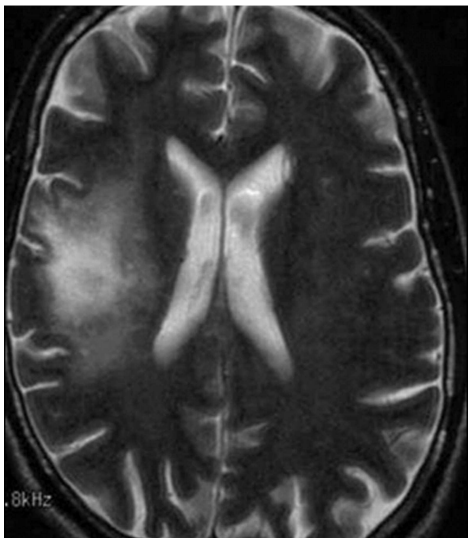
Physical examination

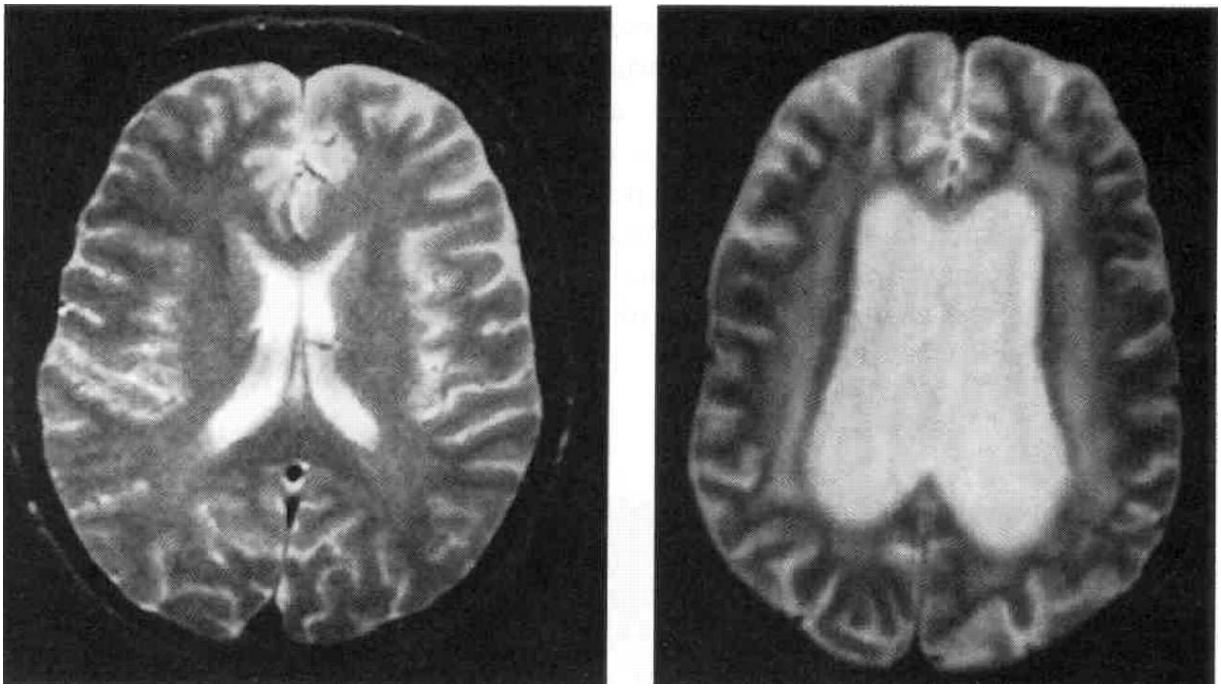
Focal neurologic signs like speech distrubance, weakness, difficulty in walking and balance, visual disturbance develop. Focal signs localizing mainly to the occipital lobes are seen. Conjugate gaze distrubances are frequent, occurings as first presentation in 30% of cases. Quadriparesis and coma can also develop as the diseases progress.

Computed tomography or magnetic resonance imaging

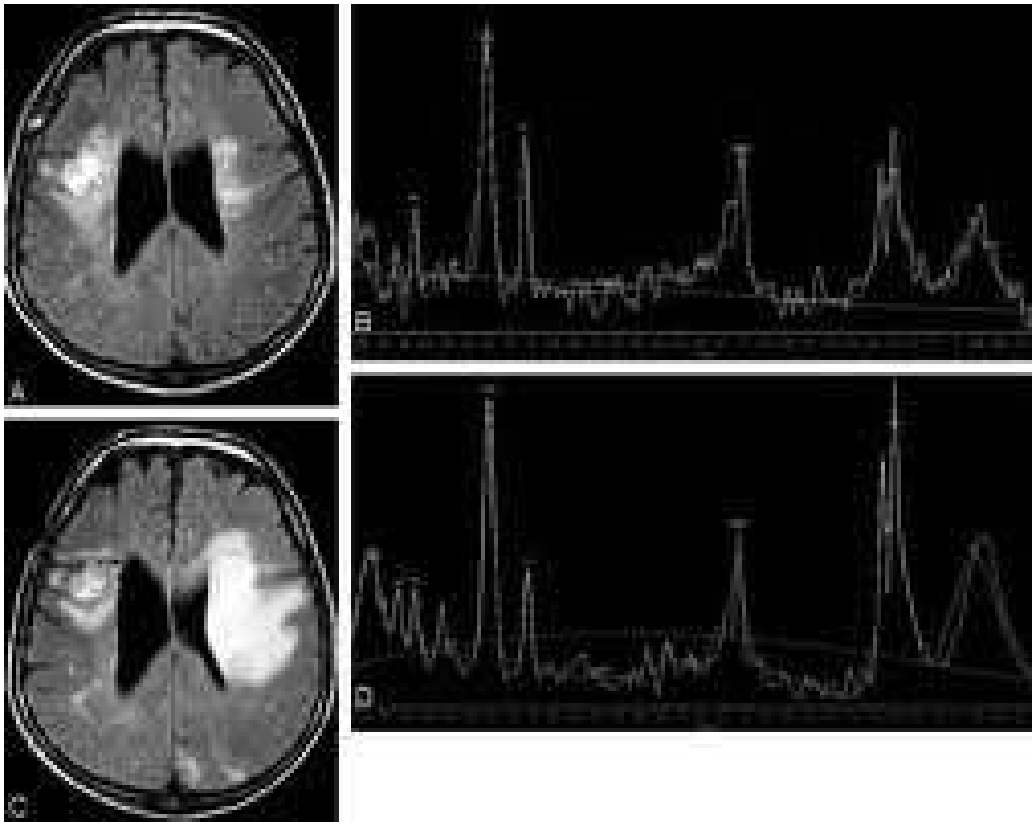
1. CT scan or MRI shows single or multiple concurrent lesions in the absence of pressure effects, mostly in subcortical whitematter. Lesions below the tentorium tend to be asymmetrical. Gray matter below the cerebral cortex and spinal cord are sometimes affected. The close mimic are lymphoma, toxoplasmosis and HIV encephalitis [162]

MRI OF A HIV PATIENT WITH PML





MR SPECTROSCOPY OF PML



Lumbar puncture

Cerebrospinal fluid (CSF) is usually normal.CSF PCR is highly specific (99%) and sensitive (93%) for demonstrating the VIRUS. For patients on retroviral theraphy, the CSF viral load is indicator of the disease activity.

BRAIN BIOPSY

Histological testimonial for a definitive diagnosis is neccessary. It shows many areas of severe demyelination, intense perivascular inflammatory infiltrates with large “ballooned” oligodendroglial cells, with nuclear viral inclusions [99]. JC virus can be demonstrated in oligodendrocytes by insitu hybridization. 100, 101].

Treatment & Management

All treatments are experimental in progressive multifocal leukoencephalopathy (PML). The principal approach is antiretroviral therapy. Anecdotal case reports of use of pulsed methyl prednisolone have shown rapid improvement in IRIS-associated PML.[163]

Cryptococcal Meningitis

Cryptococcus neoformans is a yeast covered by capsule, described Busse, a pathologist[164] *Cryptococcus* contains more than 50 types, but only *C.neoformans* and *C. gattii* are pathogenic to humans . Based on the capsular polysaccharide they divide into 5 serotypes(A, D, and AD of *C neoformans* and B and C of C. *gattii*). *C neoformans* serotype A infections occurs in immunocompromised patients, including HIV patients. *C gattii* mostly affects immunocompetent people, its response to treatment is relatively slow and have the tendency developing intracerebral mass lesions.(164). SEROTYPE A is common worldwide. In india the prevalence is between 9%-27% and is relatively under studied.

