Part ii – Neurological Disorders

Chapter 8
Neurological Illness in HIV Disease

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NEUROLOGY IN AFRICA
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NEUROLOGICAL ILLNESS IN HIV DISEASE

Neurological disorders are a frequent manifestation of HIV infection in Africa. At least a fifth of infected persons will present with a major neurological illness either as the first clinical manifestation of HIV or occurring during the course of symptomatic HIV disease. The proportion of patients with clinical evidence of neurological dysfunction and have abnormal neurological findings is however much higher at 40-70%. At post mortem examination, over 90% of AIDS cases have pathological changes in their nervous system. Neurological disorders affect all parts of the nervous system including the brain, spinal cord, peripheral nerves, muscle and eye. This chapter outlines the main neurological illnesses arising from HIV infection. After reading the chapter the student should aim to understand the main mechanisms, clinical presentations, diagnosis and management of these illnesses.

INTRODUCTION

Neurological disorders in HIV infection are caused by three main processes: loss of cell-mediated immunity, direct HIV infection, and inflammation/autoimmunity. Adverse effects of drugs used to treat HIV and its co infections are also a cause.

Disorders related to loss in immunity are caused by opportunistic processes (OP), mostly infections and occasionally neoplasms. These occur mostly but not exclusively when the CD4 count is <200 cells/cm³. The main opportunistic infections (OI) are cryptococcosis, toxoplasmosis and tuberculosis (Chapters 6 & 7) and main opportunistic neoplasm is cerebral lymphoma. The main neurological presentations occurring as a result of those processes are meningitis, focal neurological disorder (FND) and altered level of consciousness or coma depending on the cause and CNS site involved.

Neurological disorders also arise from direct HIV infection of the nervous system and muscle. These include HIV-associated dementia (HAD), distal sensory neuropathy (DSN), vacuolar myelopathy, retinopathy and myopathy. These also occur mostly during the later stages of HIV infection when CD4 count is <100 cells/cm³.

Other neurological disorders that may occur throughout the course of HIV infection include herpes zoster, Bell’s palsy, Guillain-Barre Syndrome (GBS) and polymyositis. These by contrast occur mostly during the asymptomatic stage when immunity is still relatively intact with CD4 counts typically >200 cells/cm³. GBS and polymyositis are caused by inflammation and autoimmunity. The general characteristics of the main HIV related neurological illnesses are summarized below in Table 8.1.
<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical presentation</th>
<th>CD4 cells/cm³ ( ) = range</th>
<th>Estimated frequency in HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opportunistic processes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>meningitis</td>
<td>&lt;100</td>
<td>10-20%</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>meningitis, *FND, paraplegia</td>
<td>(0-500)</td>
<td>1-10%</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>*FND</td>
<td>&lt;100</td>
<td>5-15%</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>retinitis, radiculopathy, encephalitis</td>
<td>&lt;50</td>
<td>1-1.5%</td>
</tr>
<tr>
<td>JC virus (progressive multifocal leucoencephalopathy)</td>
<td>quadriplegia, encephalopathy</td>
<td>&lt;100</td>
<td>uncommon</td>
</tr>
<tr>
<td>Tumours</td>
<td>*FND</td>
<td>&lt;100</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Primary CNS lymphoma (PCNSL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct HIV infection</td>
<td>HIV associated dementia (HAD)</td>
<td>&lt;50</td>
<td>20-30%</td>
</tr>
<tr>
<td></td>
<td>vacuolar myelopathy</td>
<td>&lt;100</td>
<td>5-20%</td>
</tr>
<tr>
<td></td>
<td>distal sensory neuropathy (DSN)</td>
<td>&lt;200</td>
<td>20-30%</td>
</tr>
<tr>
<td></td>
<td>retinopathy</td>
<td>&lt;200</td>
<td>5-10%</td>
</tr>
<tr>
<td></td>
<td>frontal lobe release signs</td>
<td>&lt;200</td>
<td>50-70%</td>
</tr>
<tr>
<td>Inflammatory/autoimmune</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bell’s palsy</td>
<td></td>
<td>common</td>
</tr>
<tr>
<td></td>
<td>GBS</td>
<td></td>
<td>rare</td>
</tr>
<tr>
<td></td>
<td>polymyositis</td>
<td></td>
<td>rare</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>zoster</td>
<td>(2-500)</td>
<td>5-10%</td>
</tr>
<tr>
<td></td>
<td>seizures</td>
<td></td>
<td>5-10%</td>
</tr>
<tr>
<td></td>
<td>stroke</td>
<td></td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>paraplegia</td>
<td></td>
<td>1-2%</td>
</tr>
</tbody>
</table>

