REVIEW ARTICLE

The Neurology of HIV Infection - A Review of the Literature

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ABSTRACT

Background: *The nervous system is widely involved in the course of infection with the human immunodeficiency virus (HIV). The manifestation may be a direct effect of the virus, the result of opportunistic infections or secondary malignancies, or a result of the therapy of various aspects of the disease. This review looks at these neurological consequences of HIV infection.*

Methods: *The review was sourced mainly by Medline search using the search terms HIV, AIDS and neurology. Relevant journals were subsequently studied.*

Results: *The major neurological manifestations of HIV infection are toxoplasmosis, cryptococcal meningitis, AIDS dementia complex, primary lymphoma, tuberculosis, progressive multifocal leukoencephalopathy, herpes zoster, Bells palsy, peripheral neuropathy, and vacuolar myelopathy. The overall effect of these is the acceleration of progression of the disease. About 30% of the mortality in HIV infection is attributed to neurological diseases.*

Conclusion: *The nervous system is significantly affected in HIV infection and the impact on morbidity and mortality is profound. All effort should be made to ensure early recognition and amelioration of the various nervous systems complications of HIV infection.*

KEY WORDS: *HIV; AIDS; Neurology.*

Paper accepted for publication10th February 2005

INTRODUCTION

The involvement of the nervous system by the human immunodeficiency virus (HIV) occurs very early in the course of its infection of the human body. Neurological complications are therefore among the first manifestations of the acquired immunodeficiency syndrome (AIDS) and arise in 10 to 75% of patients with the syndrome[1,2].

The development of neurological disease in AIDS accelerates the rate of progression of the disease, and increases the length of hospital stay and the cost of care[3,4]. About 30% of the mortality in AIDS has been attributed to neurological problems[2].

The commonest neurological diseases in AIDS are cerebral toxoplasmosis, cryptococcal meningitis, AIDS dementia complex, primary lymphoma, tuberculosis, progressive multifocal leukoencephalopathy, herpes zoster, Bells palsy, peripheral neuropathy, and vacuolar myelopathy[2]. These and other less common neurological features of HIV infection are discussed in this review.

Table I. Direct effects of HIV on the nervous system

AIDS dementia complex
Peripheral neuropathy
Vacuolar myelopathy
HIV myelitis
HIV associated cranial neuropathy
Stroke
Transient neurological deficits
Movement disorders
Psychosis
HIV Retinopathy
HIV induced optic neuropathy
Neuromyelitis optica
Motor neuron disease
Adrenal failure
Cerebellar degeneration
Granulomatous angiitis

A. DIRECT EFFECTS OF HIV ON THE NERVOUS SYSTEM

The direct effects of HIV on the nervous system are summarised in Table I.

1. AIDS Dementia Complex

AIDS dementia complex (ADC, HIV encephalopathy) is the commonest

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neuropathological finding in subjects with HIV infection, occurring in 7.5 to 25% of subjects, and also constitutes the AIDS-defining illness in 15% of these[5,6]. It occurs more commonly in intravenous drug abusers and typically presents in advanced AIDS, the onset being related to the degree of immunosuppression[5,7-9]. ADC could also present in the early course of HIV infection where it is however usually subtle and difficult to recognise[7,8].

ADC presents mainly with cognitive and behavioural problems relatively sparing motor functions. The main cognitive features are memory and attention difficulties while orientation, visuospatial and language functions are less affected[8]. Motor neurological deficits could however occur without the typical cognitive symptoms especially as cognitive deficits may be delayed in those with prior high educational attainment[10,11]. Presentations with Parkinsonism, cerebellar dysfunction and Gerstmann's syndrome (agraphia, acalculia, finger agnosia and right-left confusion) have also been reported[12,13].

The main radiological features of ADC are white matter lesions in the region of the splenium of the corpus callosum and in the crura of the fornices on magnetic resonance imaging (MRI)[5,14]. Electroencephalography (EEG) shows predominantly anterior intermittent or continuous slowing[15]. The most specific pathological finding in ADC is the presence of multinucleated giant cells[16].

