INTRODUCTION

Neurological manifestations are common in HIV infection. They occur in all stages of HIV infection, early or late; can affect any parts of neuraxis. Neurological involvement causes significant morbidity and mortality in HIV infected individuals. Next to sub-Saharan Africa, India has the second largest burden of HIV related pathology, predominantly caused by HIV-1 Clade C. Opportunistic infections constitute almost 70-80% and the remaining 20-30% is due to direct HIV infection. HIV associated cognitive disturbances, myelopathy, CNS lymphoma and PML are significantly less common compared to the west. Which is probably due to clade difference. The type of neurological involvement depends on the stage of immune dysfunction. During early stages of immune dysfunction manifestations like Bell’s palsy and Guillain-Barre syndrome are common while during late stages more severe disorders such as Neuro Infections such as cryptococcal meningitis, T,B, Meningitis CMV encephalitis, PML, HIV Dementia and polyradiculopathy appears. Nervous system involvement can result from invasion by virus itself or by numerous opportunistic infections. Virus damages the brain directly by invasion of CNS macrophages and glial cells or indirectly by release of neurotoxic cytokines such as IL-1β, TNF-α, IL-6, and TGF-β. Iatrogenic complications like drug induced neuropathies and myopathies secondary to the use of HAART do occur and add further to the morbidity of the illness. With the advent of highly active antiretroviral therapy there is a decline in the incidence of primary HIV infection related disorders like HIV associated dementia. An improvement in immune status with the initiation of highly active antiretroviral therapy (HAART) results in new group of disorders called the immune reconstitution syndromes. In this article we will approach neurological disorders as those affecting central nervous system and those affecting peripheral nervous system.

DISORDERS AFFECTING CENTRAL NERVOUS SYSTEM (MENINGES, BRAIN AND SPINAL CORD)

Meningitis

Meningitis is one of the commonest opportunistic neurological manifestations of HIV infection. Meningitis may be acute, sub-acute or chronic. In early stages of the illness when the immune function is good, an acute aseptic meningitis mimicking any other viral meningitis can occur. This resolves in 2-4 weeks by itself leaving no sequelae. Acute encephalitis can also occur but is rare. Cranial nerves may also be affected especially VII and sometimes V and VIII nerves. CSF analysis usually reveals lymphocytic pleocytosis, raised protein and normal glucose levels.

Sub-acute and chronic meningitis results either from tuberculous infection or from fungal infection mainly cryptococcal infection. Other rare cause of meningitis is lymphomatous meningitis. Tuberculous meningitis is common in HIV infected individuals especially in the developing world. Clinical manifestations of tuberculous meningitis are same as that of non-infected individuals. Neuroimaging with MRI scan is more sensitive to find the abnormalities and may show meningeal enhancement, hydrocephalus, infarcts or granulomas. Incidence of focal brain lesions is four times higher in HIV infected patients with tuberculosis when compared to non-HIV patients. CSF analysis usually reveals lymphocytic pleocytosis, with raised protein and reduced glucose levels. Normal CSF proteins can be seen in 43% of HIV infected tuberculous meningitis patients while 14% may have normal CSF glucose levels and 16% acellular CSF. Polymerase chain reaction (PCR) for detection of mycobacterium tuberculosis has a sensitivity of 80%. Anti tuberculous treatment is same as in patients without HIV infection. Short-term corticosteroid therapy is probably beneficial as adjunctive treatment in complicated life threatening situations.