*FND: hemiparesis, seizures, ataxia, cranial nerve palsies, coma

The main clinical presentations are meningitis, focal neurological deficits, seizures and altered level of consciousness; these are mostly caused by opportunistic infections and frequently occur, when more than one HIV related illness is present. Disseminated TB occurs in >50% of patients with advanced HIV disease in Africa.
CLINICAL PRESENTATIONS

MENINGITIS

Meningitis is one of the common neurological presentations of HIV infection in Africa. The main causes are *C. neoformans* and *M. tuberculosis* (Chapter 6). Both cause chronic meningitis and occur predominantly in patients with CD4 counts <100/cm$^3$ although TB meningitis (TBM) may also occur at higher CD4 levels. Acute forms of meningitis also occur but these are much less common; the main acute forms are *acute bacterial (ABM)* secondary to pneumococcus and viral meningitis. Cryptococcal meningitis (CM) is now the most common type of meningitis in many parts of Africa and after TB it is the leading cause of death in AIDS in parts of Africa, accounting for up to a quarter of all HIV related deaths there (Fig. 8.1). TBM is also common and has been shown at post-mortem in West Africa to be present in >10% of AIDS patients (Fig. 8.2).

Clinically, CM and TBM may be indistinguishable from each other, although the onset of headache coupled with fever, nausea and vomiting evolving during the preceding week or two is more suggestive of CM. Definite signs of meningism are typically absent in CM in up to 75% of patients. Raised intracranial pressure with papilloedema is more common in CM but occurs in both types of meningitis.

Laboratory investigations can help to distinguish the different types of meningitis. In both types of meningitis the CSF shows an elevation in cells (mainly mononuclear) and protein but CSF can also be normal in 10-20% of patients. Distinguishing features in the CSF in CM are the presence of encapsulated yeast cells on India ink (60-80%) and cryptococcal antigen (95%) and in TBM, AFB (<5% routine ZN staining). The percentage of positive AFB in CSF in TBM can be significantly improved (60%) by increasing the volume of CSF to 20 mls, centrifuging the sample and by microscopy for 20 minutes. The presence of cryptococcal antigenaemia may be detected in the blood during the 2-3 weeks preceding the onset of CM in some patients allowing for the possibility of earlier treatment. CT of the brain is usually not helpful but may show more basal meningeal enhancement in TBM and occasionally the presence of a tuberculoma. Supporting evidence for TBM includes the presence of concurrent systemic TB, (chest radiograph 40%) or failure to improve after 1-2 weeks of treatment for CM. Treatment of either or both CM or TBM is started immediately for suspected or confirmed infection as outlined in Table 8.2.