ADC worsens the mortality in subjects with AIDS and this is related to raised CSF levels of beta 2-microglobulin, TNF alpha and p24 antigen[6,17,18]. The outcome is however markedly improved by anti-retroviral therapy and this is especially so with zidovudine which acts prophylactically against the development of ADC[5,11]. Anti-retroviral therapy has also resulted in a lower prevalence of ADC[19].

2. HIV associated peripheral neuropathy

Peripheral neuropathy is a frequent neurological complication of HIV infection and there are six patterns of involvement[20,21]. Acute distal symmetrical demyelinating polyneuropathy is the commonest form and, although it could occur early in the course of AIDS, it is typically a late feature occurring in older subjects with marke immunosuppression and anaemia[7,21-23]. It characteristically presents with painful paresthesias, reduced pain and temperature perception, and reduced or absent ankle reflexes[20,22]. Decreased intra-epidermal nerve fibre (IENF) density has been found useful in its diagnosis[23].

Mononeuropathy multiplex and acute inflammatory demyelinating polyneuropathy may develop in the early stages of HIV infection. Autonomic neuropathy, progressive polyradiculopathies, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and diffuse infiltrative lymphocytosis syndrome (DILS) (which presents as a Sjogren's syndrome-like disorder) have also been attributed to HIV infection[20,21].

Anti-retroviral therapy has resulted in a reduction in the incidence of HIV-associated polyneuropathy and helps in improving nerve function especially in the earlier stages of HIV[19]. Recombinant human nerve growth factor injections have also been found useful in relieving neuropathic pain[24].

3. HIV myelopathy

While HIV could give rise to a myelitis, it more characteristically produces vacuolar myelopathy (VM), a distinct entity from HIV myelitis. VM is the most common disease of the spinal cord in HIV infection although it is usually unrecognised during life[25]. It is characterised by vacuoles in the spinal cord which arise from myelin sheath swellings[26]. The thoracic spinal cord is the typical site for these vacuoles.

Vacuolar myelopathy presents with slowly progressive spastic paraparesis, gait disturbance, urinary problems, hyperreflexia, and a variable degree of sensory loss[25,27]. Erectile dysfunction could also be an early feature in males[25]. MRI characteristically shows atrophy of the spinal cord with increased tract signals[28]. There is no known treatment for the disease, although therapy with methylating agents is being investigated[25].

4. HIV myopathy

HIV-associated myopathy occurs at any stage of HIV infection and may be the initial manifestation of AIDS[29]. It is typically a

polymyositis although some appear as nemaline myopathy, and the presentation is with myalgia, generalised muscle weakness and painless dysphagia[30]. There is usually good recovery either spontaneously or with immunosuppressive treatment[29].

HIV may also give rise to inclusion body myositis (IBM) by a similar mechanism to that in sporadic IBM, and that is by stimulation of an inflammatory response in the endomysium[31]. Primary HIV infection could also present with acute, self-limited rhabdomyolysis, and with myasthenia gravis[32-34]. Rarer causes of muscle involvement in HIV infection include sarcoidosis and Kaposi's sarcoma[35,36].

5. HIV associated cranial neuropathy

Facial nerve palsy has been reported in as high as 52% of HIV patients[37]. It is usually an early manifestation of HIV infection and is frequently the first feature of the disease[37,38]. Facial palsy occurring late in the course of HIV infection is however more likely to be due to opportunistic infections or tumours involving the nervous system[39]. In such cases, herpes zoster particularly needs to be excluded.

The presence of facial palsy is highly predictive of HIV infection in some parts of the world in whom about 90% of cases occur on the background of HIV infection especially if there is an elevated erythrocyte sedimentation rate (ESR)[40,41]. Facial palsy in HIV infection is typically more severe than Bells palsy occurring in HIV negative patients and takes longer to recover[41]. Recovery is however usually good although about 14% of cases experience a recurrence[37].

The olfactory nerve is another cranial nerve that is affected by HIV infection and impaired sense of smell has been reported as a marker of early involvement of the central nervous system (CNS) by the virus[42].