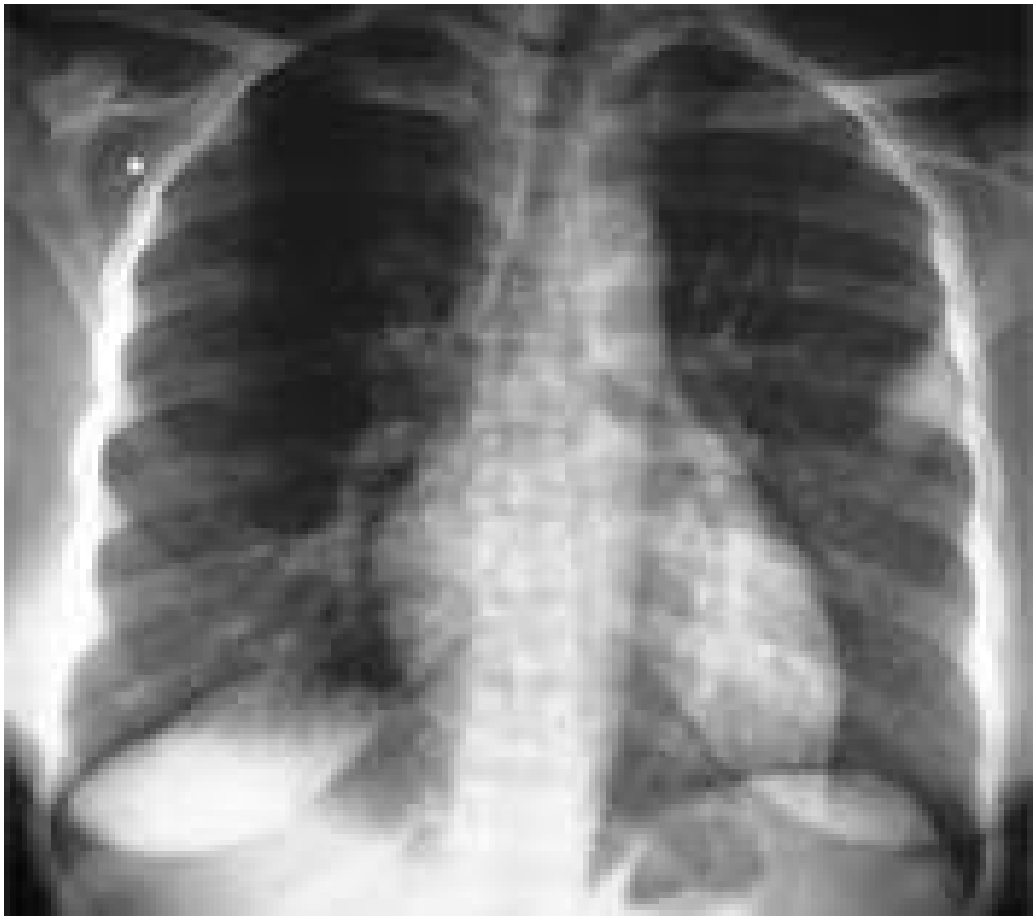
C neoformans causes an asymptomatic pulmonary infection.Meningitis can also be the first presentation. In the lungs it causes pneumonia, mass lesions, sometimes pleural effusion. Meningitis or disseminated infection is seen in immunodeficient patients,immunocompetent individual with pulmonary

manifestations alone.. Satishchandra etal study in bangalore revealed cryptococcal meningitis in 37% cases. Attili etal study showed 31% cases of HIV CNS manifestation was due to cryptococcus. Deshpanda etal and teja etal study found cryptococcal meningitis in 17% and 10.5% cases respectively.

Clinical symptoms

It is the most comman fungal infection of the CNS. Subacute meningitis is the presentation and it is fatal with out theraphy.The course of the illness depend on the associated conditions like diabetes, sarcoidosis, steroid use) and also on the immune status of the individual.It usually presents as headache,altered mental status, confusion,and coma. Nausea and vomiting indicate increased intracranial tension, whereas fever and meningial sings indicate a more intense inflammatory reaction. Archnoiditis, cranial nerve neuritis, chorioretinitis, hydrochephalus can also develop.

CXR OF PATIENT WITH CRYPTOCOCCOSIS

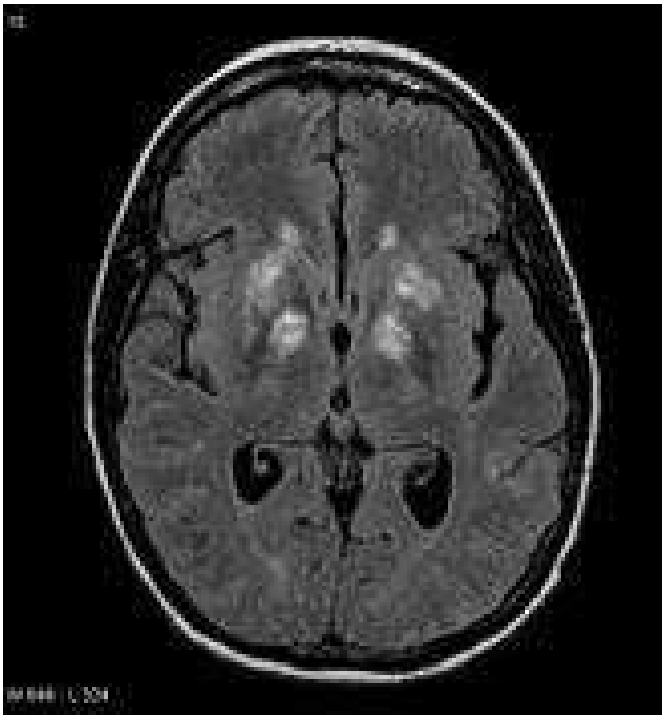


LABORATORY STUDIES

1. India ink stain.

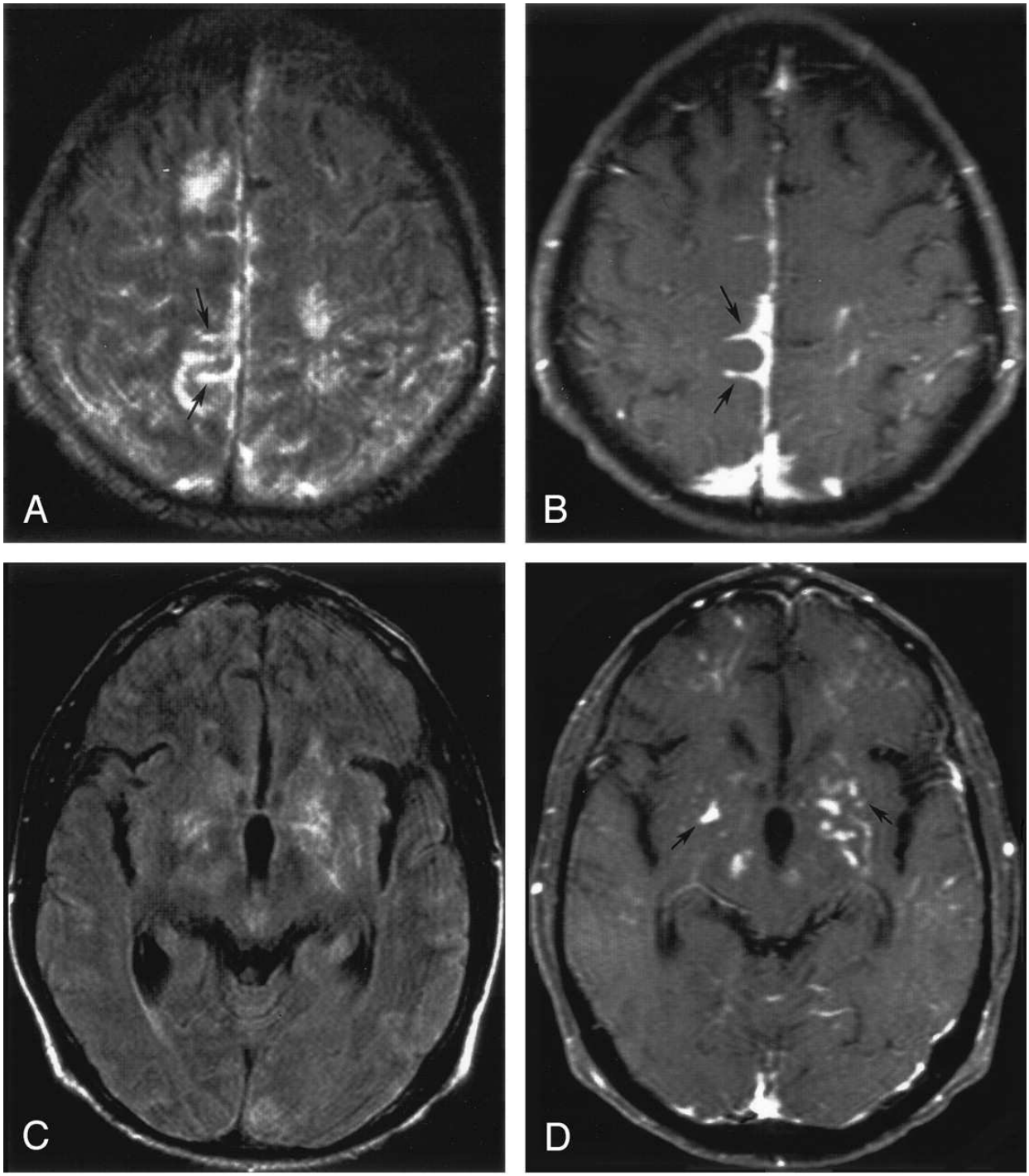
2. A CSF antigen titer >1:8 [104, 105], or a positive CSF culture [106, 107]. Cerebrospinal fluid opening pressure is elevated and may have important prognostic implications(visiual impairment) [108].

CNS CRYPTOCOCOSIS



ANNALS states, Bad prognostic factors are Altered mental status , increased CSF antigen titer, decreased CSF leukocytes , extrameningeal culture positive for the fungus and decreased serum sodium [104,105].

CRYPTOCOCCAL MENINGITIS



TREATMENT

The Management goals are to decrease intracranial pressure, treat the acute infection and to prevent relapses. Lumbar punctures, shunt procedures and

drugs like acetazolamide helps to reduce the intracranial tension. [109].Role of steroids is contraversial.

Amphotericin B (0.7 mg/kg body weight/day) with flucytosine (100 to 150 mg/kg /day) for 2 to 3 weeks, continued with fluconazole (400 mg/d) for 8 to 10 weeks is given . Fluconazole is shown to be as effective as amphotericin B in treating this fungal meningitis in HIV patients, though fluconazole causes delayed clearance of the fungus from the CSF [109,111,].

CNS TUBERCULOSIS

Central nervous system involvement accounts for nearly 1% of TB cases. World Health Organisation estimates “9.4 million incident cases as the global burden and 14 million prevalent cases , 1.3 million deaths among HIV-negative people and 0.38 million deaths among HIV-positive people.Majority of cases were in the South-East Asia(35%), African(30%) and Western Pacific regions(20%). An estimated 11–13% of incident cases were HIV-positive; the African Region accounted for approximately 80% of these cases”. “India, China, Indonesia, Nigeria, and South Africa rank first to fifth in the total number of incident cases”.

