Nervous System Involvement in HIV Infection

Abstract

Neurological involvement in HIV positive patients is very common. These conditions are either caused by direct and indirect infection of brain tissue by HIV virus or secondary to immunodeficiency status produced in HIV positive patients. The Central Nervous System (CNS) involvement varies from neoplasm, opportunistic brain infections to brain diseases resulting from exaggerated immune-reaction. Clinically, they present as diffuse non-focal or focal brain diseases. To decrease the morbidity, it is very important that these conditions are suspected and diagnosed early. Multiple infections should be considered while evaluating these patients.

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Introduction

Neurological involvement occurs in more than 40% of HIV patients. In up to 20% of AIDS cases, neurological symptoms are presenting features [1, 2, 3, 4]. Although in very recent years, HIV-associated CNS disease is declining, the mortality from these diseases continues to remain high [5]. Nervous system involvement may be caused either directly by HIV itself or indirectly by infectious, neoplastic or autoimmune processes secondary to immunodeficiency status of such patients. CNS diseases caused directly or indirectly due to HIV infection are: 1.HIV-associated neurocognitive disorder

(HAND syndrome/AIDS Dementia Complex), 2. Vacuolar myelopathy, and 3.Certain peripheral neuropathies [6]. Conditions caused secondary to immunodeficiency status of such patients include 1. CNS lymphoma, 2. Kaposi sarcoma, 3. Progressive multifocal leukoencephalopathy (PML), 4. Fungal infections, 5. Tuberculous meningitis and tuberculoma, 6. Cerebrovascular diseases, 7. Certain neuropathies and myopathies, 8. Toxoplasmosis, 9. Neurocysticercosis, 10. Cytomegalovirus (CMV) encephalitis [7, 8, 9]. In addition, some neurological conditions (i.e. peripheral neuropathy) are caused by antiretroviral drugs. In AIDS, it is difficult to explain a clinical presentation with a single diagnosis. On an ongoing process a new onset neurologic complications are often superimposed with a different etiology. Clinical features reflect the sum of deficits at several anatomic sites.

Non-Focal Brain Diseases in HIV Infection

These conditions present with diffuse alterations in cognition and symmetrical motor dysfunction. In these conditions, patient's symptoms are not readily explained by one or a few macroscopic focal lesions of the brain. There are no specific neurological symptoms to provide discrete cortical localization, nor any signs to point to a lesion in a cerebral or cerebellar hemisphere. Again, these non focal disorders clinically can be further segregated into those in which cognition is altered in the face of preserved alertness and those in which these two elements are altered in parallel. The most important disorder in the first category is AIDS dementia complex (ADC) and the other categories are cryptococcal meningitis, toxic/metabolic encephalopathies, CMV/HSV encephalitis, etc.

Focal Brain Diseases in HIV Infection

Focal brain involvement may be discrete, solitary or multifocal. Toxoplasma gondii infection, progressive multifocal leukoencephalopathy (PML) and primary CNS lymphoma are common focal neurological lesions. M. tuberculosis and C. neoformans are other infectious focal lesions. Infection with less frequent causes include pyogenic abscess and infection with Nocardia asteroids, Cytomegalovirus (CMV), Treponema pallidum, Varicella-zoster virus (VZV) and Histoplasma capsulatum. In a single patient, multicentric lesions may represent more than one disease, and the inability to biopsy all lesions may lead to chances of misdiagnoses. Biopsy-associated complications are more common in these patients.

Important Brain Diseases in HIV Infection

AIDS Dementia Complex (ADC)

In the advanced stages of HIV infection, only a minority of patients develop progressive encephalopathy. This has been termed as AIDS dementia complex (ADC) or HIV dementia. The pathogenesis of the disease is only partly understood, but HIV replication in the CNS plays a key role. Soon after the primary infection, HIV appears to be present and replicating in the CNS of most, if not all, infected individuals. The macrophages in the peri-vascular spaces and multinucleated giant cells (MGCs) are the major sites of virus accumulation [10]. Clinically, this is a sub-cortical dementia characterized by disturbances in motor performance, cognition and behavior. An essential feature in the diagnosis of ADC is the presence of well documented cognitive decline and the exclusion of other neurological complications of HIV infection,

such as cerebral toxoplasmosis, lymphoma, and progressive multifocal leukoencephalopathy [11]. Therefore, cerebrospinal fluid (CSF) examination and imaging studies of the brain are mandatory. CSF analysis should exclude infectious agents other than HIV, and imaging scans should show cortical atrophy, enlarged ventricles, diffusely decreased attenuation of the deep white matter, and an absence of focal abnormalities in patients with ADC. Neuropsychological assessment may also be helpful in confirming the clinical diagnosis of ADC.