![Pathology](Meningitis & micro abscess)   ![Histopathology](Encapsulated cryptococcal yeast cells)   ![Microscopy](Brain & CSF in cryptococcal meningitis)

**Figure 8.1** Brain & CSF in cryptococcal meningitis
FOCAL NEUROLOGICAL DISORDERS (FND)

Focal neurological disorders are among the most common neurological disorders in HIV disease. The main causes are *Toxoplasma* encephalitis (TE), tuberculoma and lymphoma. FNDs occur typically in patients with CD4 counts <100 cells/cm\(^3\) but can occur at higher CD4 counts. The main clinical presentations are hemiparesis, cranial nerve palsies and ataxia (50-60%), seizures, lethargy, confusion (40%) and coma. TE causing brain abscess is usually the most common cause of FND (Chapter 7), occurring in 5-15% of AIDS patients, although its frequency within Africa, will vary depending on the local prevalence of toxoplasmosis. Tuberculoma was reported to be the most common cause of focal brain lesions in HIV in one study area in South Africa. In TE there is usually a history of headache (60%) and fever (40-70%) over the preceding days or 1-2 weeks. Other indicators of TE include positive *Toxoplasma* serology and multiple ring-enhancing mass lesions on CT. A negative *Toxoplasma* serology makes the diagnosis of TE unlikely.

The main differential diagnosis in TE includes tuberculoma and lymphoma. However tuberculoma and primary cerebral lymphoma (PCL) are much less common and both have a slower clinical course than TE. On CT, while both tuberculoma and lymphoma can appear to be similar to TE, (Figs. 8.3-5) they may differ in their site and distribution in the brain (Chapter 7). Other less common causes of FND in HIV to be considered include stroke, occasionally syphilis and progressive multifocal encephalopathy (PML).

The choice of treatment in the management FNDs is based mostly on clinical suspicion and likely cause and the results of available investigations including a CT scan of the head (Table 8.2). Treatment is started immediately with high dose trimethoprim-sulfamethoxazole in those patients with suspected TE (Table 8.2). Clinical improvement is expected by day 3 in around 50% and by day 14 in 90% and if resources allow a follow up CT confirming improvement is helpful. TB treatment is indicated from the outset in all those suspected TB cases particularly if there is evidence of concurrent disseminated TB (e.g. AFB in sputum/typical chest radiograph findings for tuberculosis). The diagnosis of CNS TB should also be considered, if there is a failure or a poor response to treatment for TE after 7-14 days. If there is any indication from the start of either CM or ABM, then appropriate antimicrobials should be added from the start of treatment.
States of confusion, altered level of consciousness and coma are common clinical presentations particularly in the advanced stages of HIV disease in Africa. These states are mostly caused by the same opportunistic processes, usually infections that result in meningitis and FNDs but representing more advanced disease. Other causes of confusion and coma in HIV should also be considered, including metabolic disorders, organ failure particularly renal and cardiac, and side effects of ART medication, in particular efavirenz. If the cause is not known, then presumptive treatment should be started for the main OIs, CM, TE and ABM together until the precise diagnosis becomes clear (Chapters 6-7). If there is clinical evidence of TB, then TB treatment should also be added (Table 8.2).

STROKE

Stroke typically occurs during the otherwise asymptomatic phase of HIV infection when CD4 counts are 200-500 cells/cm³. An association between stroke and the persistent generalized lymphadenopathy (PGL) stage of HIV has been shown in South Africa. The accumulated lifetime prevalence of stroke in HIV disease is <1%. Stroke can be difficult to diagnose clinically, mainly because the presentation is very similar to the non vascular causes of focal brain lesions in HIV infection. The clinical diagnosis of stroke is suggested by its acute onset, non progressive course and better clinical outcome. A CT scan of the brain may be necessary to
confirm the correct diagnosis. The majority of strokes are ischaemic and occur in the anterior circulation. Mechanisms include vasculitis, coagulopathies, meningitis and emboli secondary to cardiac disease. Investigations and management are the same as for any stroke patient and should include a serology test for syphilis.

SEIZURES

New onset seizures occur in up to 5-9% of HIV infected persons at some stage throughout their long illness. Seizures occur most commonly during the later stages of HIV infection mostly as a complication of focal brain lesions secondary to opportunistic processes, in particular toxoplasmosis and tuberculoma. However, they may also occur at higher CD4 levels during the asymptomatic stage of HIV infection without any obvious underlying focal cause when their aetiology is related mostly to vasculitis. The seizures, although focal in origin are secondary generalized tonic-clonic in type. Management is directed at investigating and treating the suspected cause and suppressing the seizures (Table 8.2).