Risk factors for CNS tuberculosis include1. age (children> adults)2. HIV-coinfection, malnutrition measles in children[135], alcoholism, malignancies, immunosuppressives and prevalence in the community[134,135]. HIV co infection is a strong predictor of rapid progression of the active TB(10% per year),. Inspite TBM is common in hiv patients , its course is not altered by HIV.Nonspecific headache with or without neckstiffness mark the onset of disease.Focal neurological deficits, behavioral abnormalities and distrubances in consciousness level develop along the course of the disease.[136]. A TB history is present only in 10% of patients[136]chest X- ray changes in 30 to 50%.

Cerebro vascular complications of tuberculous meningitis(Tuberculous vasculopathy) presents as multiple or bilateral lesions in middle cerebral artery territory and is due to immersion of the artery in local inflammatory exudate. Cranial nerve palsies (mostly 6 th) occur in 20–30% of cases and can be the lone feature. Optochiasmatic arachnoiditis , third ventricular compression of optic chiasma , optic nerve granuloma all lead to vision loss. Ophthalmoscopic examination may shows papilloedema,choroid tubercles(indicating miliary tuberculosis and are virtually pathognomonic).Other Cranial nerves can also be involved. Stoke can also occur along the entire course of the disease.

TB Meningitis

British Medical Research Council TBM grade (severity of TBM):

1. Grade I TBM is defined as a Glasgow coma score of 15 , absent focal deficit.

2. Grade II TBM as a Glasgow coma score of 15, presence of focal neurological deficit or a GCS of 11 to 14

3. Grade III TBM is defined as a Glasgow coma scale of ≤10.

Rockie . et.al noted clinical presentations of tuberculoma or tuberculous abscess(140) depends mainly on their location, presenting mostly as headache, seizures, papilledema. The presentation of brain abscess is more subacute (1 week to 3 months) than tuberculoma but slower than bac terial brain abscesses[132]. Ahuja etal diagnostic criteria were used for diagnosis of TB meningitis.

Investigations

Definitive diagnosis of tuberculous meningitis demonstration of the tubercle bacilli in the CSF, (smear or by culture). Stains such as Ziehl Neelsen, Kinyoun or auramine rhodamine are used.Culture and sensitivity helps in choosing the antibiotic and also in prognosis.

CSF typically has a pleocytosis, an increased protein level and marked decreased glucose levels.

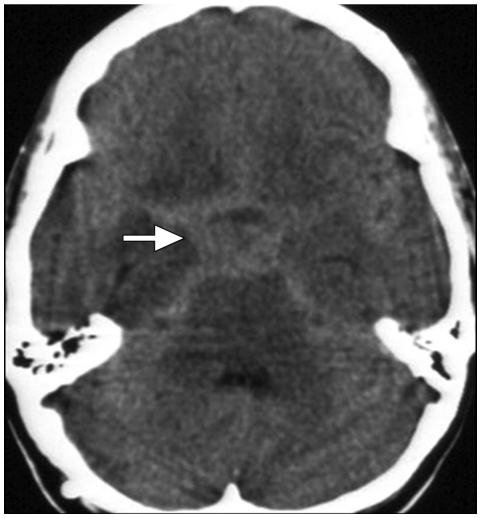
Chest radiography may show hilar lymphadenopathy, pneumonia, fibronodular infiltrate/cavitation, and pleural effusion. ADA is related to lymphocytic proliferation and differentiation,(marker of cell-mediated immunity)[141] . ADA has a sensitivity of 44% to 100% and specificity of 71 to 100%.[143] Standard

ADA values for the diagnosis of TBM are yet to be established.A range from >5.0 to >15 IU/liter is used in most studies. ADA activity lacks specificity but can predict prognosis. Raised CSF ADA activity is also seen in malaria, brucellosis,bacterial meningitis, cryptococcal meningitis, and cerebral lymphomas[145].

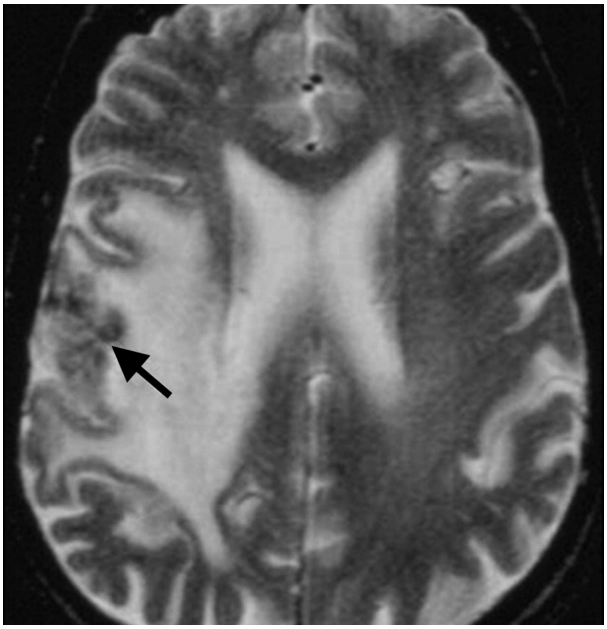
Brain and Spinal Imaging

CT scanning and MRI of the brain reveal hydrocephalus, basilar meningeal thickening, infarcts, edema, and tuberculoma , and also in monitoring complications that require neurosurgery.

CT BRAIN Showing Basal Meningitis

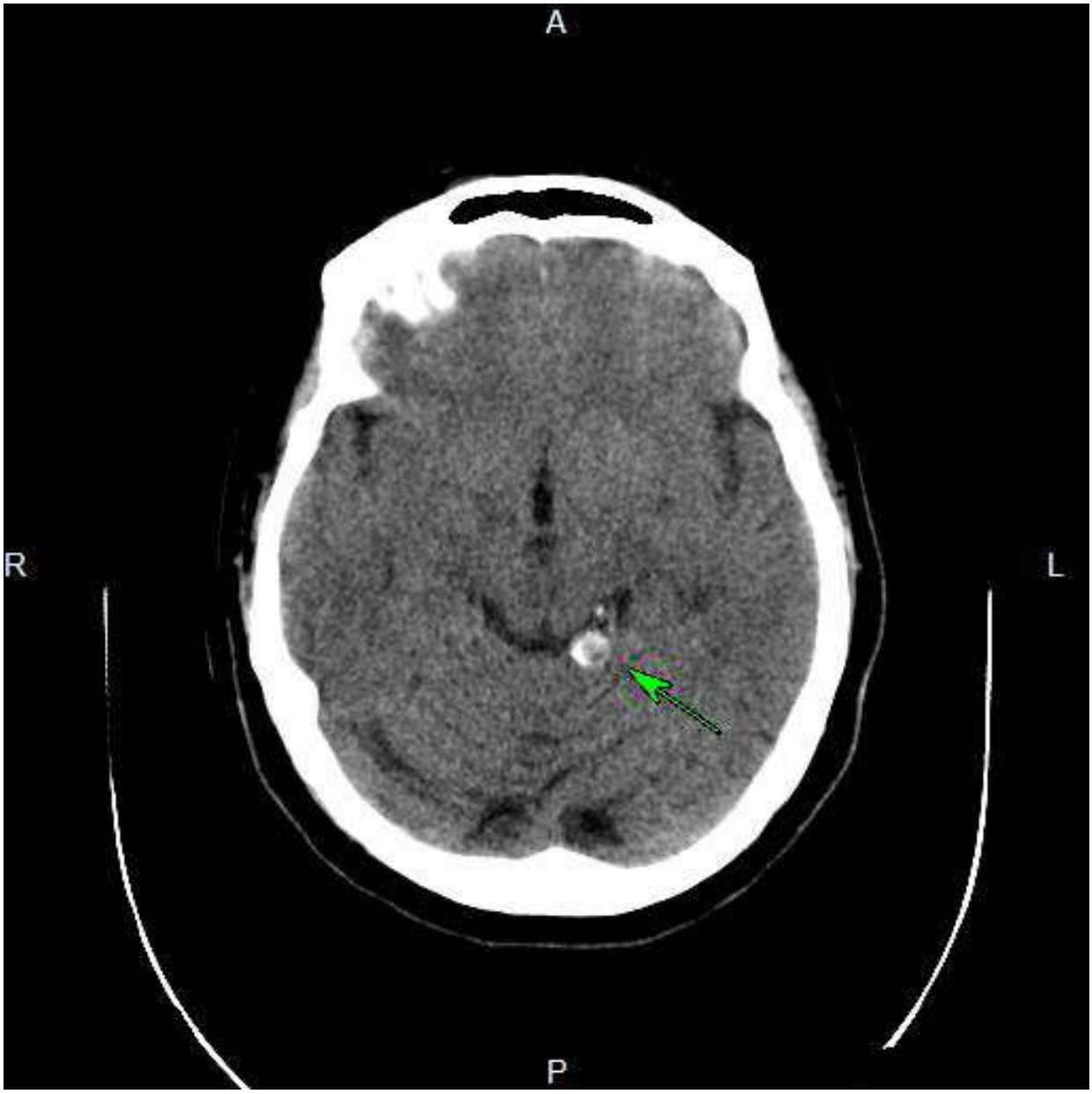


MRI Showing Tuberculoma



Basal cisterns enhance strikingly(quadrigeminal cistern, interpeduncular fossa, ambient cisterns).There is enhancement of meninges in HIV patients. Enhancing nodular lesion with central hypodensity is typical of tuberculoma[156]

CNS Tuberculoma



Treatment of CNS TB

The recommended first-line agents for all forms of CNS tuberculosis are Isoniazid, Rifampicin, Pyrazinamide and Ethambutol taken daily either individually or in combination form.