The treatment of ADC is highly active antiretroviral therapy (HAART) with drugs that have good CSF penetration. The therapeutic and prophylactic efficacy of zidovudine in ADC has been well documented. Encouraging preliminary results have been seen with lamivudine, abacavir and stavudine. At this point, it is impossible to make definitive recommendations about the optimum antiretroviral therapy for HIV dementia. Good CSF virologic suppression has been reported for regimens consisting of NRTIs plus indinavir, efavirenz, nelfinavir, or nevirapine, but not for ritonavir/saquinavir without NRTIs.

Toxoplasma Encephalitis

Cerebral toxoplasmosis is the most common cerebral mass lesion in patients with AIDS. The sero-prevalence for Toxoplasma gondii in HIV infected individuals is estimated to be 10% to 40%. The frequency of symptomatic toxoplasma encephalitis (TE) in seropositive HIV infected patients varies from about one fourth to one half of cases in the absence of antimicrobial prophylaxis [12]. Cerebral toxoplasmosis is due to reactivation of latent infection as a result of progressive loss of cellular immunity. The most frequent clinical manifestations of TE in HIV infected patients are headache, confusion, fever, and lethargy. Seizures may be an initial manifestation. 50% to 60% of patients complain of or demonstrate focal neurological signs. Occasionally, TE may also present as diffuse encephalitis [13].

Cryptococcal Meningitis

Cryptococcal meningitis (CM) is the most common manifestation of systemic fungal infection in HIV infected patients and is the third most frequent neurological complication in patients with AIDS [14,15]. Patients often present with non-specific complaints such as headache, fever, altered mental status, nausea, and vomiting. Focal neurologic signs and seizures occur in about 10% of patients [14]. Elevated intracranial pressure (ICP) occurs in excess of 50% of HIV infected patients with CM, without accompanying hydrocephalus or cerebral edema [15]. The pathophysiology of increased ICP has not been fully elucidated in this condition.

Primary Central Nervous System Lymphoma

Primary central nervous system lymphoma (PCNSL) is an extranodal, non-Hodgkin's B-cell type neoplasm. In HIV infected patients, the incidence of this neoplasm is more common than in the general population. At present, PCNSL occurs in 2%–5% of patients with AIDS, and is the second most frequent space occupying lesion of the brain after central nervous system toxoplasmosis [16]. These lymphomas typically occur in HIV infected individuals with CD4+ T-lymphocyte counts less than 50 cells/μL. In HIV infected patients, the finding of PCNSL is considered an independent criterion for the diagnosis of AIDS. In patients with AIDS, the age of presentation of PCNSL is usually in the fourth decade. Men are more commonly affected than women (ratio 9:1). The majority of these tumors are located supratentorially. Lymphomatous meningitis is estimated to occur

in 25% of patients with AIDS and PCNSL. Single or multiple lesions may be present. The Epstein-Barr virus (EBV) is almost always found in tumor specimens from patients with AIDS-related PCNSL. The clinical presentation of PCNSL in patients with AIDS usually consists of altered mental status, focal neurologic deficits, seizures, or evidence of increased intracranial pressure, with symptoms present for a mean of approximately two months prior to presentation [17]. Patients with HIV infection in whom PCNSL is suspected should promptly be evaluated with CT or MRI of the brain.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an often fatal, demyelinating disease of immunocompromised patients caused by the JC virus. Although relatively uncommon at one time, PML is now encountered more frequently, mainly due to the presence of HIV and AIDS. Though survival with PML remains low, the introduction of HAART now offers some hope in improving survival with PML. Because PML is a multifocal disease, a wide variety of neurologic symptoms can occur, and PML should be considered in any HIV infected patient with neurologic symptoms. Common signs and symptoms include mono- or hemiparetic limb weakness, gait abnormality, cognitive dysfunction, and dysarthria. Less frequently, there may be seizures, sensory loss, vertigo, and visual impairment. Fever and headache are usually absent. Without intervention, most patients with PML will die within 4–6 months, though prolonged survival has been reported in a small number of patients, even in the pre- HAART era [18, 19].