6. Stroke

HIV infection increases the risk for cerebrovascular disease which could present as stroke or as a transient neurological deficit, and this may be the initial manifestation of AIDS[43]. Stroke occurring as a direct effect of HIV is typically infarctive and a result of HIV associated vasculopathy. This could be a result of direct HIV affectation of the endothelial lining. It could also be a result of immune complex deposition on the vessel wall as well as the development of prothrombotic antibodies. Other causes of stroke-like syndromes in AIDS however need to be excluded and these include opportunistic infections, cardiogenic embolism or thrombocytopaenic haemorrhage[43,44]. Vasculitis and spasm could also occur in the early or late stages of HIV infection and could give rise to recurrent transient neurological deficits[45,46].

7. HIV induced movement disorders

About 1-3% of patients with HIV infection develop movement disorders and these could be the initial presentation of AIDS[47-49]. Hemiballism, hemichorea, tremor, dystonia, spinal myoclonus, tics, paroxysmal dyskinesias, Parkinsonism and rubral tremor could all occur[13,50]. While focal lesions are responsible for most cases, primary HIV infection, with or without ADC, is the only factor identified in many instances. Parkinsonism is the most common movement disorder with primary HIV infection but chorea and dystonia are also common[12,50,51]. In patients with ADC, there also seems to be an increased risk of acute onset Parkinsonism and dystonia when treated with dopamine antagonists and for this reason, clozapine is the preferred antipsychotic agent in ADC as it does not interfere with dopamine receptors[51,52]. Anti-retroviral drugs may be useful in the treatment and prevention of movement disorders in patients with HIV infection[48].

8. HIV Psychosis

HIV infection could manifest with psychotic features and this is usually as mania, major depression and schizophrenia[53,54]. Mania occurs in about 8% of patients with AIDS while major depression is increased up to four fold in HIV infected patients[54,55]. Anxiety symptoms and personality disorders are also prevalent in HIV patients[55,56]. Fatigue, apathy, irritability and insomnia are also frequent complaints, but it is not clear whether these are related to major depression or to the level of immunosuppression[57-59]. The fatigue results in impaired daytime alertness which adversely

affects all activities[58]. The quality of life of patients with HIV is worsened by psychiatric complications which also, by interfering with adherence to treatment, worsen the outcome of AIDS[60].

9. HIV ophthalmopathy

A specific retinopathy could develop at HIV sero-conversion and is characterised by cotton wool spots[61,62]. HIV infection also produces a primary optic neuropathy and this is due to axonal degeneration mediated by HIV-infected macrophages[63,64]. This could be bilateral and present acutely but is typically responsive to anti-retroviral drugs and to steroid therapy[65,66]. HIV-induced optic nerve demyelination could also manifest as neuromyelitis optica mimicking multiple sclerosis[67].

10. HIV induced motor neuron disease

There have been various case reports of typically rapidly progressive motor neuron disease in AIDS which is responsive to anti-retroviral therapy[68-70]. Possible ways by which HIV causes this is by neuronal infection, by secretion of toxic viral substance, by inducing the immune system to secrete cytokines, or by inducing an autoimmune disease[69].

11. Miscellaneous HIV-induced neurological features

HIV infection involving the hypothalamic-pituitary-adrenal axis could give rise to primary or secondary adrenal failure. This could however also be due to opportunistic infections, neoplasms and drugs. HIV infection may also cause marked cerebellar atrophy which manifests with prominent cerebellar features in the absence of cognitive, motor or sensory deficits, and without any other identifiable cause[71]. A rare manifestation of HIV infection is granulomatus microvascular inflammation of the brain and meninges which is associated with a poor outcome[72].

B. OPPORTUNISTIC INFECTIONS OF THE NERVOUS SYSTEM IN AIDS

The opportunistic infections of the nervous system are shown in Table II.