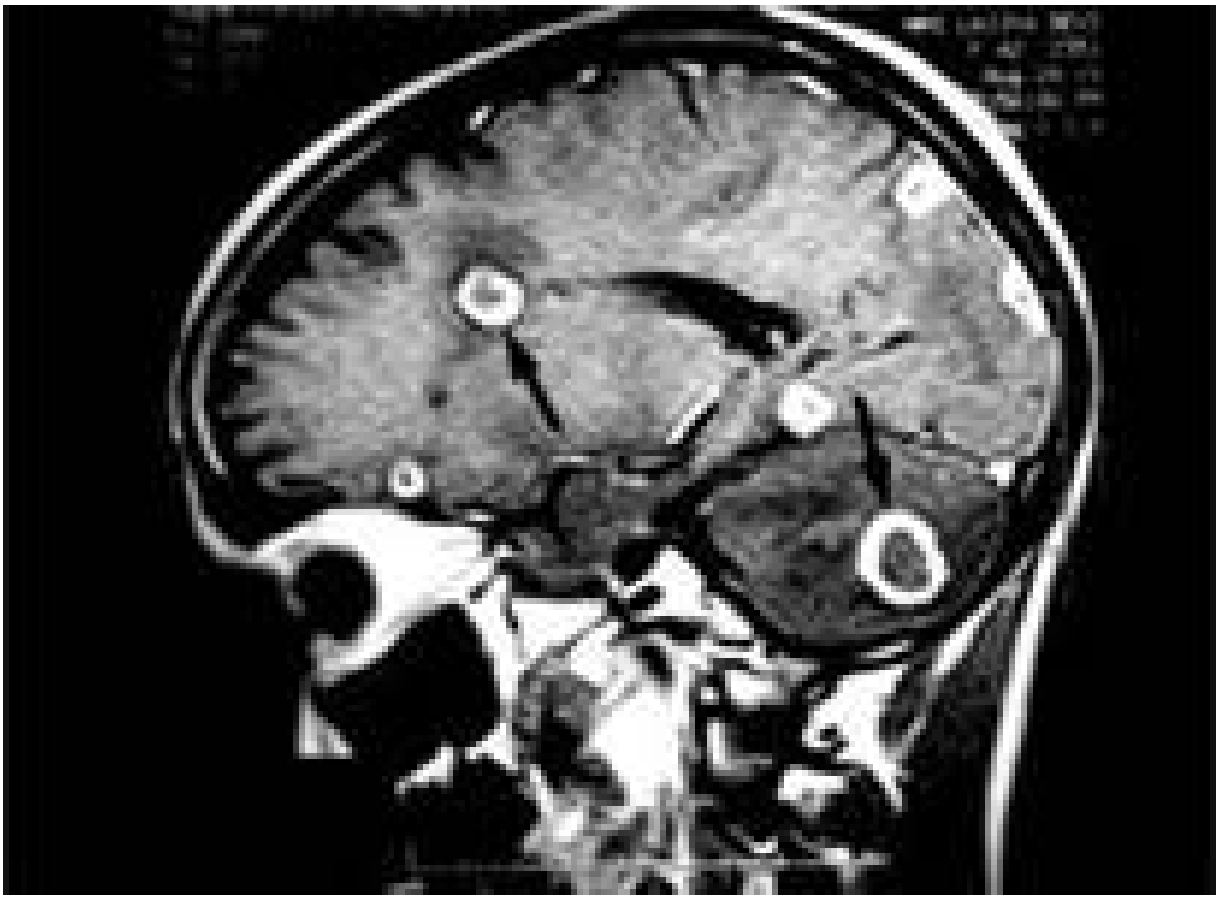
Patients should be treated for a minimum of 10 months. In cases of failure to respond or interruption it can be for 12 months. INH has a good CSF penetration and early bactericidal activity . At standard doses isoniazid achieves CSF levels 10–15 times the minimum inhibitory concentration of *M. tuberculosis*[148]. The disadvantages being drug resistance when used as monotherapy though it does occur for chemoprophylaxis. Pyridoxine is used to treat INH ovredose(stops seizures, reverses coma and corrects the metabolic acidosis).The standard dose is 1 mg of pyridoxine for every mg of isoniazid, given as rapid intravenous infusion[149]. Prompt treatment is given as it is very fatal(fatal dose- 90 mg/kg) [150]. Rifampicin slightly less CSF penetration (maximum concentrations around 30% of plasma), but the high mortality from rifampicin resistant TBM has confirmed its key role in the treatment of CNS disease[151].

The incidence of ethambutol induced optic neuritis is less than 3% (standard dose of 15–20 mg/kg), though it is a concern especially when treating comatose patients[152]. Fluoroquinolones are an effective fourth agent (if ethambutol is

contraindicated), but contraindicated in pregnant or breastfeeding women and children[153].

All patients with TBM may receive adjunctive corticosteroids regardless of disease severity(154) at presentation. Adults (>14 years) should start treatment with dexamethasone 0.4 mg/kg/24 hours tapered over 6 to 8 weeks. Children (d″14 years) should be given(154) prednisolone 4mg/kg/24 hrs (or equivalent dose dexamethasone: 0.6 mg/kg/24 hrs) for 4 weeks, tapered over 4 weeks.

CO EXISTANT TUBERCULOMA AND MENINGITIS



Neurocysticercosis

Neurocysticercosis is caused by Taenia solium and is the most common helminth infection of the central nervous system . It is endemic in areas where pigs are reared. The number,size, and location of cystic lessions and immune response determine the presentation of the disease. It accounts for 27% of CNS lesions in HIV patients with neurologic manifestations. There is very little information about the relation between NCC and HIV infection. Parija etal study in jipmer revealed seropositivity 5% in 100 hiv positive patients.

The accurate clinical diagnosis of neurocysticercosis in HIV is difficult due to deranged immunological parameters. Cysticerci can be found anywhere in the body(brain, cerebrospinal fluid , muscle). Neurologic manifestations are the most common **.** Seizures(generalized, focal, or Jacksonian)are associated with inflammation around cysticerci in the suurounding brain tissue. Hydrocephalus(communicating), papilledema results from obstruction csf by cysticerci and arachnoiditis. Stroke and chronic meningitis are also reported.Del brutto etal (167) diagnostic criteria were used for diagnosis of neurocysticercosis

For the treatment of patients with brain parenchymal cysticerci, antiparasitic drugs, including albendazole (15 mg/kg per day for 8–28 days) or praziquantel (50–100 mg/kg daily in three divided doses for 15–30 days must be given.

ACUTE TRANSVERSE MYELITIS

Transverse myelitis (TM) is a neurologic syndrome caused by inflammation of the spinal cord.It is a unusual manifestation of hiv infection.

Transverse Myelitis Consortium Working Group(168) Proposed diagnostic criteria for idiopathic acute transverse myelitis.

LERNER.”DEMYELINATING DISORDERS”,

“CURRENT CLINICAL NEUROLOGY.2006 GIVES “

INCLUSION CRITERIA

Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord , Bilateral signs and/or symptoms (though not necessarily symmetric),Clearly defined sensory level, Exclusion of extra-axial compressive etiology by neuro imaging (MRI or myelography) ,Inflammation within the spinal cord demonstrated by CSF pleocytosis or elevated IgG index or gadolinium enhancement. If none of the inflammatory criteria is met at symptom onset, repeat MRI and lumbar puncture evaluation between 2 and 7 d following symptom onset meet criteria Progression to nadir between 4 h and 21 d following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening).

EXCLUSION CRITERIA:

History of previous radiation to the spine within the last 10 yrs. Clear arterial distribution clinical deficit consistent with thrombosis of the anterior spinal artery, Abnormal flow voids on the surface of the spinal cord consistent with AV Malformation, Serologic or clinical evidence of connective tissue disease.

MATERIALS AND METHODS

A prospective study was conducted about CNS MANIFESTATIONS IN HIV/AID at THANJAVUR MEDICAL COLLEGE. THANJAVUR, from JANUARY 2012 to October 2012. All HIV/AIDS patients admitted in TMCH with CNS manifestations included in this study.

SELECTION OF CASES

- ✓ HIV seropositive patients
- ✓ Greater than 14 yrs of age
- ✓ Presenting with CNS manifestations

PATIENT WORK UP

A Performa was developed and supplied to all concerned departments. The Detailed history of patient's illness, findings of clinical examination, routine investigation reports pertaining to the disease and special investigation reports were collected and entered in the Performa.

PROFORMA

FEVER	
HEADACHE	
VOMITING	
MENINGEAL SIGNS	
PYRAMIDAL SIGNS	
OTHER NEUROLOGICAL MANIFESTATIONS	
Papillodema	
Co-Existing Illness	

CT SCAN / MRI :

RING ENHANCING LESIONS

TOXOPLASMA Ig G

NEURO CYSTICERCOSIS ANTIBODY

DIAGNOSIS

CSF EXAMINATION

CSF FINDING

ACID FAST STAIN

INDIAN INK STAIN

FUNGAL CULTURE

CSF VDRL

TREATMENT

DIAGNOSTIC CRITERIA

DIAGNOSTIC CRITERIA FOR TB MENINGITIS

Diagnosis of TB meningitis is done with history (subacute illness), CSF findings (↑protien level, lymphocytic plecytosis and demonstration of AFB). Sputum examination, x-ray chest, FNAC of lymph nodes, USG abdomen positive cases strongly supports the diagnosis particularly in space occupying lesions. Ahuja etal diagnostic criteria (165) were used for categorization of TB meningitis patient.

I. Clinical symptoms and signs

Mandatory: Fever and headache >2 weeks

Optional: Vomiting, neck stiffness, altered sensorium, seizures or focal Neurologic deficit

Supporting criteria

1. CSF: Cells : >20/cmm, lymphocytes : >60%, proteins: 100 mg%, sugar: <60% of corresponding blood sugar, negative gram stain, India stain and VDRL where relevant
2. CECT/MRI Showing one or more of: exudates in basal cisterns / Sylvian fissures, gyral enhancement, hydrocephalus. Infarcts, tuberculoma.
3. Active extraneural TB : as evidenced by appropriate mycobacterial tests, radiology, histopathological examination
4. Clinical response to ATT and relief of symptoms

DIAGNOSIS OF CNS TUBERCULOMA

CNS Tuberculoma were diagnosed by evidence of concomitant TB meningitis,radiological or bacteriological evidence of pulmonary or extra pulmonary TB, negative serological test for toxoplasma and neurocysticercosis and respond to antitubercular therapy.

M.Tuberculosis on staining appears long, filamentous, club shaped with beaded or barred forms. On culture forms rough raised irregular colonies with a wrinkled appearance it is slow growing, non pigmented, niacin test and nitrate reduction test positive catalase test weakly positive.