Table 8.2 Treatment based on presenting neurological disorder & likely cause

<table>
<thead>
<tr>
<th>Neurological Disorder</th>
<th>Opportunistic infection</th>
<th>Treatment Regime</th>
<th>When to start</th>
</tr>
</thead>
<tbody>
<tr>
<td>FND</td>
<td>toxoplasmosis (TE)</td>
<td>TMP-SMX#</td>
<td>immediate</td>
</tr>
<tr>
<td>Meningitis</td>
<td>cryptococcus (CM)</td>
<td>fluconazole/ amphotericin B</td>
<td>immediate</td>
</tr>
<tr>
<td>Coma</td>
<td>toxoplasmosis cryptococcus</td>
<td>TMP-SMX &amp; fluconazole/ amphotericin B</td>
<td>immediate</td>
</tr>
<tr>
<td>Meningitis or FND or Coma</td>
<td>tuberculosis*</td>
<td>isoniazid pyrazinamide rifampicin ethambutol &amp; steroids</td>
<td>immediate/or added@ 2/52**</td>
</tr>
</tbody>
</table>

# trimethoprim/sulphamethoxazole
* TB treatment is started or added if chest radiograph or other findings indicate TB
** if there is treatment failure after 2/52 for either TE or CM
PROGRESSIVE MULTIFOCAL LEUCCOEENCEPHALOPATHY (PML)

PML is caused by the reactivation of a latent virus (JC virus) which is carried by most healthy people. It appears to be uncommon in AIDS in Africa (<1%). PML occurs in advancing states of immunosuppression when the CD4 count is <50/cm³ but can occur in patients with higher CD4 counts <200 cm³. The clinical presentation is one of a devastatingly severe progressive neurological disorder occurring over weeks and months. It is characterized by motor dysfunction (hemiparesis, quadriplegia), ataxia, seizures and cognitive changes (60-70%) and aphasia, visual problems and cranial nerve palsies (30-40%). CSF examination is usually normal. Neuroimaging may show hypodense disease in the white matter brain and cerebellum (15%). The diagnosis is confirmed by brain biopsy showing the typical JC inclusions in the oligodendrocytes (Fig 8.6). There is no effective treatment for PML but all suspected patients should start ART with some showing stabilization or improvement.

Key points

- major neurological disorders occur in >20% of HIV infected patients
- neurological infections are the leading cause of death in AIDS after systemic TB
- main presentations are meningitis, focal neurological disorder and coma
- main causes are cryptococcal meningitis, toxoplasmosis & tuberculosis
- management is frequently presumptive based on likely cause

VARICELLA-ZOSTER

The reactivation of latent varicella-zoster virus infection results in herpes zoster (HZ) or shingles. Primary infection causes chicken pox. The frequency of HZ is increased in HIV infection and characteristic residual scarring from previous zoster infection is present in 5-10% of AIDS patients in Africa. HZ occurs mostly during the otherwise asymptomatic stage of HIV infection (CD4 200-500 cells/cm³). Acute HZ in HIV is recognizable clinically, by its local aggressiveness, involvement of multiple adjacent dermatomes and its tendency to occur at atypical sites including chest, face, back, neck, arms and leg (Fig. 8.7).

It also has a higher rate of complications including varicella dissemination (Fig. 8.7), myelitis, encephalitis and cranial nerve palsies. Post herpetic neuralgia is also more common.
Treatment for HZ involves both systemic and local measures. Aciclovir 800 mg/iv/po/tds for 5-7 days is recommended in the acute phase. The local application of a 1% gentian violet solution at the vesicular stage helps to prevent secondary infection and the application of a 1% phenol solution with calamine helps with local pain and itching. Analgesics may be required in addition to carbamazepine 200-400 mg/po/bid for post herpetic neuralgia. Survival in Africa in the pre ART era from onset was on average 3-4 years.