Cytomegalovirus Infection

Cytomegalovirus (CMV) infection of the central and peripheral nervous system in patients with HIV infection and AIDS may result in various clinical syndromes. Encephalitis, polyradiculitis, and polyradiculomyelitis, and peripheral neuropathies can occur due to CMV infection. CMV encephalitis usually occurs in patients with very low CD4+ T-lymphocyte counts (<50 cells/μL), and CMV infection is often present at other sites (retina, adrenal glands, gastrointestinal tract, or blood) at the time of presentation. Two distinct clinical and neuropathological entities of CMV encephalitis have been described [20]. The first, encephalitis with dementia, is characterized by subacute dementia with periods of delirium, confusion, apathy, and focal neurologic deficits. Autopsy in these patients reveals diffuse microglial nodules in the grey matter of cortex, basal ganglia, brain stem, and cerebellum. The second form of CMV encephalitis is a ventriculo-encephalitis. CMV infection of the ependymal cells lining the ventricles typically results in a rapidly progressive syndrome of delirium, cranial nerve deficits, and ventriculomegaly. Death due to CMV encephalitis usually results within 4 to 6 weeks of presentation [20, 21].

Tuberculosis

Tubercular involvement may occur at any stage of HIV infection. Multiple infections should always be kept in mind. The presenting signs and symptoms vary according to the stages of the disease. Two patterns of focal involvement have been described. Tuberculomas are small foci of caseation surrounded by a collagenous capsule, inflammatory cells, and few bacilli. The MRI appearance may vary, showing multiple or solitary lesions smaller than 1cm in size, with nodular or ring enhancement, and no associated mass effect or edema. In contrast, tuberculous abscesses are large solitary lesions with central liquefaction containing numerous tubercle bacilli. They appear hyper-intense on T2-

weighted MRI images and are generally associated with mass effect, ring enhancement, and edema. Lesions may be located in the supratentorial area, posterior fossa, or brain stem. Hydrocephalus, basilar meningitis, or cerebral infarction develops in at least one third of the patients diagnosed with CNS tuberculosis [22].

Neurologic Immune Reconstitution Inflammatory Syndrome

Neurologic immune reconstitution inflammatory syndrome (NeuroIRIS) is a newly recognized complication which usually occurs after starting combination antiretroviral therapy. As host immunity improves after starting ART, the body immune system produces an exaggerated immune reaction against underlying subclinical opportunistic infectious agent. In a recent retrospective study of 461 patients started on combination antiretroviral therapy, 7 patients (0.7%) developed Neuro IRIS [23]. In general, the risk of IRIS appears to be high in patients whose CD4+ lymphocyte count is below 50 cells/mL at the start of antiretroviral therapy [24].

Diagnostic Approaches

The basic principle of the diagnostic approach is neuro-anatomic localization. The advantages of this approach is to differentiate disease processes including opportunistic infections which have a tendency to damage particular structures and thus, causing anatomically defined syndromes. Anatomic localization helps for further diagnostic evaluation like electrophysiological testing in diseases of peripheral nervous system and neuroimaging in case of CNS diseases. The time course of the evolution of symptoms and signs are the important diagnostic elements. The temporal profile reduces the different possibilities. The third important variable in diagnostic approach is the patient's risk background. Here, the stage of systemic HIV infection and the resultant immune suppression are the most important variables. Severe compromise of cell-mediated immunity increases vulnerability to a group of disorders that dominate the course. Bacterial meningitis, tuberculosis, syphilis, etc., can occur at any CD4 count. However, progressive multifocal encephalopathy, cryptococcal meningitis, toxoplasma encephalitis and CMV encephalitis occur in AIDS patients with CD4 count <200/ cubic mm. CNS involvement may be diffuse like HIV encephalopathy, or associated with more discrete solitary or multifocal lesions.

Conclusion

CNS involvement in HIV infection/AIDS is common. To decrease the morbidity, it is very important that these conditions are suspected and diagnosed early. Multiple infections should always be kept in mind while evaluating these patients. Diagnostic approach includes staging of HIV and whether disease is nonfocal or focal. If disease is non-focal, without constitutional symptoms, and major defect is cognitive, then the possible diagnosis is ADC. In the presence of constitutional symptoms, headache and some alteration of sensorium, cryptococcal or tuberculous meningitis should be ruled out. In the presence of focal disease with constitutional symptoms, mass effect and ring enhancement on imaging, toxoplasmosis, tuberculosis and primary CNS lymphoma should be considered. CSF toxoplasma serology and PCR for tuberculosis can be helpful investigations. A typical MRI brain finding with JC virus serology or PCR is suggestive of PML. A diagnostic approach, thus, minimizes both empiricism and the need for brain biopsy.

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