DIAGNOSIS OF CRYPTOCOCCAL MENINGITIS

Crypto coccal meningitis is diagnosed by Indian ink method or culture demonstrating organism. Indian ink stain demonstrate the capsule which is seen as an unstained halo around the organisms distributed in a black background. 3. In culture, Crypto coccus neo formans appears as creamywhite to yellowbrown colonies. Wellcapsulated strains appear glistening because of their mucous.Poorly encapsulated strains look dry.

DIAGNOSIS OF CNS TOXOPLASMOSIS

CNS Toxoplasmosis was diagnosed by CT/MRI showing multiple ring enhancing lesions,raised igG levels and responds to treatment.

DEL BRUTTO ETA CRITERIA(167) FOR DIAGNOSIS OF NEUROCYSTICERCOSIS

1. Absolute criteria
a. Demonstration of cysticerci by histologic or microscopic examination of biopsy material **b.** Visualization of the parasite in the eye by funduscopy **c.** Neuro radiologic demonstration of cystic lesions containing a characteristic scolex
2. Major criteria
a. Neuro radiologic lesions suggestive of neurocysticercosis b. Demonstration of antibodies to cysticerci in serum by enzyme-linked immune electro transfer blot c. Resolution of intracranial cystic lesions spontaneously or after therapy with albendazole or praziquantel alone
3. Minor criteria
a. Lesions compatible with neurocysticercosis detected by neuroimaging studies b. Clinical manifestations suggestive of neurocysticercosis c. Demonstration of antibodies to cysticerci or cysticercal antigen in cerebrospinal fluid by ELISA d. Evidence of cysticercosis outside the central nervous system (e.g., cigar-shaped soft-tissue calcifications)

4. Epidemiologic criteria
a. Residence in a cysticercosis-endemic area **b.** Frequent travel to a cysticercosis-endemic area **c.** Household contact with an individual infected with *Taenia solium*

Acute transverse myelitis is diagnosed by transverse myelitis consortium working group (168) proposed diagnostic criteria except inclusion of HIV in the criteria.

CRITERIA FOR DIAGNOSIS OF CARIE, S SPINE (177)

- Signs and symptoms consistent with tuberculosis
- Clinical features of spinal cord compression,
- Complete or partial collapse of one or more vertebrae on X-ray spine and
- One of the criteria (a to e) shown below
- Magnetic resonance imaging (MRI) or CT spine showing destruction of intervertebral disc and adjoining vertebrae causing compression of spinal cord or myelography with obstruction at the level of vertebral collapse as seen on plain X-ray of the spine.

  a. History of TB in the family

  b. Chest x-ray (CXR) consistent with tuberculous infection of lungs

  c. Induration of > 10 mm with Tuberculin skin testing after 48 to 72 hours irrespective of prior Bacillus-Calemette-Guerin (BCG).

d. *Response to antituberculous therapy OR Mycobacterium tuberculosis (MTB) detected on polymerase chain reaction (PCR) OR Isolation of MTB from CSF or gastric aspirate on acid-fast stain or culture.*

Table-1

AGE distribution

Age group	Case (n=40)
14-29	9
30-39	20
40-49	10
50-59	1
>60	0
Mean	35.2
S.D	9.4

Table-1 shows age distribution of HIV (+) patients with neurological manifestations. Majority of patients were in age group of 30-39 years with mean age of 35.2 years and S.D (9.4)

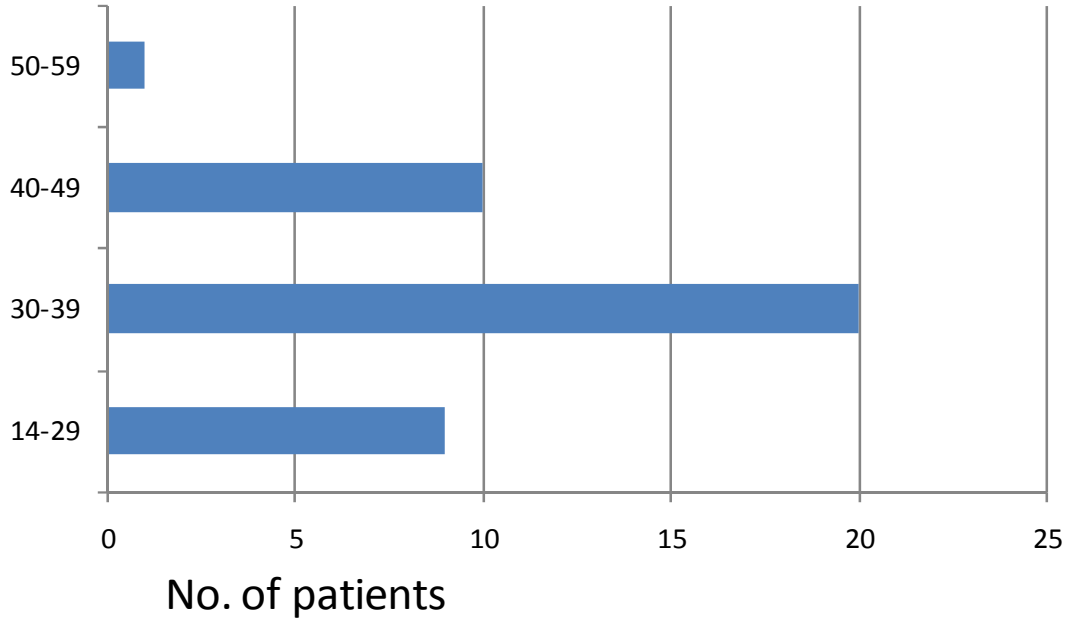
TABLE 2

SEX DISTRIBUTION

SEX	CASE
Male	28(70%)
Female	12(30%)

Gender distribution shows that out of 40 patients 28 (70.0%) patients were males and 12(30%) patients were females with male female ratio 2.3:1

Age distribution



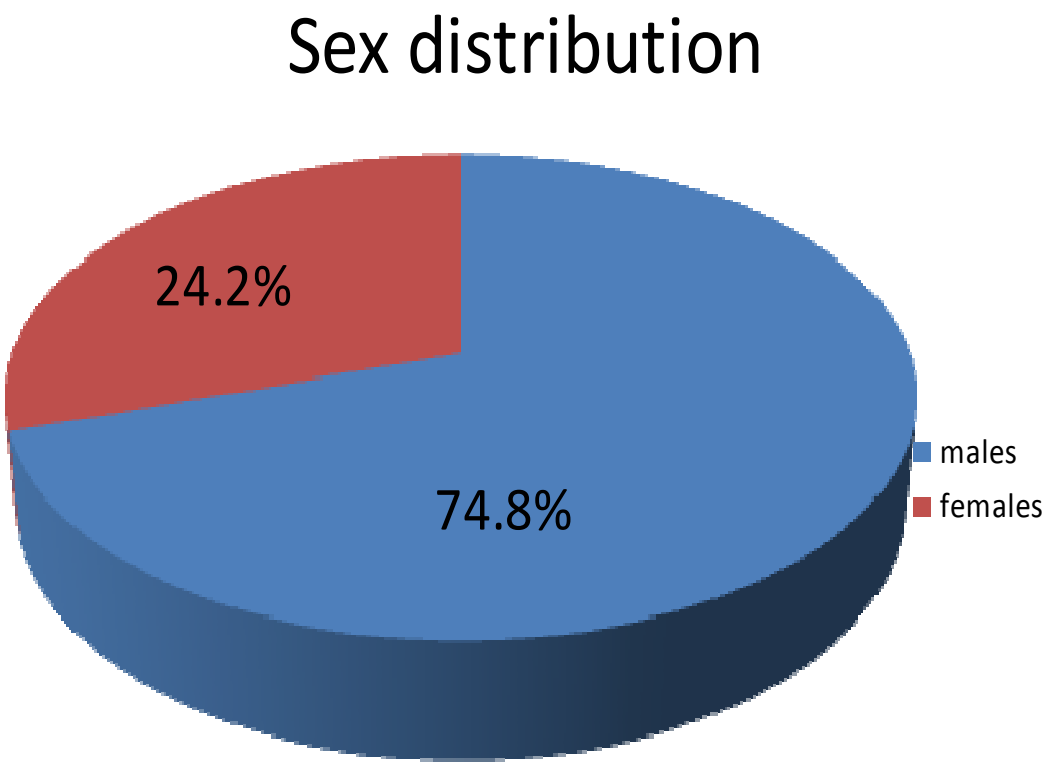

Sex distribution
24.2%
74.8%
males
females

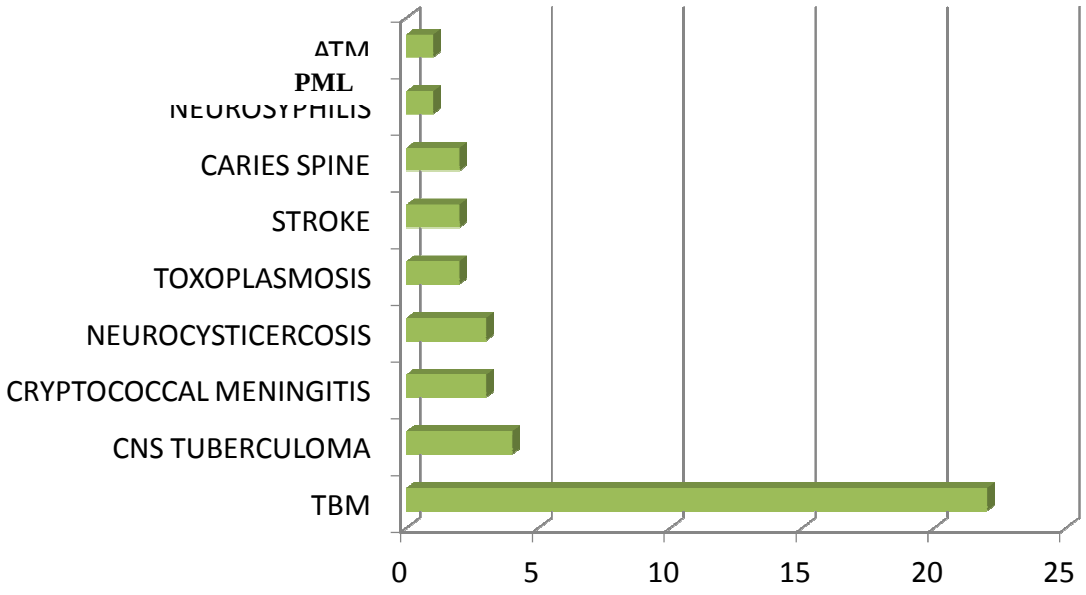
TABLE-3 Revealed clinical profile of patients presented with neurological manifestation. Presence of fever indicates either TB meningitis or cryptococcal meningitis. Headache is fairly common in all our patients except spinal cord involvement. Presence of focal neurological deficit argue in favor of toxoplasmosis,stroke. CNS tuberculoma patients presented with a higher incidence of focal neurological deficit compared to TB meningitis. 22% patients with TBM have multiple cranial nerve palsy. Meningeal signs were present in 77% patients with TBM and 66% patients with cryptococcal meningitis. Seizure was a predominant symptom in patients presented with space occupying lesions.Altered sensorium was more common in CCM (66.6%) patients compared to TBM (40.9%) Toxoplasmosis (50%), CNS tuberculoma 2 (50%). About 33.3% patients with CCM had papilloedema. Out of 4 patient of CNS tuberculoma 2 had papilloedema and out of 2 patients of toxoplasmosis 1 had papillodema. All 3 Neurocysticercosis patients presented with seizures.

