Neurological Manifestations of HIV

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As the HIV pandemic spreads relentlessly, the numbers of infected individuals who present to the physician with complications of HIV or opportunistic infections related to the consequent immunosupression must needs increase. Neurological manifestations occur in HIV infected individuals across the spectrum of immune depletion and involve various aspects of the nervous system both peripheral and central.

For the sake of clarity and to detail a useful clinical approach it would be best to discuss the common neurological manifestations of HIV and related opportunistic infections and the method of diagnosis and treatment in the Indian setting, rather than attempt an all encompassing review of the various known neurological conditions seen in the HIV infected individual.

MENINGITIS IN THE HIV PATIENT

Cryptococcal meningitis is a common opportunistic infection that occurs in patients with advanced HIV/AIDS and CD4 counts of <200. The primary symptom is headache which is often severe and this may be associated with mild fever and in severe cases drowsiness and vomiting. Neck stiffness is uncommon as are focal neurological signs or evidence of papiloedema and it is important that a constant headache in the HIV infected patient not be disregarded. Imaging findings are generally unhelpful, though in rare instances a concomitant cryptococcoma may reveal itself on CT or MRI. The diagnosis is established by examination of the CSF which is usually under significantly elevated pressure. The CSF protein levels may be marginally elevated but significant pleocytosis is uncommon. An India Ink preparation will reveal the presence of multiple cryptococci and the CSF cryptococcal antigen study (CRAG) will be positive, often in very high dilution. This test alone is enough to warrant a diagnosis of cryptococcal meningitis and should never be omitted when a CSF study is performed. Fungal cultures of the CSF are often positive when larger volumes of CSF are inoculated. In patients in whom a CSF study is contraindicated or unavailable it may be possible to obtain confirmation of the diagnosis by means of a serum CRAG which is usually positive.

Treatment consists of administering Amphotericin B which is given in a dose of 0.7mgs-1.0mgs/Kg-wt daily for 14 days. A cumulative dose of 1.-1.5gms of Amphotericin may be required in order to achieve a clinical cure. Flucytosine in a dose of 25mgs/kg orally qds, is given in conjunction with the Amphotericin B but this drug is associated with an increased incidence of hematological toxicity in the HIV infected individual and may require early discontinuation. Amphotericin B is itself associated with significant toxicity which consists of phlebitis, anaemia, renal dysfunction and hypokalemia all of which require to be monitored and managed. Liposomal Amphotericin B is equally effective and significantly less toxic but is associated with a much higher cost.

Management of the raised intracranial pressure is important and in these individuals daily or alternate day large volume CSF drainage may be required. In general fluconazole is ineffective orally or intravenously as monotherapy for cryptococcal meningitis except in very mild cases associated with low CSF CRAG levels. It is important however that all patients with cryptococcal meningitis be placed on secondary prophylaxis with fluconazole in a dose of 400 mgs daily until the immune system is reconstituted with antiretroviral therapy and the CDF counts are above 300 for over 6 months to 1 year. Most patients with cryptococcal meningitis recover well but in some instances the disease is difficult to control and in these instances aggressive management of the elevated intracranial pressure until adequate quantities of amphotericin have been administered remains crucial.

Tuberculous meningitis (TBM) though uncommon in western series remains a common cause of morbidity in the HIV infected patient. In general TBM presents at higher levels of CD4 counts than would be expected (>200) and the clinical picture is similar to that seen in the non HIV infected patient with fever, headache, vomiting, mental obtundation, neck stiffness and focal neurological signs. All the complications of TBM viz. seizures, hydrocephalus, arteritis, SIADH etc are also seen in these patients however, a cerebritis with markedly raised intracranial pressures may occur on therapy with anti-retroviral drugs as part of an immune reconstitution syndrome. It should be kept in mind that multi-drug resistant (MDR) TB is common in the HIV infected individual and a lack of response to primary agents should alert the clinician to this possibility. The CSF picture of elevated proteins, a lymphocytic pleocytosis and a low CSF sugar is the usual one and attempts at culture of AFB from the CSF are generally unrewarding unless undertaken by a BACTEC technique. We have been unimpressed with PCR technology that attempts to identify mycobacterial DNA from the CSF and both false positive and negative results of this test are common. Individuals who have had dual infection with TBM and cryptococcal meningitis or who have developed both diseases in a sequential manner may be seen, and this should be

kept in mind to avoid the possibility of not treating a serious and possibly fatal opportunistic infection.