Cryptococcal meningitis has emerged as a leading cause of infectious morbidity and mortality in patients with AIDS. Cryptococcal meningitis is the second most common cause of opportunistic neuroinfection among HIV positive subjects and is one of the AIDS-defining illnesses. It occurs in patients with advanced HIV infection when CD4 count is below 100 cells/μl. Patients usually present with subacute to chronic, severe unbearable headaches with or without fever almost mimicking subarachnoid hemorrhage (SAH) and in severe cases with changes in the mental status. Neuroimaging is done to exclude hydrocephalus and cryptococcomas but is usually normal or may
show associated diffuse cerebral atrophy with ventriculomegaly. (10) MRI brain may show punctate non-enhancing foci of CSF density correlating with the presence of cryptococci in the Virchow-Robin spaces. CSF analysis shows mild to moderate mononuclear pleocytosis, elevated protein, normal or decreased CSF sugar in 75% of cases. India ink for cryptococci is positive in about 70% of cases, while CSF for cryptococcal antigen is almost always positive except in very early disease and in those with high titers (prozone effect). (11) CSF should be subjected to fungal culture to detect the type of cryptococcal infection and to ascertain the drug sensitivity. Fungal cultures are positive in almost 90-95% of cases. Treatment of cryptococcal meningitis in HIV infected patients involves IV Amphotericin B at a dose of 0.75 mg/kg daily with total cumulative dose of not more than 1.5 / 2 grams, with fluycytosine 25 mg/kg qid for 2 weeks or fluconazole, 400 mg/day for 10 weeks, and then fluconazole, 200 mg/day until the CD4 T cell count has increased to > 200 cells/μl for 6 months. Fungal meningitis can also result from rarely Coccidioides immitis and Histoplasma capsulatum. Meningoencephalitis may also caused by Acanthamoeba or Naegleria. (12, 13) Syphilitic meningitis can occur similar to non-HIV patients.

Headaches

Headaches are common in HIV infected patients. Patients with early HIV disease (CD4 count above 500 cells/μl) usually have headaches of benign nature such as tension-type headaches or that due to underlying depression. In those with advanced HIV (CD4 less than 200 cells/μl) the headaches are due to more ominous causes and detailed evaluation with neuroimaging and CSF analysis should be done to exclude opportunistic infections and lymphomas. Cryptococcal meningitis patients can present with severe headaches mimicking subarachnoid hemorrhage. The cause for this headache is not known but may be due to meningeal involvement, raised intracranial hypertension or sionovenous thrombosis. (10) These patients may require repeated therapeutic lumbar punctures to drain of CSF to reduce the raised intracranial tension. Drug induced headaches can occur from zidovudine and stavudine. (14)

Seizure

Seizure may be a presenting manifestation of HIV infection. Seizures occur in patients with HIV due to retroviral infection per se or due to various opportunistic infections or neoplasms. (15) In majority of patients (7-50%) it may be due to HIV itself or due to CNS toxoplasmosis (15-35%). 25 % of patients with HIV associated dementia. CNS tuberculosis, lymphomas, cryptococcal meningitis and progressive multifocal leukoencephalopathy can also be associated with seizures. (16) Foscarnet or gancyclovir can result in hypocalcemia and hypomagnesemia, which in turn can cause seizures. Seizures are usually focal or generalized and have a high recurrence rate. Patients are usually evaluated with MRI of brain to exclude focal lesions. CSF analysis is done if MR imaging is unremarkable to rule out cryptococcal and tuberculous meningitis. In view of high propensity for recurrence, anticonvulsant therapy should be initiated even after a single episode of seizure. Of the various anticonvulsants sodium valproate appears to be more appropriate for patients with HIV disease due to less chance of drug interactions. Other drugs such as enzyme inducers – such as phenytoin should be avoided. (3)