TABLE-4

NEURODIAGNOSIS	**PERCENTAGE**
TB MENINGITIS	22(55%)
CRYPTOCOCCUS MENINGITIS	3(7.5%)
CNS TOXOPLASMOSIS	2(5%)
STROKE	2 (5%)
PML	1(2.5%)
NEUROCYSTICERCOSIS	3(7.5%)
CNS TUBERCULOMA	4(10%)
CARIES SPINE PARAPLEGIA	2(5%)
ATM	1(2.5%)

TABLE-4 Shows distribution of cases in HIV patients with CNS manifestation in our study. Of the 40 cases TB meningitis was the most common CNS infection (55%), cryptococcal meningitis(7.5%). Of the various space occupying lesions CNS tuberculoma (10%) was most predominant,followed by toxoplasma(5%), Neurocysticercosis(7.5%). There were 2 patients with stroke (5%) that could be caused by the virus itself.Two cases of Caries spine were diagnosed both of them presented with compressive myelopathy. Progresive multifocal leukoenchepalopathy (PML) was found in 1 (2.5%) patient and 1 case of acute transverse myelitis (ATM) was reported.

CNS manifestations in HIV



CNS MANIFESTATIONS IN HIV

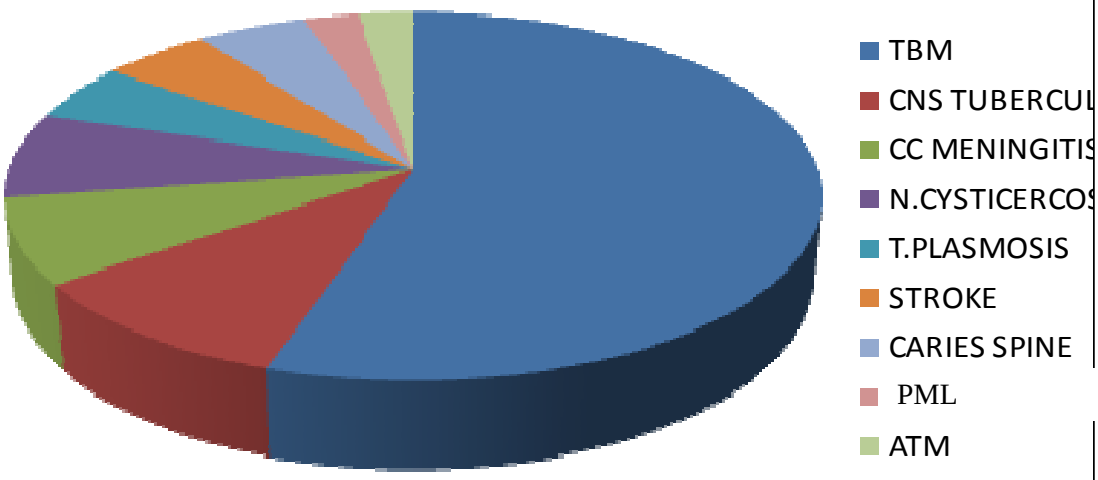


TABLE-5

CSF FINDING	CCM 3	TBM 22	CNS TUBERCULOMA 2	TOXOPLASMA 2	PML
CELLS/MM3	13.3 ± 6.11	109.1 ± 48.5	75 ± 7.07	8	6
neutrophil	2.6 ± 2.30	29.3 ± 14.9	15 ± 7.17	0	0
Lymphocyte	10.6 ± 4.61	79.4 ± 37.9	60 ± 14.14	8	6
protein	75.3 ± 5.033	212.2 ± 61.77	145 ± 7.07	70	90
sugar	34 ± 2.00	33.8 ± 5.78	35 ± 4.24	52	48
Indian ink	3				

All our patients with TB meningitis had marked Lymphocytic pleocytosis (mean cell count of 109.1 ± 48.5), Lymphocyte count (79.4 ± 37.9) with raised

protein levels (212.2 ± 61.77). In cryptococcal meningitis although pleocytosis was seen, it was low as in compared to TBM (13.3 ± 6.11). There was a mild raise in protein content (75.3 ± 5.33), CSF sugar levels were low (34 ± 2). Out of 2 patients of toxoplasmosis 1 was without papillodema and undergone CSF study which was normal. Out of 4 CNS tuberculoma patient 2 were without papillodema and undergone CSF study which revealed elevated protein levels and lymphocytic pleocytosis.

TABLE-6

CORRELATION WITH CD4 COUNT

	<200	200-350	>350
CNS TB	13	9	4
CCM	2	1	0
CNS TOXOPLASMOSIS	2	0	0
PML	0	1	0
STROKE	1	1	0
CARIES SPINE	0	1	1
Neurocysticercosis	0	2	1
ATM			1

TABLE-6 Shows correlation of various CNS manifestations in HIV patients in our study with their respective CD4 count. Among CNS TB cases 50%cases had CD4<200, 34.61% cases had CD4 count 200-350, 15.38% cases had CD4 count >350. Among crypticoccal meningitis 66.66% cases had CD4 count<200 and 33.33% cases had CD4 count>200. All the patients of CNS toxoplasmosis had CD4 count<200. Out of 3 cases of neurocysticercosis 2(66.66%) patients had CD4 count between 200-350 and one (33.33%) patient had CD4 count above 350. Out of 2 patients of caries spine with paraplegia one(50%) patient had CD4 count between 200-350, One (50%)patient had CD4 count above 350.Case of acute transverse myelitis revealed CD4 count>350.. Out of 2 cases of hiv related stroke 1 had CD4 count<200 and 1 had CD4 count above 200.

CORRELATION WITH CD4 COUNT

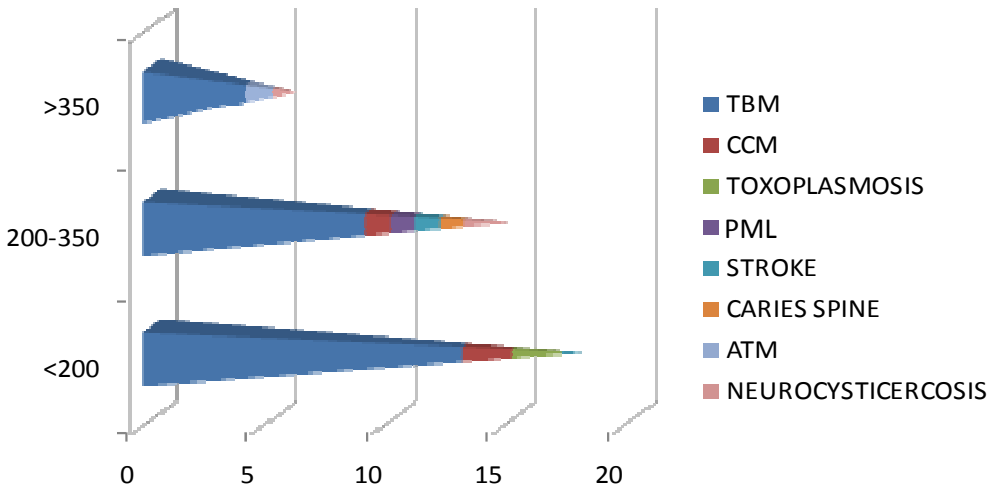


Table-7

MEAN LEVEL OF CD4 ACC0RDING TO NEURODIAGNOSIS

CNS INFECTION	CD4 MEAN+_S.D
CNS TB	217.7_+119.29
CRYPTOCOCCAL INFECTION	130.0+_72.02
TOXOPLASMA INFECTION	104+_82.2
PML	286
STROKE	205+_38.18
CARIES SPINE	299+-123.03
NEUROCYSTICERCOSIS	323.3+_110.02
ATM	562

Mean CD4 count of CNS TB was 217.7 with 68% values were between108-336. Mean CD4 count of Cryptococcal meningitis was 130 with 68% values between58-202.Mean CD4 count of HIV related stroke was 205 with 68% values between167-233.Case of progressive multifocal leukoenchepalopathy

had CD4 count 286.Neurocysticercosis cases presented with mean CD4 count 323, acute transverse myelitis had CD4 count 562.Toxoplasmosis cases had mean CD4 count 104.

Table - 8

Correlation of CNS TB with pulmonary & Extra pulmonary TB

		CNS TB(n=27)
PULMONARY TB	SPUTUM(+)	04
	SPUTUM(-)	04
EXTRAPULMONARY TB	TB LYMPHADENITIS	02
	INTESTINAL TB	03
	TB PERICARDITIS	01

Table-8 shows correlation of CNS TB with pulmonary & extrapulmonary TB.Out of 26 cases detected as CNS TB 8 patients also suffered simultaneously from PTB.Out of them 4 patients were positive for sputum AFB 4 patients had radiological evidence of PTB.2 patients had evidence of TB lymphadenitis,stool AFB were positive for 3 patients.One patient had TB pericarditis.

