CHAPTER 12

HIV-RELATED NEUROLOGICAL DISORDERS

Abstract

Headache, fever, and neck stiffness occurring during the stage of seroconversion are due to aseptic meningitis. In advanced disease, patients may have generalised headache with photophobia for many weeks or months. Seizures and transient neurological deficits may occur. Underlying illnesses may precipitate AIDS-related dementia, where markers of immune activation may be present in CSF. The clinical severity exceeds the neuropathological abnormalities and viral load.

Key Words

AIDS dementia, HIV-related headache, Mononeuritis multiplex, Myopathy, Peripheral neuropathy, Seizures, Sensory neuropathy, Vacuolar myelopathy, ZDV-associated myopathy

12.1 – AIDS DEMENTIA COMPLEX

Before the advent of strong and effective ARV drugs, about 15–20 per cent of HIV-infected persons developed dementia and another 20–25 per cent had cognitive or motor dysfunction, when the CD4 cell count dropped below 100 cells per μL. The risk factors for development of dementia are anaemia and elevated levels of beta-2-microglobulin in CSF (McArthur *et al*., 1993). Underlying illnesses that may precipitate this condition include cerebral lymphoma or toxoplasmosis, cryptococcal meningitis, depression, metabolic disorders, progressive multifocal leucoencephalopathy (PML), and systemic opportunistic illnesses. ARV drugs such as ZDV, stavudine, abacavir, and nevirapine easily cross the blood-brain barrier.

Clinical Manifestations: It is initially a subcortical dementia. Stage 0 (normal) to Stage 4 (severely impaired) have been described (Sidtis & Price, 1990). In the initial stages, the reflexes are brisk and symmetrical. Primitive reflexes may be seen in later stages. The clinical manifestations include poor concentration, disturbed short-term memory, slowing of thought processes and psychomotor slowing, impairment of rapid alternating and repetitive movements, motor incoordination, tandem (heel-to-toe) gait, bradykinesia, social apathy and withdrawal (rare), and abnormal ocular saccades (Currie *et al*., 1988; Brew & Currie, 1993). The clinical severity exceeds the neuropathological abnormalities and

viral load (Glass *et al.*, 1993), and is associated with the presence of markers of immune activation in the CSF (Brew, 1992). Neuropsychological assessment reveals impairment of cognitive domains of memory, executive function, psychomotor speed, reaction time, and complex attention (Maruff *et al.*, 1994). Patients may need extra help in remembering to take their medications, making simple arithmetic calculations in daily life, and remembering commonly used telephone numbers. They may get lost in familiar places.

Investigations: CSF is to be examined for protein, glucose, culture, syphilis, and cryptococcal antigen. Levels of beta-2-microglobulin and neopterin are to be estimated. Serological tests are essential to rule out syphilis and cryptococcal infection. Computerised axial tomography (CAT) of the cranium shows cortical atrophy, enlargement of ventricles, widened sulci, and attenuation of white matter. Magnetic resonance imaging (MRI) shows similar changes as the cranial CAT scan, but is more sensitive in detecting illnesses such as PML.

Chemoprophylaxis: Early initiation of ZDV prophylaxis (at least 600 mg per day) has been recommended, but its efficacy is unclear.

Management: In the early stages of the disease, the patient and family should be counselled and medical power of attorney recommended (Wright *et al.*, 1997). The response to ARV drugs takes 6–8 weeks to be clinically apparent. Improvement is seen in 50 per cent of cases. Total blood counts are to be done every 2 weeks when patients are on high-dose ZDV therapy (Wright *et al.*, 1997). The clinical assessment is repeated every 4–6 weeks to determine response to treatment. Of the new drugs being studied, selegiline appears promising. Some studies have found ongoing brain damage even in patients taking ARV drugs (Fact Sheet 505, 2006).