Table II. Opportunistic infections affecting the nervous system in AIDS

Cryptococcal meningitis
CNS toxoplasmosis
Tuberculosis
Progressive multifocal leukoencephalopathy
Cytomegalovirus
Herpes zoster
Neurosyphilis
Mycobacterium a vium complex
Aspergillosis
Acanthameba
E. coli meningoencephalitis
Neurocysticercosis

1. Cryptococcal infection

Cryptococcal meningitis is the initial manifestation of HIV infection in more than 80% of patients with HIV infection in parts of the developing world where it is highly predictive of HIV infection[40,73-78]. Cryptococcal meningitis in HIV-infected patients is more likely to present with headache, fever, convulsions, neck stiffness, and neurological signs than in non-HIV infected subjects[77]. It could also present with optic neuritis and may give rise to hemichorea and hemiballism[79,80].

The CSF indices in cryptococcal meningitis are frequently non-specific and may be completely normal. Diagnosis therefore requires CSF culture, Indian ink staining and cryptococcal antigen test, and treatment is with amphotericin B, fluconazole or itraconazole[77,81].

2. Cerebral Toxoplasmosis

Cerebral toxoplasmosis is the most common cause of mass lesions in patients with HIV infection[82]. It could be the initial presentation of HIV and commonly presents with seizures[83,84]. It could however also present with movement disorders when the basal ganglia are involved, and this accounts for almost all cases of hemichorea, hemiballism, and hemidystonia in AIDS, as well as many cases of Parkinsonism[50]. The occurrence of movement disorders in developing countries should suggest the diagnosis of AIDS due to the high prevalence of cerebral toxoplasmosis and other brain opportunistic infections[85]. Tuberculous meningitis, primary cerebral lymphoma and progressive multifocal leukoencephalopathy could however also give rise to movement

disorders in AIDS and need to be excluded. CNS toxoplasmosis could also present with spinal cord involvement.

3. Tuberculosis

HIV infected subjects with tuberculosis have an increased risk of developing CNS involvement and this develops in about 10-20% of them and manifests as meningitis, cerebral abscesses or tuberculomas[86-88]. It is less common in the developed world where it affects intravenous drug users more frequently[87].

Tuberculous meningitis in AIDS has similar features as in those without HIV infection; there is usually evidence of tuberculosis elsewhere in the body and the computerised tomography (CT) scan is abnormal in more than two thirds of cases[86,88]. The response to standard anti-tuberculosis drugs is good but there is a higher mortality than in HIV-uninfected subjects and this is related to low CD4 counts as well as to delayed commencement of treatment[86,88].

Tuberculomas are characteristically rounded or lobulated masses with an irregular wall and show intense homogenous or ring enhancement after contrast administration on CT scan[1,87]. They may be single or multiple and typically frontal and parietal in location with a predilection for the parasagital areas[86]. The 'target sign' central calcification surrounded by ring enhancement is pathognomonic of tuberculoma[87]. Tuberculomas could also give rise to non-osseous spinal cord lesions which are clinically indistinguishable from intradural tumours[87].

4. Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the CNS caused by a papovirus, the JC virus[89,90]. It occurs in about 5% of HIV infected patients, and in 50% of these, it is the initial presentation of AIDS[91,92]. PML is much rarer in Africans but it occurs at a frequency of 1.5% and is usually due to the JC virus types 3 and 6[93].

The clinical features of PML are focal weakness, gait abnormalities, visual loss, and altered mentation[91]. It may however rarely present as progressive myoclonic ataxia[94]. It is differentiated from HIV dementia by the presence of focal findings, a more rapid rate of disease progression, the absence of cerebrospinal fluid markers of HIV dementia, and by a positive polymerase chain reaction (PCR) for the JC virus in the CSF[91]. A definite diagnosis however requires brain biopsy. Anti-retroviral therapy improves the outcome of PML and it may also be of prophylactic value[95].

5. Cytomegalovirus infection

Cytomegalovirus (CMV) infection in AIDS typically involves the spinal cord producing an acute, rapidly progressive myeloradiculitis with flaccid paraplegia, radicular pain, areflexia and incontinence[96]. Anti-CMV antibody titres are elevated in the serum and the CSF, while the spinal cord and cauda equina show necrotic and inflammatory lesions with numerous CMV inclusion bodies[96].