DISCUSSION

A prospective study on CNS MANIFESTATIONS IN HIV/AIDS was carried out at Medicine department of, THANJAVUR MEDICAL COLLEGE, THANJAVUR from JAN 2012 to OCT 2012. All HIV/AIDS patients admitted in TMCH with CNS manifestations were included in this study.

The sample size consisted of 40 HIV + patients presented with various neurological manifestations affecting brain and spinal cord.

Among cases majority were in age group of 30-39 years (mean- 35.2 years ;S.D- 9.6).Earlier studies done also supports the fact that the mean age group affected was between 31.6 – 40.9.

The present study showed a male preponderance with 28 males and 12 females (male female ratio 2.3:1). Males had also outnumbered females in similar studies done earlier .Study done by attili etal in BHU Varanasi (32) 2001-2003 revealed male female ratio 3.7: 1. Teja etal study (24) in NIMS revealed male to female ratio 3.9:1. Alaka etal study (160) showed male:female ratio 2.3:1.

Our gender distribution parallels the demographic pattern of hiv infection in india(M: F=3:1). Predominance of Male cases may be due to migration to urban areas for job, staying away from families and promiscuous sexual habits resulting in acquiring HIV infection .Generally females particularly of low socioeconomic status who tend to avoid health check ups leading to a low

detection rate. More and more females are being infected through hetero sexual mode of transmission as the epidemic expands.

Clinical profile of patients presenting with neurological manifestation revealed around 90% patients presented with TB meningitis had fever and headache.attili etal[32] reported fever in 90% and headache in 80% cases. Meningeal signs and papillodema were present in 77.7% ,36.3% patients respectively. Focal neurological deficit and seizure were present in (18.2%),(18.1%) patients .Exudate within subarachnoid space is the primary pathological lession, more prominent at the base. This leads to inflammation of adjacent blood vessels and occlusion. Cerebral infarction, resulting from vascular occlusion, is a common sequele most often found in the distribution of the middle cerebral artery and striates arteries as they penetrate the base of the brain. CT scan revealed lacunar infarct in MCA territory in 2 patients.

According to various studies seizures are the initial presenting manifestation in 10-15%cases. Cranial nerve palsy was present in (22.7%) of our patients. Various literatures shown cranial nerve palsy in 20-30% cases. Sixth cranial nerve was most commonly affected.

Cryptococcal meningitis patients presented with headache in (100 %) cases and fever in (66.6%)cases. Meningeal signs and papillodema were present in (66.6%),(33.3%) cases respectively. Attili etal study reports meningeal signs in (87.5%) cases and papillodema in 50% cases. Lower incidence of meningeal

signs in our study may be because of the altered immune defences with minimal inflammatory reaction in AIDS patients. Seizures were present in (33.3%) cases. Focal neurological deficit were observed in our patients. Attili etal study showed neurological deficit in 15% cases.and seizure in 50% cases.

Headache was present in all 4 cases of CNS tuberculoma. Seizures, focal neurological deficit, papilloedema were found in 50% cases. M .wasay etal study (170) of 102 patients diagnosed cases of CNS tuberculoma in Pakistan found fever (59%),headache (57%) cases, meningeal irritation in 35% cases.

Out of 2 cases of CNS toxoplasmosis headache and focal neurological deficit were present in both cases. Seizures and papillodema were present in 50% cases. Various literatures shown that headache (55%) and focal neurological deficit (69%) as the predominant finding.

We had 2 cases of stroke both were young with age< 50 years. One patient presented with hemiparesis and other monoparesis.Case of progressive multifocal leukoenchepalopathy presented with headache and worsening loss of conciosness and all 3 cases of neurocysticercosis patients had seizures .Acute transverse myelitis and caries spine cases presented as cases of paraplegia.

Out of 40 patients 27 had CNS TB (67.51%), 55% patients had TB meningitis, 10 % patients had CNS tuberculoma, 5 % had caries spine. Our study revealed CNS TB most common cause of neurological manifestations in HIV patients. Attili etal study in Varanasi (32) found TB meningitis in 52% cases and CNS

tuberculoma in 4% cases. Satish Chandra etal study in NIMHANS (169) found CNS TB IN 36% cases. Deshpandal study (160) in Bombay showed out of 300 cases with HIV CNS manifestation 48 were due to CNS tuberculoma and 24 cases due to TB meningitis. Rakendra singh etal study in Punjab reported CNS tuberculosis in 65.5% of cases. Studies from western studies show a lesser tuberculosis compared to Indian studies probably because of the increased prevalence of tuberculosis in our country.(According to WHO report 40% (171) Indian population are infected with tuberculosis and INDIA contributes 20% world TB cases).

Cryptococcal meningitis was present in 7.5% cases.Prevalence was lower compared to other studies in India. Satishchandra etal study revealed cryptococcal meningitis in 37% cases. Deshpanda etal and teja etal study found cryptococcal meningitis in 17% and 10.5% cases respectively. Studies from various parts of the world show contrasting prevalence rates with marked geographical variations. In sub-Saharan Africa, meningitis due to cryptococcas is more frequent than tuberculosis.

CNS toxoplasmosis was found in 5% cases. Attili etal study shown toxoplasmosis in 10% cases.Satishchandra et al and teja etal study revealed toxoplasmosis in 13% and 9% cases respectively.Deshpandey etal study in Bombay revealed toxoplasmosis in 20% cases.They found toxoplasmosis as the

most common cause of CNS infection. Study done in brazil (8) shown toxoplasmosis in (42.3%) cases.

First national serological prevalence of *Toxoplasma gondii* in India done in2007 by M. dumni etal (162). In total, 23,094 serum samples were tested, toxoplasma igG were found in 24.3% cases. sero prevalence was 31.5% in Maharashtra,21.5% in tamil nadu, 21.2 % in Orissa,15.8% cases in delhi. Lowest sero prevalences were in northern parts of India, probably reflect the effects of significantly drier conditions and, therefore, a negative impact on the survivability of *T. gondii* oocysts.This probably explains high incidence of CNS toxoplasmosis in Bombay based study .In south American countries toxoplasma serology prevalence is 40-60%.

Stroke related to HIV virus infection was found in 5% cases. Deshpandey etal study shown stroke in 5% cases. Rakendra singh etal sudy done in Punjab revealed stroke in 1.44 % cases.We had two cases of stroke.HIV induced vasculitis, prothrombotic state(anticardiolipin Ab, decreased protein S level and dysfunctional heparin cofactor 2 level) leads to stroke syndrome.

Our study revealed three cases of neurocysticercosis. Adequate data regarding the rate of this co-infection is lacking. Parija etal study (173) in Jipmer,Tamilnadu. revealed seropositivity 5% in 100 HIV positive patients. Our patients were from ARIYALUR district .Altered immunological parameters make the diagnosis of neurocysticercosis difficult in patient with HIV .The

disease is under reported in India and systematic population-based studies are lacking (178). However an association between the CD4 counts and neurocysticercosis could not be arrived with this limited data.

Tubercular meningitis was marked by lymphocytic pleocytosis(mean count = 109.1+_48.5) ,lymphocyte count(79.4+_37.9) with raised protin levels(212.2+_61.77. neutrophil count was(29.3 +- 14.9).Sometimes the lymphocytopenia of advanced diseases leads to low lymphocyte counts in the CSF.

In cryptococcal meningitis mild pleocytosis (13.3+_6.11) with mild elevation in protein (75.3+_5.03),low CSF sugar levels (34.2+_2) are seen.Out of 2 patients of toxoplasmosis 1 was without papillodema and undergone CSF study which was normal.Out of 4 CNS tuberculoma patient 2 were without papillodema and undergone CSF study which revealed elevated protein levels and lymphocytic pleocytosis indicating concomitant tuberculous meningitis supporting the diagnosis of CNS tuberculoma. Retrospective study of 102 CNS tuberculoma patients at a territory care level in Pakistan (170) with CSF analysis in 63 patients showed elevated protein(88%),low glucose(83%),pleocytosis(84%). 50% had clinical or biochemical evidence of concomitant TB meningitis. Even though the sample size is too small, we got a conclusion that all the patients with space occupying lesions without

papillodema should undergo CSF study particularly in our state where prevalence of TB is high.

Our study demonstrated a higher incidence of CNS manifestations at a low CD4 count. Among cases 18 patients had CD4 count <200,15 patients had CD4 count within 200-350, and 7 patients had CD4 count > 350. Out of 26 patients of CNS TB 50% had CD4 count <200, 7% cases had CD4 count 200-350,3%cases had CD4 count > 350.Mean level of CD4 count was 217.7 +- 119.29. It indicates the presence of TB in all stages of HIV diseases. CD4 count of the TB patients were variable from 26-562. CNS TB in HIV patients from endemic places occurs over a wide spectrum of CD4 counts and caries a good prognosis than other AIDS defining illness. Studies revealed increased mortality rate of CNS TB with low CD4 count.

Cryptococcal meningitis were associated with mean CD4 count of 130+_72., CNS toxoplasmosis with mean CD4 count 104 +-82.2. Inclusion of both diseases under AIDS defining illness is justified .Mean CD4 count of HIV related stroke were 205.Deshpande etal study shown a mean CD4 count of 212. Acute transverse myelitis occurred at a CD4 count of 562.Polyclonal hypergammaglobulinemia of early diseases causes demyelinating and inflammatory disorders.PML was associated with a CD4 count of 286 and 3 cases of neurocysticercosis with mean CD4 count of 323.

Out of 22 patients of TB meningitis 45.4% patients had grade 1 TBM according to clinical findings, with a mean CD4 count of 238. 31.8% patients were in grade 2 category with mean CD4 count of 192.8. 22.8% patients were in grade 3 category with a mean CD4 count of 152.4. It indicates patients presented with TBM and AIDS with lower CD4 count had more severe clinical manifestations and had bad prognosis than patient presented with TBM in earlier stages of HIV infection.Corbett elal study of HIV virus and prevalence of TB in African gold miners (175) shown that the marked reduction in life expectancy of advanced diseases shortens the duration of tuberculosis. Badri etals (176) prospective cohort study of TB-HIV coinfection shown that 67% TB cases occurred in CD4 level > 200/mm3 and patient survival in pulmonary and extrapulmonary TB was comparable to other benign illness .