CYTOMEGALOVIRUS (CMV)

CMV is a common virus affecting most persons in Africa. Primary infection is mostly acquired during early childhood, when it is either asymptomatic or associated with a mild febrile illness with a rash. Reactivation of CMV in HIV disease typically occurs during the later stages of infection when CD4 counts are <50 cells/cm³. CMV retinitis affects around 1-1.5% of AIDS patients in Africa and although this figure may vary slightly with location, it is lower than that reported from high income countries. CMV retinopathy presents clinically with a characteristic painless haemorrhagic chorioretinitis, with loss of visual acuity first affecting one eye and later the other eye. Painless loss of vision is the main presenting complaint and blindness is inevitable unless treated. Fundoscopy appearance has been described as like that of a bush fire or pizza like and once seen is not subsequently easily missed (Fig.8.8). The main differential diagnosis is direct HIV retinopathy which is characterized by cotton wool spots and occasional haemorrhages which is seen in about 10% of patients with advanced disease (Fig. 8.9). However direct HIV retinopathy characteristically does not result in loss of vision. Other late but uncommon neurological presentations of CMV disease are encephalitis (Fig. 8.10) and infrequently a flaccid paraplegia secondary to lumbar radiculopathy.
The diagnosis of CMV in HIV is mainly clinical and treatment is with ganciclovir 5mg/kg/bd for 14 days and/or foscarnet. Thrombocytopenia is a side effect of treatment and blood counts should be checked regularly.

Key points

- HZ affects 5-10% of patients mostly during the asymptomatic stage of HIV infection
- HZ typically affects multiple adjacent dermatomes at atypical sites
- treatment is with local measures and aciclovir
- CMV infection results in characteristic retinopathy and blindness in about 1% of AIDS patients
- HIV retinopathy occurs in about 10% of AIDS patients
- CMV may infrequently (<1%) cause a lumbar sacral radiculopathy resulting in paraplegia

**IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)**

The immune reconstitution inflammatory syndrome is a complication of ART where the immune system directs an increased inflammatory response at an opportunistic infection. This results in paradoxical worsening in the patient’s condition despite adequate treatment of the OI, hence the term paradoxical IRIS. It may also unmask other hidden OIs. IRIS may occur with several of the main neurological CNS OIs. These include CM, TB, TE, CMV and PML. It can occur in 20-30% of treated CNS OIs, usually occurring within the first weeks of starting TB treatment or sometimes months, in the case of CM treatment. Concurrent CNS TB IRIS may arise as a complication in treated pulmonary TB. Management of patients suspected of
having IRIS frequently involves hospitalization and excluding other possible causes. Treatment with steroids for up to 2-3 months is frequently recommended, particularly in the case of TBM once other OIs have been excluded. The mortality rate in patients with IRIS is high, >30% in the case of treated CM and >10% in case of treated TB.

**DIRECT HIV INFECTION**

The HIV virus enters the CNS within days of primary infection and neurological disorders related to direct HIV infection have been observed occurring during all stages of the disease including early infection. Primary HIV infection of the nervous system is usually asymptomatic, but a viral meningoencephalitic illness can occur at this early stage. Also isolated self limiting aseptic meningitis can occur during the long period of asymptomatic HIV infection. The main clinically recognizable neurological disorders arising from direct HIV infection are HIV-associated neurocognitive dysfunction (HAND), HIV-associated dementia (HAD), peripheral neuropathies, vacuolar myelopathy and HIV retinopathy. These are found mostly during the later symptomatic stages of HIV disease when the CD4 counts are low.