Dementia

HIV-associated neurocognitive impairment (HCNI) encompasses a spectrum of disorders characterized by subsyndromic cognitive deficits, mild cognitive impairment (MCI) to very severe cognitive impairment. Latter is called HIV associated dementia (HAD) or AIDS dementia complex or HIV encephalopathy. (12) HAD is a subcortical dementia and is usually seen in advanced stages of HIV infection when the immune dysfunction is moderate to severe. The incidence HAD has been on the decline after the commencement of antiretroviral therapy. (3) The exact prevalence of HAD in India is unknown but is found to be much less when compared to western population probably due to the strain difference (17). But in a small study from south India the prevalence of cognitive deficits in HIV-1 clade C infected drug-naive patients were reported similar to that of HIV-1 clade B infected patients from the western world. (18) HIV-infected individuals with the E4 allele for apoE are at increased risk for HAD and neuropathy. Patients often present with poor concentration, memory impairment, behavioral disturbances, personality changes, slow thought process and inability to perform complicated tasks. Other associated features are clumsiness, bradykinesia, apathy, gait instability, tremor and seizures suggestive of predominantly sub cortical dementia. They may also have mood disorders like depression and hypomania. Detailed neuropsychological assessment will help to assess the extent of cognitive impairment. All patients with a diagnosis of HIV infection should have their baseline Mini-Mental Status Examination (MMSE) done for future reference and follow up. (12) MR imaging of the brain should be done to rule out opportunistic infections and progressive multifocal leukoencephalopathy (PML), which may mimic or unmask dementia. (19) Cerebrospinal fluid (CSF) analysis should be obtained to exclude the possibility of a chronic meningitis. Serum and CSF VDRL also should be performed to rule out neurosyphilis. (20) More than 50% of patients of HAD improve with antiretroviral therapy hence it is important to recognize this entity early. Low dose dopaminergic drugs can be used for extrapyramidal symptoms while atypical antipsychotics with minimum extrapyramidal side effects may be used for behavioral disturbances, as these sero-positive individuals are very sensitive to neuroleptics. (3)

Space occupying lesions

Focal space occupying lesions in the brain can be due to toxoplasmosis, tuberculosis, progressive multifocal leukoencephalopathy and lymphomas. (21) Cryptococcomas usually occur in the context of cryptococcal meningitis. These space-occupying lesions may manifest with seizures or focal deficits. Incidence of CNS toxoplasmosis is on the decline with the advent of antiretroviral therapy. Toxoplasmosis usually occurs during the advanced stage of HIV infection when the CD4 count is usually less than 200 cells/μl. Patients of CNS toxoplasmosis usually present with fever,
headache, focal neurological deficits and seizures. (12) Gadolinium enhanced MRI Brain scan will help to differentiate between various lesions. Tuberculomas are usually of mixed density, single or multiple and will show a solid type or ring enhancement on contrast administration. Patients with toxoplasmosis may have multiple ring enhancing lesions with special predilection to basal ganglia or posterior fossa with evidence of blooming on FLAIR. Lymphomas are usually solitary, periventricular and enhance uniformly on contrast. (14) Differentiating features of toxoplasma granuloma from lymphoma are shown in table 1. A stereotoxic biopsy may be needed to confirm the diagnosis, if neuroimaging techniques and a therapeutic trial with antitoxoplasma drugs fail. (22) Standard treatment for toxoplasma consists of sulfadiazine (3-4 gram/day) and pyrimethamine (75mg/day) with leucovorin for a minimum of 4-6 weeks. The above drugs are given for maintenance usually half of their standard dose as long as their CD4 count is less than 200 cells/µl. If CD4 count remains above 200 cells/µl for 6 months with effective antiretroviral treatment the maintenance therapy for toxoplasmosis can be discontinued. (12)

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disorder occurring in HIV infection due to infection by JC virus a human polyoma virus. It is a feared complication of HIV disease and occurs even in patients on anti retroviral therapy. (23) Prevalence of PML is less in the Indian HIV infected population when compared to the western world. (24) Cerebral and cerebellar white matter and brainstem can be affected. Patients can present with ataxia, hemiparesis, visual field defects, aphasia and seizures. (3) Headache and fever are characteristically absent. Lesions of PML are confined to white matter with the involvement of U fibers and does not enhance on contrast. They are hypointense on T1-weighted images and hyperintense on T2-weighted images. Occipital and parietal lobes are commonly affected. CSF PCR for JC virus DNA has a diagnostic sensitivity of 76% and specificity close to 100%. There is no specific treatment for PML other than HAART. 50% of patients will show significant neurological improvement with HAART. (3)