Aseptic meningitis occurs early in HIV infection as part of a seroconverting illness and is generally seen not in isolation but associated with the overall picture of fever, lymphadenopathy, rash and oral lesions that are seen in the seroconverting HIV patient. It is important to identify patients with aseptic meningitis as being seroconverting HIV infected individuals and test appropriately, as in these cases the HIV serology by standard ELISA techniques will be negative and diagnosis will only be possible by a viral load or p-24 antigen study. Early identification and treatment of these individuals is important as this preserves HIV specific T- cell responses with a chance of maintaining such patients as "long term non-progressors" without any therapy.

Other causes of meningitis in HIV are uncommon and include syphyllis, histoplasmosis and infiltrative lymphomatous meningitis.

CNS MASS LESIONS IN THE HIV PATIENT

Patients with advanced HIV/AIDS often present with drowsiness and obtundation which may be associated with focal neurological deficits. On investigation many of these patients are found to have a mass lesion in the CNS. The differential diagnosis of these conditions includes CNS toxoplasmosis, primary CNS (B cell) lymphoma and progressive multifocal leukoencephalopathy (PML). It is important to differentiate these conditions so as to target therapy accurately.

CNS toxoplasmosis occurs as a result of reactivation of remote and previously dormant infections consequent upon a loss of cell mediated immunity in advanced HIV disease. The clinical presentation is similar to that of any brain tumor with drowsiness, confusion, disorientation and evidence of some focal neurological deficits. The diagnosis is essentially made on three grounds i.e.- the presence of multiple ring enhancing lesions on CT or MRI often present at typical sites such as the basal ganglia and the thalamus, a positive Toxoplasma IgG antibody test and a significant improvement clinically and radiologically with an adequate trial of antitoxoplasma therapy. Radiological features are generally distinctive but need to be distinguished from multiple tuberculomas and primary CNS lymphoma. In difficult circumstances a brain biopsy may be required but most clinicians would prefer to assess the response to 7-14 days of therapy against toxoplasmosis with sulphadiazine (25mgs/kg 6hourly to a max of 8gms per day) combined with pyrimethamine (200 mgs per day on day 1 followed by 50-75mgs per day) or in cases where there is sulphonamide allergy, azithromycin (500mgs per day) combined with pyrimethamine. Steroids should be avoided as the response to steroids that might occur in patients with CNS lymphomas may confuse the picture.

Primary CNS lymphomas generally present as a solitary mass lesion with features of increased intracranial tension and focal neurological signs. Symptoms and signs evolve more slowly than those in CNS toxoplasmosis. Radiological imaging is required to differentiate between toxoplasmosis and CNS lymphomas. Both may show local edema and variable contrast enhancement. Lymphomas tend to occur in a periventricular or even intraventricular in distribution. Where available, Positron Emission Tomography (PET) scans may help in differentiation; toxoplasma lesions take up the isotope locally and appear as hot lesions in contrast to the cold lesions of CNS lymphoma. It may be possible to identify the presence of Epstein Barr virus fragments by PCR in the CSF which may correlate well with the presence of CNS lymphomas.

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection caused in the white matter by a human papovavirus, JC virus. The time course of this disease is insidious and differs from both of the above conditions due to the presence of more firm focal deficits and the lack of an encephalopathy or the clinical features of a mass lesion. Radiologically the disease tends to be distinctive, with numerous white matter lesions (white on T2 weighted MRI images) and no edema or mass effect. Where available the diagnosis may be confirmed by detection of JC virus on PCR analysis of the CSF. Treatment of PML is generally unsuccessful though spontaneous remissions have been known. Most patients should be treated aggressively with antiretroviral therapy and benefit should ensue.