**HIV-ASSOCIATED DEMENTIA (HAD)**

Chronic HIV infection of the brain leads to cognitive dysfunction in over 50% of patients (Fig 8.11). This is termed HIV associated neurocognitive dysfunction (HAND) and can range from mild impairment in functional performance to its severest form a frank dementia called HIV-associated dementia (HAD). HAD is reported to occur in up to a third of patients in high income countries but has virtually disappeared there because of the widespread use of ART. Varying frequencies of HAD have been reported from Africa with generally lower reported rates there (10-20%) being attributed to under diagnosis and poor survival outcomes. However, a recent study from South Africa, using appropriate investigations reported HAD in over one third of HIV patients. HAD occurs increasingly with advancing levels of immunosuppression and is most commonly seen in association with CD4 counts <100/cm³. Factors associated with increased frequency of HAD include increasing age, treated CNS OIs and a history of substance abuse.

The defining early clinical characteristic of HAND/HAD is psychomotor retardation or a slowing down of both mental and motor activities. Established HAD presents typically with abnormalities in multiple domains including cognition, memory and motor function. The dementia ranges from early features such as mild apathy, disinterest and loss of attention with a general slowing of both mental and motor functions. In the later stages, there is a frank global loss of cognitive function with immobility and incontinence in end stage disease. Frequently associated neurological findings are frontal lobe release signs (FLRSs) (Fig. 8.12), signs of vacuolar myelopathy and distal sensory neuropathy (DSN). However, many patients in Africa die of opportunistic processes, mostly infections before reaching these later stages.

The clinical diagnosis of HAD may require a confirmatory CT of the brain to demonstrate the characteristic changes including cerebral atrophy and to exclude alternative causes, in particular opportunistic processes. In HIV encephalitis MRI of the brain shows increased signal in white matter (Fig. 8.11). Histopathology includes characteristic multi-nucleated giant cells and the presence of P-24 antigen on special staining. Management of HAD involves early diagnosis, treating any reversible cause and using ART treatment. The rate of HAD in Africa has been shown to significantly decrease after 6 months of ART treatment.
Frontal lobe release signs (FLRSs)

The frequency of some primitive reflexes or FLRSs is increased in HIV disease and increases with advancing stages of HIV. The snout reflex (70%) and the palmomental reflex (50%) are found in the majority of patients with advanced HIV disease and in particular in association with HAD (90%) (Fig. 8.12). Their presence in a mainly younger age group helps to provide useful additional clinical evidence to help establish a diagnosis of HIV infection. It is however important to note that a snout or palmomental reflex may be present in association with other neurological disorders and are found occasionally in otherwise healthy persons. However, in healthy persons they are usually less pronounced and tire easily on repeated testing, this is in contrast to their presence in HIV disease when they are more pronounced and persist on repeated testing.

The **snout reflex** is elicited by pressing or tapping lightly on the patient’s closed lips. In positive cases this causes a puckering or protrusion of the lips and occasionally the chin giving the appearance of a snout. (A slight or brief contraction of the lips may not be significant).
The Palmomental reflex is elicited by stroking in a distal direction the palm of the hand at the base of the thenar eminence. In positive cases it causes a brief contraction of the ipsilateral chin muscles and occasionally the corner of the mouth.

Key points

- HAND/HAD results from direct infection of the brain with HIV virus
- early HAND/HAD is characterised by slowing down of both mental & motor function
- late HAD is characterised by impairment/loss of cognitive function & memory
- affects >1/3 of patients in advanced HIV disease in Africa
- FLRSs are found in the majority of patients with AIDS & HAND/HAD
- HAD improves significantly 6 months after the start of ART

SPINAL CORD

The spinal cord is frequently involved in HIV disease. The causes vary with the stage of HIV infection and similar to the brain, are mostly related to either opportunistic processes (OPs) or to direct infection of cord with the HIV virus itself. Spinal cord disease presents clinically as paraparesis occurring typically in an otherwise asymptomatic person. The main opportunistic infections causing paraparesis are tuberculosis, herpes zoster, herpes simplex, CMV, syphilis and occasionally co-infection with HTLV-1 in endemic areas (Chapter 10). The main opportunistic neoplasm is lymphoma.