<table>
<thead>
<tr>
<th>Toxoplasma granuloma</th>
<th>Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually multiple lesions</td>
<td>One or two lesions</td>
</tr>
<tr>
<td>Basal ganglia, thalamus, grey white matter junction</td>
<td>Periventricular, corpus callosum</td>
</tr>
<tr>
<td>Ring lesion/ecentric nodule</td>
<td>Homogenous enhancement</td>
</tr>
<tr>
<td>Not on PCP (pneumocystis Carinii) prophylaxis</td>
<td>Patient on PCP prophylaxis</td>
</tr>
<tr>
<td>Response to empirical antitoxoplasma treatment</td>
<td>No response</td>
</tr>
<tr>
<td>Thallium brain SPECT: 50% uptake</td>
<td>100% uptake</td>
</tr>
<tr>
<td>Thallium brain SPECT – uptake ratio</td>
<td>&gt; 2.9</td>
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<tr>
<td>&lt; 2.9</td>
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</tr>
<tr>
<td>CSF PCR for Toxoplasma positive (60%)</td>
<td>Negative</td>
</tr>
<tr>
<td>CSF PCR for Epstein-Barr virus negative</td>
<td>Positive</td>
</tr>
</tbody>
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Transient ischemic attacks and strokes both ischemic and hemorrhagic do occur in HIV infection. (25) In about 50% of cases there is no cause apart from HIV infection itself and these events happen usually during the advanced stages of HIV infection when CD4 count is usually less than 200 cells/µl. 50% of patients will have associated HIV dementia and 25% will eventually develop dementia. (3) The exact mechanism of thrombosis is not known but may be due to elevated anti cardiolipin antibodies, decreased protein S levels and HIV vasculopathy/vasculitis. (26) Secondary causes of stroke that should be excluded with appropriate investigations include meningovascular syphils, varicella vasculopathy, and tuberculous or cryptococcal meningitis with arteritis. (12) Eighteen cases of cortical venous thrombosis leading to haemorrhagic infarction secondary to HIV infection has been reported recently by us (Satishchandra P et al 2009 under publication) Various precipitating factors have been implicated. These include chronic alcoholism which is very common morbidity with HIV, deficiency of substance P and elevated anticoagulants. However this has acute on chronic course and relatively benign prognosis. Anti retroviral therapy along with low dose antiplatelet agents may be given to these patients with ischemic strokes after excluding thrombocytopenia. Anti-coagulants are required for the management of venous thrombosis along with anticoagulants measures.

**Extrapyramidal Syndromes**

Movement disorders like parkinsonism, choreoathetosis, dystonia nad hemiballism can develop in patients with HIV infection. (27) They result from the affection of basal ganglia either by HIV itself or due to opportunistic infections. (28) Of these opportunistic infection commonest is toxoplasma infection. Neuroimaging with gadolinium enhanced MRI brain should be done to rule out toxoplasma infection in all immunocompromised patients presenting with movement disorders. In patients on antiretroviral therapy a chronic low level immune activation can develop and may facilitate the development of neurodegeneration and accelerate the appearance of diseases such as Parkinson disease (PD) by mechanisms including inflammation, mitochondrial dysfunction, and interference with the ubiquitin proteasome pathway (29).

Other than anti-retroviral therapy and treatment of opportunistic infections, management of these movement disorders is similar to those of its non-HIV counter parts but lower doses of drugs may used in these patients.

**Myelopathy**

Spinal cord disease is seen in 20% of HIV infected individuals and is often associated with HIV encephalopathy. Patients with myelopathy often present with weakness, spasticity or unsteady gait. Myelopathy as is the case with any level of neuraxis can be due to HIV infection itself or due to opportunistic infections like tuberculosis, toxoplasmosis, herpes simplex, herpes zoster, cytomegalovirus and syphilitic infections. HTLV-I and II can also cause myelopathy especially in endemic areas. HTLV I and II
myelopathy usually occurs during the early stages of HIV infection unlike the myelopathy due to HIV per se which happens during the late stage of infection. HTLV I myelopathy in HIV infected patients can be treated with anti retroviral therapy and corticosteroids. (3) There is no known therapy for HTLV II myelopathy. Myelopathy due to HIV is mainly of following types — vacuolar myelopathy mimicking subacute combined degeneration of spinal cord, pure sensory ataxia secondary to dorsal column involvement or HIV myelitis. (12, 30) These are very less commonly reported from India where HIV clade C is the predominant strain. MR imaging of the spinal cord is done in all patients with myelopathy to rule out opportunistic infections like tuberculosis and lymphoma. MRI in patients with vacuolar myelopathy may show cord atrophy or symmetric hyperintense signals on T2-weighted sequences. Focal or serpiginous enhancing lesions may be seen in herpes zoster myelitis. (14) Cytomegalovirus myelopathy usually occurs in association with polyradiculopathy. Serum vitamin B12 and folate levels should be estimated in patients suspected to have vacuolar myelopathy. CSF analysis may show non-specific changes like lymphocytic pleocytosis, raised protein and normal CSF glucose. CSF VDRL test should be carried out to exclude syphilitic myelopathy. Serum and CSF HTLV- I and II antibodies may be done in endemic areas to diagnose HTLV I and II associated myelopathy. CSF may be subjected to PCR for herpes simplex, varicella zoster and cytomegalovirus as these organisms can rarely cause myelopathy. Primary HIV related spinal cord syndromes do not respond well to antiretroviral therapy but it may help those with HIV myelitis. (3)