Multiple tuberculomas due to disseminated tuberculosis may occur at any stage in HIV patients and differentiation from toxoplasmosis may be a matter of concern. CSF analysis when available may help in identifying tuberculosis, in which the lymphocytic pleocytosis is prominent. The location of lesions in the thalamus and basal ganglia and a positive toxoplasma serological test all favour toxoplasmosis though in many cases differentiation will only be possible by an effective therapeutic trial or a brain biopsy.

THE AIDS DEMENTIA COMPLEX

The AIDS dementia complex was seen very frequently in patients with end stage AIDS but the effective use of antiretroviral therapy has made this disease somewhat uncommon. The clinical features of this condition consist of a cognitive impairment which at best may consist of minor degrees of inattention and forgetfulness and at worst consist of a severe global dementia. Associated with the cognitive impairment is a motor dysfunction consisting of a reduction in fine and repetitive movements, gait disturbances and hyperreflexia with released primitive reflexes. This condition is associated with an altered personality, apathy and occasionally agitation. In general the AIDS dementia complex is a diagnosis of exclusion and is associated with severe reductions in the CD4 count (<50cells/mm^3) and the presence of prolonged disease. Neuroimaging studies show a marked cerebral atrophy with enlargement of the ventricles and reduction in the basal ganglia. The pathology of this condition is caused by proliferation of the HIV virus in the CNS. Treatment is therefore the use of effective antiretroviral therapy with 3 or 4 drugs especially those that penetrate the CNS effectively such as zidovudine, stavudine, abacavir, nevirapine, efavirenz and indinavir.

MYELOPATHY, MYOPATHY AND NEUROPATHY IN HIV

Myelopathy is rare in HIV disease and may be segmental when it is due to infection with viruses such as CMV, Varicella zoster or even toxoplasmosis. In these instances the presentation is one of a transverse myelitis with or without a polyradiculopathy. A more subacute and diffuse myelopathy which is chronic and progressive tends to be disabling and may occasionally be part

of the AIDS dementia complex. This slowly progressive vacuolar myelopathy is more commonly seen and patients present with gait disturbances, motor weakness and bladder and bowel disturbances. When possible tests should be undertaken to detect the concomitant presence of either HTLV-I or HTLV-II viruses which are associated with similar presentations.

Myopathy in HIV medicine was more commonly seen with the use of high doses of zidovudine. An inflammatory polymyositis has been described but this is also uncommon. Asymptomatic elevations of the CPK are more usual but may not be of much clinical significance.

Neuropathy in HIV is common and can cause considerable discomfort to the HIV infected patient. In many instances the cause is one of the nucleoside reverse transcriptase inhibitors (NRTIs) particularly stavudine, didanosine and zalcitabine. Where possible these drugs should be stopped and equally effective agents substituted, however in our setting this is not an easily available option, as alternate therapy may multiply the cost of medication significantly, and lead to interruptions in treatment. HIV disease itself produces a distal symmetrical neuropthy that results in painful parasthesias and dysaesthesias. In such cases HIV disease is advanced with CD4 cell counts that are < 200. In both drug induced and HIV induced neuropathy, adequate pain control with gabapentin and tricyclics will be required but may be ineffective.

In conclusion HIV and opportunistic infections may cause a constellation of clinical findings across the entire nervous system; however with the effective use of early antiretroviral therapy many of these manifestations should become increasingly rare. It is worth remembering that patients with HIV infection are also prone to all the common problems endemic in our country and in all instances a broad differential diagnosis that includes common problems with a neurological manifestation such as cerebral malaria, tuberculosis, typhoid, the encephalitides etc. must be entertained in addition to the opportunistic infections described above.

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