CMV also presents with encephalitis and this is frequently in association with multiple extra-cerebral organ infections[97]. CMV optic neuritis could occur with or without associated CMV retinitis[98,99]. Detection of CMV deoxyribonucleic acid (DNA) is the ideal means of diagnosis in the CSF while the plasma load of CMV DNA rather than the CD4 count is the best indicator of risk and of outcome[100].

6. Herpes Zoster

Herpes zoster typically presents as a dermatomal skin eruption, which in AIDS could evolve subacutely over months[101]. Herpes zoster could however also present as cranial (including optic) neuropathy, aseptic meningitis, acute polyneuropathy, myelitis, or encephalitis[80,102]. It is an important predictor of AIDS especially in young people and its occurrence is not related to either to the level of immunosuppression or to the duration of HIV infection[40,103]. Recovery from herpes zoster is slower and less complete than in immunocompetent subjects[103].

Rapid diagnosis of herpes zoster may be made by PCR for the Varicella zoster virus (VZV) in the CSF. Treatment with the antiviral agents acyclovir, famciclovir or valacyclovir may reduce the duration and severity of infection[104,105]. VZV vaccine may boost the immunity and prevent virus reactivation while VZV immune globulin (VZIG) prevents or modifies clinical illness in persons who have

been exposed to the virus[105]. The risk of post-herpetic neuralgia (pain persisting for more than 3 months after resolution of the rash) may be reduced by the use of amitriptyline, opioid analgesics and gabapentin[104].

7. Neurosyphilis

HIV infection increases the risk of development of neurosyphilis although this may be occult in some instances[106]. In 40% of cases, neurosyphilis is the initial presentation of AIDS[107]. It differs from neurosyphilis in non-HIV infected subjects by predominantly occurring in younger subjects and by being more frequently associated with features of secondary syphilis[107]. HIV infected patients with neurosyphilis are also more likely to present with syphilitic meningitis, cranial nerve abnormalities (especially optic and vestibulocochlear) and cerebrovascular accidents[107,108]. They also have higher CSF cell counts, higher protein levels and lower glucose levels than non-HIV positive patients[107]. The CSF should therefore be examined serologically for evidence of syphilis in all HIV positive subjects with a history of syphilis or serological evidence of syphilis in the blood regardless of prior treatment because the development of frank neurosyphilis could be prevented by early treatment with penicillin[106].

8. Miscellaneous infections

Myocobacterium avium complex (MAC) may manifest in the nervous system as a distal symmetric polyneuropathy in HIV[109]. It may also cause single or multiple brain mass lesions[87]. Aspergillosis is a rare neurological feature of AIDS and typically presents as focal brain abscesses but could also manifest as basal meningitis with pontine infarction[110]. Acanthamoeba presents as granulomatous amoebic encephalitis in AIDS and responds favourably to treatment with fluconazole and sulfadiazine, and to surgical excision[111,112]. *Escherichia coli* meningoencephalitis and neurocysticercosis also occur with a high frequency in AIDS[2].

C. MALIGNANT LESIONS INVOLVING THE NERVOUS SYSTEM IN AIDS

AIDS-related malignancies are those with significantly increased incidence and prevalence after the onset of the AIDS era, and inability to control infections may contribute to the initiation of these. Such malignancies affecting the nervous system in AIDS are listed in Table III and are discussed below.

Table III. Neurological manifestations of malignancies in AIDS

Primary CNS lymphoma
Systemic lymphoma with CNS involvement
Gliomatosis
CNS Kaposis sarcoma
Kaposis sarcoma muscle infiltration
Glioma
Astrocytoma

1. Primary CNS Lymphoma

The incidence of primary CNS lymphoma (PCL), which used to constitute less than 2% of all primary brain tumours, has increased tremendously with the onset of the AIDS epidemic[113]. Three percent of patients with HIV infection develop PCL although the incidence has reduced significantly with the use of highly active anti-retroviral therapy (HAART)[113]. It usually occurs late in the course of AIDS and is usually associated with low CD4 counts and other systemic or cerebral disorders like toxoplasmosis, CMV and HIV encephalitis[114].