**DISORDERS AFFECTING PERIPHERAL NERVOUS SYSTEM – PERIPHERAL NERVES AND MUSCLES**

**Neuropathies**

All patterns of peripheral nerve involvement are seen in HIV infected individuals. Cranial nerves and peripheral nerves can be affected. During the early stages when the CD4 count is above 500 cells/µl, Bell’s palsy and Guillain-Barre syndrome (GB syndrome) can develop identical to its non-HIV counter parts. Unlike GB syndrome in immunocompetent subjects lymphocytic pleocytosis are common in those with HIV infection. This is a clue for clinician to rule out associated HIV infection. Similarly in patients with more advanced HIV infection can have a chronic inflammatory demyelinating polyradiculoneuropathy(CIDP). Treatment of these demyelinating neuropathies is similar to those without HIV infection (3). Mononeuritis multiplex can occur due to HIV vasculitis. In patients having electrophysiological evidence of sural nerve involvement, a sural biopsy will help to confirm diagnosis and will assist to exclude lymphomatous infiltration. (31) Serology for hepatitis B and C should be done in patients presenting with mononeuritis multiplex. Distal symmetric sensory polyneuropathy (DSPN) occurs in patients with advanced HIV infection. Patients have a length dependent neuropathy affecting the feet first resulting in painful burning sensations and loss of pain, touch and temperature in a stocking distribution. There can be mild weakness of intrinsic foot muscles and ankle reflexes are usually absent. (12) Treatment consists of antiretroviral therapy, correction of associated nutritional abnormalities and avoidance of neurotoxic antiretroviral drugs (‘d’ drugs) like stavudine (d4T), zalcitabine (ddC) and didanosine (ddl). Symptomatic treatment of paresthesias with gabapentin, carbamazepine or tricyclic antidepressant is important. (3) Autonomic neuropathy may be associated with DSPN and can result in postural hypotension and gastroparesis. In advanced stages of HIV infection, CMV polyradiculopathy can occur. These patients present with sacral and lower limb paresthesias, ascending sensory loss and difficulty in walking. The reflexes are usually absent. CSF analysis reveals predominantly neutrophilic pleocytosis, raised proteins and reduced glucose levels. CSF PCR for CMV DNA is positive in majority of patients (90%) and confirms the diagnosis. Treatment is initiated either with ganciclovir or foscarnet as early as possible to reduce neurological damage and hasten recovery. (12) In patients previously treated for CMV disease combination therapy with both drugs should be considered. The causes of peripheral neuropathy according to various stages of HIV disease are summarized in table 2.