12.1.1 – Progressive Multifocal Leucoencephalopathy (PML)

Leucoencephalopathy is a disease of the white matter of the brain. As its name denotes, the disease gets worse in a short time and occurs in multiple sites at the same time. The disease is difficult to diagnose and before strong ARV drugs became available, most patients died within 2 years. There is no approved treatment for PML, though several treatments may be helpful. Cytosine arabinoside, a toxic drug that can damage the bone marrow, seemed to be effective against PML in one study, but not in others. Acyclovir, dexamethasone, cidofovir, beta interferon, heparin, peptide-T, n-acetyl cysteine, and topotecan are among the drugs that have been studied, with varying degrees of success (Fact Sheet 516, 2006).

12.2 – VACUOLAR MYELOPATHY

This condition is rare in HIV-infected children (Brew & Currie, 1993; Glass *et al.*, 1993). It affects about 10 per cent of AIDS patients (Dal Pan *et al.*, 1994). It is due to vacuolar degeneration of the posterior and lateral columns of the

spinal cord (Wright *et al.*, 1997). Toxins, metabolic disorders, or excessive production of cytokines may cause vacuolar myelopathy. It manifests as a progressive spastic paraparesis, with impaired perception of vibration and proprioception in feet and legs. Sensory loss of posterior-column type may be present, which lacks a definite sensory level. There may be loss of sphincter control in late stages of the disease. This condition responds poorly to ARV drugs. Addition of another ARV drug may be helpful. Management includes occupational therapy, physiotherapy, using walking aids, and tackling incontinence (Wright *et al.*, 1997).

12.3 – MYOPATHIES

ZDV may cause myositis. The inflammatory type of myopathy is similar to polymyositis, while non-inflammatory type is not yet understood (Simpson & Wolfe, 1991). Both HIV-related polymyositis and ZDV-associated myopathy manifest as progressive proximal muscle weakness, myalgia, and loss of more than 10 per cent of body weight. ZDV-associated myopathy mainly affects the lower limbs and causes wasting of buttocks. Serum creatine kinase (CK) levels are elevated. Electromyography (EMG) and muscle biopsies are abnormal. A trial of corticosteroids or intravenous Ig is indicated for HIV-related polymyositis. Patients with ZDV-associated myopathy usually recover in 6–12 weeks after withdrawal of the drug. Once the myopathy has resolved, ZDV may be reintroduced at a lower dose. If relapse occurs, another ARV drug should be used.

12.4 – PERIPHERAL NEUROPATHY

HIV-1 Sensory Neuropathy: This type of neuropathy is rare in asymptomatic HIV-infected persons but occurs in up to 35 per cent of AIDS patients (So *et al.*, 1988); disease is due to axonal degeneration with macrophage infiltration that affects all types of nerve fibres. This condition has been associated with infection by MAC. An identical and indistinguishable type of neuropathy is caused by ARV drugs (didanosine, zalcitabine, and stavudine). The neuropathy is distal, symmetrical, and predominantly sensory. Its manifestations include symmetrical numbness, hyperaesthesia, impaired perception of pain, temperature, light touch, vibration, and proprioception. Ankle jerks may be decreased or absent. Burning sensation in soles is a rare manifestation. There is no known specific treatment (Simpson & Wolfe, 1991). Management of HIV-1 sensory neuropathy involves withdrawal of all neurotoxic drugs (ARV drugs, isoniazid, alcohol, diabetes, high-dose metronidazole, thalidomide, and dapsone) and replacement with another non-neurotoxic drug. Mild to moderate neuropathic pain is treated with a *combination* of paracetamol and codeine. Tricyclic antidepressants (amitriptyline 10 mg at night or sodium valproate 200 mg thrice daily) are to be administered and the dosage may be increased if pain is not controlled. For severe neuropathic pain, narcotic analgesics such as morphine

are indicated. Clinical improvement may take up to 12 weeks (Wright *et al*., 1997).