Direct infection of the spinal cord with HIV may result in vacuolar myelopathy (VM) of the cord which gives rise to clinical signs in about a fifth of HIV patients, particularly in those with advanced HIV disease. The main signs of VM are isolated brisk reflexes in the legs with extensor plantar responses, typically without any associated loss of power. Frequently, these upper motor neurone signs overlap with distal sensory neuropathy and then the ankle reflexes are absent. In <1% of patients, mainly in those with advanced HIV disease VM results in a spastic paraparesis with immobility and incontinence. Investigations of spinal cord disease are directed at diagnosing and treating the underlying cause.
**Key points**

- main spinal cord disorder in HIV is paraparesis
- paraparesis is caused mainly by opportunistic processes and infrequently by direct HIV infection
- main causes are TB, herpes zoster & simplex, syphilis, HTLV1 & lymphoma
- direct HIV infection of cord results in vacuolar myelopathy in >20% of patients
- signs of VM are isolated brisk knee reflexes, up going toes & rarely paraparesis

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**PERIPHERAL NEUROPATHIES**

HIV frequently affects peripheral nerves. The main mechanisms are direct HIV infection, ART associated neuropathy and inflammation/autoimmunity (Chapter 11). The use of drug treatment in co-infections in HIV is also a cause of neuropathy e.g. isoniazid in TB treatment. The most common neuropathy in HIV disease is distal sensory neuropathy (DSN).

**Distal sensory neuropathy (DSN)**

DSN is the main HIV related neuropathy. It arises as a result of direct HIV infection of the dorsal root ganglion, thereby affecting peripheral nerves mostly on the sensory side. DSN affects about one quarter to one third of HIV patients, occurring mainly but not exclusively in those with advanced disease (Fig. 8.13). It can occur in association with CD4 >200/cm$^3$. The symptoms of DSN include painful, hot, burning, numbness or paraesthesia in feet and stocking distribution, developing slowly bilaterally over weeks or more commonly months. Power is usually maintained but may be decreased infrequently around the ankle joint. The ankle and very occasionally the knee reflexes are absent or decreased and areflexia may be the only finding to indicate the presence of DSN. Sensation involving light touch is mostly intact but is perceived as painful or dysesthetic or hyperaesthetic particularly on the soles of the feet and palms. Vibration and pinprick are usually normal but may be impaired distally in the feet in advanced DSN. The upper limbs are mostly unaffected but the palms may be painful to touch.

**Histopathology**

*Figure 8.13 Peripheral nerves in HIV*
The mainstay of management is to start ART as early as possible. Symptomatic relief from pain may be obtained using simple analgesics and/or amitriptyline. The use of carbamazepine or gabapentin either alone or in combination with low dose tricyclics is helpful in some patients. However, opiates may be necessary in severe cases.

**ART associated neuropathy**

DSN may arise as an adverse effect of antiretroviral therapy. In particular this occurs with the use of the nucleoside reverse transcriptase inhibitors, stavudine (d4T). Other ART drugs associated with peripheral neuropathy include didanosine (ddl), lamivudine (3TC) and zalcitibine (ddC). The incidence of DSN in HIV has been shown to increase with the use of d4T and in particular the higher dosage (40 mg) and the duration of its use. ART neuropathy may affect up to 20% of patients who have been on dT4 for 6 months or more and increases the overall rate of DSN in HIV to >40%. The symptoms and signs are very similar to HIV related DSN, although sensory signs may be more marked in ART associated neuropathy. However, the two cannot easily be distinguished from each other clinically and hence they may both be termed DSN.