PCL is an aggressive multifocal high grade B cell immunoblastic tumour with plasmablastic differentiation[114]. It is typically periventricular with a characteristic diffuse and prominent enhancement pattern on magnetic resonance imaging (MRI)[115]. Diagnosis by PCR for the Ebstein Barr virus (EBV) in the CSF is very sensitive and specific[114]. Stereotactic biopsy is however recommended before commencing treatment even in debilitated patients as it is considered a safe procedure[116]. Chemotherapy is now the favoured therapeutic approach but palliative radiotherapy and steroids may have a role in treatment[116]. Death in treated patients is usually from opportunistic infections and these need to be treated aggressively to improve mortality.

2. Systemic lymphoma with CNS involvement

The incidence of non-Hodgkin's lymphoma (NHL) is increased by approximately 100-fold in patients with advanced HIV infection[116]. It is the AIDS defining feature in about 35% of HIV infected patients and there is a rising incidence with improved survival of patients[117]. There is a preponderance of NHL in intravenous drug abusers as well as in homosexually infected men[118]. Prognosis is poor with a survival of only 10-35%[116].

3. Miscellaneous CNS malignancies in AIDS

Gliomatosis is a widely infiltrating glial tumour of the CNS which relatively spares the underlying cerebral and spinal cord architecture. Clinical features are vague with multifocal neurological deficits. Radiologically, it simulates an infective lesion, and the diagnosis is usually suspected only if there is no response to antibiotic therapy. The risk of development of glioblastoma and astrocytoma is increased by HIV infection[119,120]. Metastatic lesions from systemic Kaposi's sarcoma (due to herpes virus type 8) could also affect the CNS[121].

D. DRUG INDUCED NEUROLOGICAL FEATURES IN AIDS

1. Toxic myopathy

Toxic myopathy is reported to be infrequent with currently used doses of anti-retroviral drugs[122]. The usual agent involved is zidovudine which is toxic to mitochondria, and the manifestation is with weakness, myalgia, raised creatinine kinase levels and ragged red fibers[122]. A positive reaction for cytochrome C oxidase is helpful in the diagnosis of zidovudine-induced myopathy[123]. Toxic myopathy is potentially reversible on discontinuation of zidovudine although steroids may be needed, and thalidomide has also benefited some cases[123,124].

2. Toxic neuropathy

About 10% of patients on HAART develop a polyneuropathy which is typically distal and sensory, and the implicated drugs are usually didanosine, zalcitabine and stavudine, of whom about 1-2% discontinue treatment on this account[125]. It usually develops in very immunosuppressed subjects with a prior history of peripheral neuropathy and of use of other neurotoxic agents like alcohol. It has been related to impaired mitochondrial DNA synthesis as well as to reduced levels of acetyl-carnitine (which regulates peripheral nerve function)[125]. Neurotoxic anti-retroviral drugs should preferably not be prescribed to those at risk of peripheral neuropathy, but if this is not possible, careful monitoring should be instituted and the dosages reduced or the drugs discontinued if neuropathy develops. Tricyclic antidepressants, the anticonvulsant agent levacecarnine (acetyl-L-carnitine) and recombinant human nerve growth factor may be used in the treatment of drug-induced neuropathy[126].

Anti-retroviral therapy also been associated with the onset of Leber hereditary optic neuropathy in genetically predisposed subjects and this is due to the toxic effects of the anti-retroviral drugs on mitochondria[127,128].

3. Toxic psychosis

Nevirapine could cause neuropsychiatric complications like delirium, suicidal tendency, labile affect, visual hallucinations and paranoid delusions[129]. Neuropsychiatric features could also present as a result of drug interactions between anti-retroviral drugs and antibiotics like clarithromycin presenting with suicidal and homicidal ideation, pressure of speech, poor concentration, and extreme anxiety[130].

CONCLUSION

The nervous system is significantly affected in HIV infection and the impact on morbidity and mortality is profound. All effort should be made to ensure early recognition and amelioration of the various nervous systems complications of HIV infection.

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