Inflammatory Demyelinating Polyneuropathy: This condition occurs during seroconversion or asymptomatic phase. The acute manifestations of this condition are similar to that of Guillian–Barré syndrome. It is probably an autoimmune disorder (Simpson & Wolfe, 1991). It manifests as progressive weakness, loss of reflexes and rarely, mild sensory disturbances. EMG and nerve conduction studies are essential for confirming the diagnosis. Corticosteroids are to be used cautiously. Plasmaphresis and intravenous administration of Igs have been successfully tried. Physiotherapy and long-term rehabilitation are essential components of management (Wright *et al*., 1997).

Mononeuritis Multiplex: During the asymptomatic or early symptomatic phases of HIV infection, acute nerve palsies may occur. One or more nerves may be involved. This mild form of mononeuritis is probably an autoimmune disorder (Simpson & Wolfe, 1991). This condition may resolve without specific treatment (So & Olney, 1991). In advanced disease, widespread neuropathy may occur, which requires hospitalisation. Nerve conduction studies are indicated. Since cytomegalovirus has been linked to severe form of mononeuritis multiplex, a trial of ganciclovir may be necessary (Wright *et al*., 1997).

12.5 – HIV-RELATED HEADACHES

During the stage of seroconversion, patients may present with headache, fever, and neck stiffness due to aseptic meningitis. Examination of CSF may or may not show pleocytosis. Headaches are commonly seen in advanced disease. Patients may have generalised headache with photophobia for many weeks or months. The patient should be explained that most headaches resolve within several weeks. HIV-related headaches need to be differentiated from that due to sinusitis, migraine, depression, cryptococcal meningitis, cerebral toxoplasmosis, and cerebral lymphoma. Investigations include CAT or MRI of the cranium with sinus views, CSF examination (cytology, culture, cryptococcal antigen) and serology for cryptococcal antigen. Headache is treated with a combination of paracetamol and codeine. Tricyclic antidepressant (amitriptyline 50–75 mg at night) may also be used.

12.6 – SEIZURES

Seizures are seen in a variety of conditions that include cerebral space-occupying lesion, subclinical HIV-associated CNS involvement or dementia, metabolic disturbances, and cryptococcal meningitis (Holtzman *et al*., 1989). The cause cannot be determined in up to 46 per cent of patients (Wong *et al*., 1990). A complete history of the seizure should be recorded and withdrawal effects from alcohol or drugs are to be ruled out. CAT or MRI of the cranium may be undertaken to

exclude cerebral lymphoma, toxoplasmosis, and PML. If CAT or MRI is normal, CSF examination (protein, glucose, cytology, culture, cryptococcal antigen) is essential. Haematological and serological investigations include total blood count, blood sugar, liver function tests, serum electrolytes, serum calcium and magnesium, and cryptococcal antigen. Electroencephalogram (EEG) helps to exclude focal seizures. If left untreated, seizures may recur. Clonazepam or sodium valproate is the recommended front-line drug. Use of phenytoin and carbamazepine is associated with adverse drug reactions such as skin rash, leukopenia, and abnormal liver function tests (Holtzman *et al*., 1989).

12.7 – CEREBROVASCULAR DISEASE

Transient Neurological Deficits (TNDs) may occur in advanced HIV disease. These are similar to transient ischaemic attacks. This condition is associated with thrombocytopenia, deficiency of protein S, and presence of anticardiolipin antibodies. Some patients have responded to ARV agents. Cardiac disease, cerebral lesions, cryptococcal meningitis, and neurosyphilis are among the causes of cerebral infarction or haemorrhage. The patient must be hospitalised (Wright *et al*., 1997). Investigations include CAT or MRI of the cranium, carotid doppler studies (for recurrent TNDs), EEG to exclude focal seizures, echocardiogram, chest radiography, total blood count, clotting profile (bleeding time, clotting time, prothrombin time, estimation of activated C, protein C, and protein S), and serological tests – cardiolipin antibody, syphilis serology, and cryptococcal antigen titre. Underlying cardiac or cerebral disease must be treated. If TNDs are recurrent, without underlying pathology, switch to a new ARV drug. Some patients may require anticoagulation therapy with low dose aspirin or warfarin (Wright *et al*., 1997).

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