In Sub-Saharan Africa, DSN remains one of the main limiting side effects of first line ARTs. Management involves either reducing the standard dose of d4T from 40 to 30 mg (as recommended by WHO) or stopping and replacing d4T or the likely causal ART drug. Two thirds of patients may improve if switched to a non d4T regime. Many countries in Africa are now moving away from the use of stavudine based ART in order to reduce the problem of ART associated DSN. Other risk factors increasing the risk of DSN include a history of prior or active antituberculous therapy, older age, alcohol use and malnutrition. Care should be taken to ensure that pyridoxine 20 mg/po/daily has been prescribed in those patients taking isoniazid, and thiamine 100 mg/po/daily should be given in suspected cases of B-1 vitamin deficiency. Symptomatic management is otherwise the same as in HIV disease.

**Key points**

- HIV affects peripheral nerves by direct infection, ARTs and autoimmunity
- DSN secondary to direct HIV occurs in about 1/4 of patients & responds well to ART
- ART usage for >6 months with d4T, is associated with development of DSN
- majority of ART related neuropathies respond to stopping the offending drug
- analgesics may be necessary in both types of neuropathies

**INFLAMMATION/AUTOIMMUNE**

Bell’s palsy, Guillain-Barre syndrome (GBS) and polymyositis occur mostly during previously asymptomatic HIV disease. With the exception of Bell’s palsy these are uncommon illnesses but frequently prove to be the first indication of underlying HIV infection.

**BELL’S PALSY**

Bell’s palsy is the most frequent presentation of mononeuritis in HIV in Africa. On screening for HIV in some high endemic areas in Africa, over 50% of patients presenting with idiopathic Bell’s palsy early on in the epidemic tested positive for HIV. Therefore, an isolated Bell’s palsy is now an indication for HIV screening. Bell’s palsy typically occurs during otherwise
asymptomatic HIV infection. A unilateral facial weakness develops over 24 hours and the clinical course is similar to that in non HIV associated Bell’s palsy. However facial weakness may be bilateral in HIV infection (Fig. 8.14). The treatment and management is the same as for non HIV related Bells palsy (Chapter 12). Other cranial and mononeuropathies in HIV infection occur either individually or in combination (mononeuritis multiplex); but these are generally much less common than Bell’s palsy.

**GUILLAIN-BARRE SYNDROME (GBS)**

GBS or acute inflammatory demyelinating polyneuropathy (AIDP) is an uncommon form of autoimmune acute polyneuropathy and when it occurs in HIV, its onset is associated with a relatively intact immunity or an elevated CD4 count. Clinically, it is indistinguishable from classical or the non HIV associated GBS, apart from the increased number of lymphocytes found in the CSF in HIV infection. The clinical course and outcome are also similar (Chapter 11). Rarely, a more chronic form of polyneuritis occurs, this is called chronic inflammatory demyelinating polyneuropathy (CIDP).

**MYOPATHY**

There are two main types of muscle disease in HIV disease; myopathy and polymyositis (Fig 8.15). The most common type is myopathy which is characterised by painless, severe, generalised muscle wasting and weakness which occurs in association with systemic illness in advanced HIV infection. The severe wasting, myopathy (and diarrhoea) seen first in AIDS in East Africa gave rise to the name “Slim Disease”. The second type of muscle disease, polymyositis is uncommon and occurs at an earlier stage, typically asymptomatic HIV infection. It is characterized by a painful marked proximal muscle weakness affecting the limbs and trunk. It is considered to be an autoimmune inflammatory disorder and responds well to steroids, although TB needs to be excluded before starting steroid treatment. Myopathies may also occur as a side effect of some ART medications.
**Key points**

- Bell’s palsy, Guillain-Barre syndrome & polymyositis occur during asymptomatic HIV
- Bell’s palsy is the most frequent mononeuropathy in HIV disease
- GBS is the same as in non HIV apart from increased lymphocytes in CSF
- myopathy is common in the later stages of HIV infection
- polymyositis is uncommon but responds well to steroids

**References**