Out of 27 cases detected as CNS TB 8 patients also suffered simultaneously from PTB.Out of them 4 patients were positive for sputum AFB, 5 patients had radiological evidence of PTB.2 patients had evidence of TB lymphadenitis,stool AFB were positive for 3 patients,one patient had TB pericarditis. Thus our study substantiates the theory of decrease in sputum AFB detection rate and increase in incidence of EPTB with progression of HIV infection.

CONCLUSION

A prospective study on CNS MANIFESTATIONS IN HIV/AIDS was carried out at Medicine department of TMCH, During the 2 year's 162 cases of HIV/AIDS were admitted in our hospital out of which neurological manifestations constitutes 40 cases (24.6%). Detailed history,clinical examination,routine blood investigations, CSF study, Toxoplasma serology,Neurocysticercosis IgM antibody, CT/MRI, sputum examination,X-RAY chest ,FNAC of peripheral lymph nodes, CD4 count estimation were done according to protocol.

The various neurological manifestations in our studies were TB meningitis (55%), CNS tuberculoma (10%), Cryptococcus meningitis (7.5%), Neurocysticercosis (7.5%), Stroke (5%),CNS toxoplasmosis (5%), caries spine with paraplegia (5%), PML (2.5%), acute transverse myelitis (2.5%).

Average CD4 count in CNS TB was 217.7, Cryptococcal meningitis patients had mean CD4 count of 130,CNS toxoplasmosis patients presented with mean CD4 count of 104, stroke patients had mean CD4 count of 205, CD4 count in Neurosyphilis was 286,neurocysticercosis patients with mean CD4 count of 323, acute transverse myelitis with 562.

The incidence of PTB in our study was 29.6%, intestinal TB (11.1%), TB lymphadenitis (7.4%), TB pericarditis (3.7%).

PROFORMA

FEVER	
HEADACHE	
VOMITING	
MENINGEAL SIGNS	
PYRAMIDAL SIGNS	
OTHER NEUROLOGICAL MANIFESTATIONS	
Papilloedema	
Co-Existing Illness	

CT SCAN / MRI :

RING ENHANCING LESIONS

TOXOPLASMA Ig G

NEURO CYSTICERCOSIS ANTIBODY

DIAGNOSIS

CSF EXAMINATION

CSF FINDING

ACID FAST STAIN

INDIAN INK STAIN

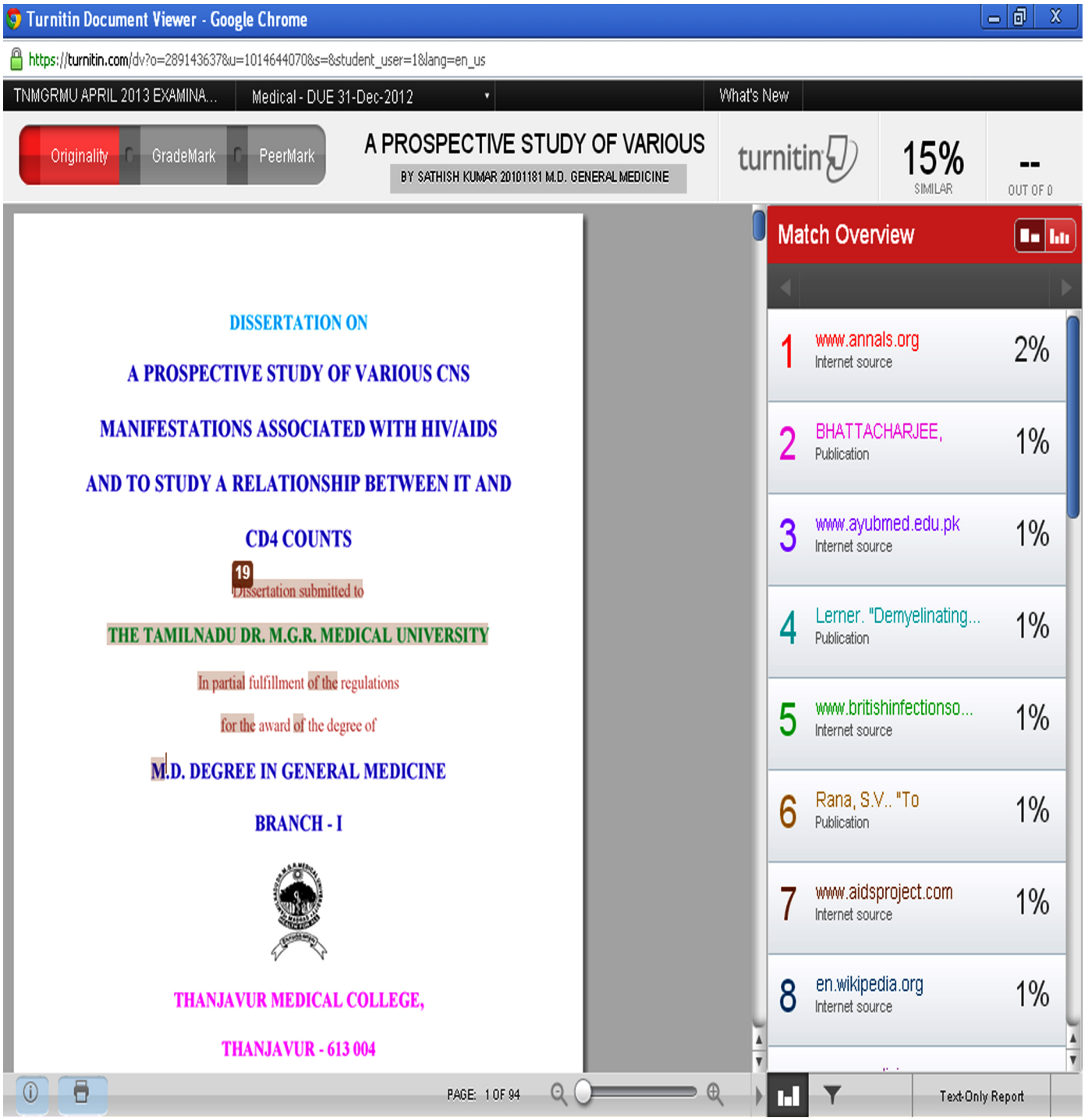
FUNGAL CULTURE

CSF VDRL

TREATMENT

S.No	NAME	IP.NO	AGE	SEX	TB MENINGITIS	TUBERCULOMA	CRYPTOCOCCAL MENINGITIS	NEURO CYSTICERCOSIS	TOXMOPLASMASIS	STROKE	CARIES SPINE	PML	ATM	CD4 COUNT
1	PANEER SELVAM	1394001	49	M			Y							212
2	RAMU	1388074	41	M			Y							133
3	MANOHARAN	1390758	49	M			Y							129
4	SUBRAMANIAN	1388103	48	M						Y				156
5	GANESAN	1416545	49	M						Y				296
6	VADIVEL	1354671	48	M								Y		286
7	JAYARAMAN	1417625	49	M	Y									168
8	SUBRAMANIAN	1415848	47	M	Y									155
9	SHAHUL HAMEED	1377314	35	M	Y									185
10	ANBALAGAN	1415854	36	M	Y									189
11	SHANMUGAM	1414214	35	M	Y									160
12	RAMESH	1389595	35	M	Y									185
13	KOLANJI	1388843	30	M	Y									189
14	MURUGESAN	1365137	38	M	Y									189
15	MOOKAIYAN	1364477	35	M	Y									177

16	YESUDASS	1375600	38	M									Y	562
17	SURESH	1418117	37	M	Y									168
18	MURUGESAN	1415824	35	M	Y									198
19	RANGAN	1407993	30	M	Y									26
20	MUTHU	1368461	29	M	Y									180
21	VIJAYAKUMAR	1394049	20	M				Y						296
22	CHINNADURAI	1370070	26	M	Y									312
23	KALIMUTHU	1371950	26	M	Y									340
24	VAITHIYANATHAN	1391072	26	M	Y									756
25	SETHU	1365836	25	M	Y									948
26	SELVARAJ	1469978	29	M				Y						410
27	MURUGESAN	1365137	27	M					Y					120
28	SURESH	1364789	24	M		Y								419
29	MALLIKA	1369557	38	F	Y									256
30	SUBULAKSHMI	1365352	45	F	Y									278
31	ANNAM	1365355	40	F		Y								348
32	KANNAKI	1314235	35	F		Y								312
33	SHAKUNTHALA	1400530	52	F	Y									296
34	SELVI	1421085	38	F	Y									312
35	SUMATHI	1376184	30	F					Y					86
36	MARIAMMAL	1391872	30	F	Y									268
37	KAVITHA	1378125	35	F		Y								418
38	SUBULAKSHMI	1365352	35	F				Y						299
39	CHITHRA	1387521	35	F							Y			356
40	PUSHPAVALLI	1394177	33	F							Y			250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AND TO STUDY A RELATIONSHIP BETWEEN IT AND
CD4 COUNTS
Dissertation submitted to
THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
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ABBREVIATIONS

CNS - CENTRAL NERVOUS SYSTEM

HAD - HIV ASSOCIATED DEMENTIA

PML - PROGRESSIVE MULTIFOCAL LEULOENCEPHALOPATHY

TBM - TUBERCULOUS MENINGITIS

ATM - ACUTE TRANSVERSE MYELITIS

CCM - CYPTOCOCCAL MENINGITIS

NCC - NEUROCYSTICERCOSIS

HAART – HIGHLY ACTIVE ANTI RETROVIRAL THERAPY

CMV – CYTOMEGALOVIRUS

VCZ – VARICELLA ZOSTER

HSV - HERPES SIMPLEX VIRUS

CSF - CEREBROSPINAL FLUID

PET – POSITRON EMISION TOMOGRAPHY

ADC – AIDS DEMENTIA COMPLEX

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