**Myopathies**

Muscle can be involved in HIV disease resulting in HIV related polymyositis which is similar in clinical manifestation to its non-HIV counter part (32). Patients often present with subacute onset progressive proximal limb and neck flexor weakness. They also have fatigue, myalgia, cramps, dysphagia and wasting. Dermatomyositis like picture can also occur in HIV infected patients. Elevated creatine phosphokinase levels and muscle biopsy showing histopathological features of polymyositis will confirm the diagnosis. Treatment is with low dose steroids with adequate prophylaxis against opportunistic infections. HIV may also lead to inclusion body myositis and a variety of other myopathies like nemaline rod myopathy or mitochondrial myopathy. (3) Opportunistic pathogens like toxoplasma gondii, mycobacterium avium-intracellulare and microsporidia may cause diffuse myositis.
usually in the context of systemic disease. Non-Hodgkin's lymphoma and Kaposi's sarcoma may occasionally infiltrate muscle resulting in a painful muscle mass. Long-term use of zidovudine can result in myopathy. Patients with zidovudine myopathy have elevated creatine kinase levels and ragged red fibers on modified Gomori's trichrome staining. An elevated plasma lactate may be seen in some patients. (33)

**Immune Reconstitution Inflammatory Syndromes (IRIS)**

The use of highly active antiretroviral therapy (HAART) to treat HIV infection, is associated with significant reductions in morbidity and mortality. However, in certain patients after the institution of antiretroviral therapy occurs a paradoxical worsening of clinical status and/or appearance of new signs and symptoms, this worsening of clinical status is known as Immune Reconstitution Inflammatory Syndrome (IRIS). (34) Usually occurs within the first 4 to 8 weeks after initiation of antiretroviral therapy. This is often noticed when ART is instituted directly with very low CD4 counts (often below 50 cells/cm). IRIS is well described in the non-neurologic literature, however exact incidence of neurological manifestations of “Neuro-IRIS” is still not known. Types of Neuro-IRIS according to severity can be asymptomatic (only radiological changes such as enhancement), symptomatic (deterioration in neurological function and accompanied by new radiological changes) and catastrophic (such as raised ICP with impending herniation or coma). The reconstituted immune system after initiation of antiretroviral therapy generates an inflammatory response, resulting in either a worsening of a known, underlying infection, or the unmasking of a subclinical, indolent infection. This exaggerated “dysregulated” inflammatory response is characterized by massive infiltration of CD8+ cells. Neuroimaging features include development of, or increase in, contrast enhancement. Intracranial pressure may also increase due to improved immune status. (35,36) The most common CNS infections reported to be involved in IRIS are HIV encephalitis, toxoplasma encephalitis, cryptococcal meningitis, progressive multifocal leukoencephalopathy. (37,38) GB syndrome has also been reported as a manifestation of IRIS. (39) Paradoxical neurologic tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) occurs within 3 months after starting combination antiretroviral therapy (ART) and causes significant morbidity. (40) Steroids are often used to treat these patients. At present there are no good clinical criteria or biomarkers which can accurately identify IRIS. The current management of IRIS remains controversial and it is uncertain if corticosteroids are really helpful. Theoretically antiretroviral therapy and subsequent improvement in the immune status is the immediate cause for IRIS and hence stopping ART may improve symptoms. However stopping antiretroviral therapy increases the risk of HIV progression and opportunistic infections. Therefore stopping ART is not advisable and most conditions will begin to improve after the initial period of deterioration. Risk factors for IRIS include taking antiretroviral therapy for the first time, active or subclinical opportunistic infections, CD4+ counts of less than 50 cells/mm3, high CD8+ cells, anemia, and a rapid decline in HIV viral load. (41,42)

**CONCLUSION**

HIV infection can affect any level of neuraxis either directly or indirectly due to various opportunistic infections or neoplasms. More than 60% of HIV sero positive individuals develop neurological involvement at some time or the other during their course. Direct HIV related complications can either be inflammatory, demyelinating or degenerative in nature and can occur through out the course of illness. Clinicians managing these patients should be aware of these neurological manifestations as it can occur at any stage of HIV infection. Use of HAART has resulted in decline of primary HIV related disorders like AIDS dementia complex and distal symmetric sensory neuropathy but has not affected the incidence of certain diseases like PML. It also has resulted in a new group of disorders called the immune reconstitution inflammatory syndromes (IRIS). Drug induced neurological disorders also can develop during the course of treatment and clinician should be on watch out for these complications.

**REFERENCES**

Neurological Manifestations Associated with HIV Infection: Indian Perspective


