Neurological and neurosurgical manifestations of human immunodeficiency virus (HIV) infection in Africa

Adelola Adeloye MS FRCS FRCP
Professor
Department of Surgery, College of Medicine
Blantyre, Malawi

Introduction
AIDS was first recognised in the United States of America in the late 1970s among homosexual men suffering from atypical pneumonia, herpes simplex and Kaposi's sarcoma which were associated with an acquired immunodeficiency state. Their disease was christened Acquired Immunodeficiency Syndrome with the now universally dreaded acronym of AIDS. Within three years of the discovery French and American scientists isolated a retrovirus, the human immunodeficiency virus type 1 (HIV-1) as the cause of AIDS.

AIDS in Africans was encountered about the middle of the 1970s and presented as cases of atypical pneumonia among affluent Africans from sub-Saharan countries who sought consultation in European clinics. The disease is now worldwide and is a serious health problem, particularly in Africa. AIDS is the leading cause of death among adults in Abidjan, Cote d'Ivoire and in Kinshasa and among inpatients in Ugandan hospitals. Ninety per cent of deaths among child-bearing women in Kigali, Rwanda are due to HIV infection. In 1993, when adult HIV infections in the world numbered 13 million, more than 8 million occurred in sub-Saharan African countries.

The first AIDS epidemic occurred between 1981 and 1985 when the disease manifested as either opportunistic infections or as unusual neoplasms such as Kaposi's sarcoma and lymphomas of the nervous system. During that period, less than 10 cases per annum were diagnosed in South Africa. Since then, the number of AIDS cases in that part of the world rose. It was at the end of that epidemic, in 1985 that it was also found that the central nervous system (CNS) was more susceptible to AIDS than were other parts of the body. It is now known that about 50% of patients with AIDS manifest disease of the nervous system before they die and that 75% of autopsy examinations of victims of AIDS reveal involvement of the nervous system through direct invasion, opportunistic infections or unusual neoplasms.

This paper briefly reviews the neurological and neurosurgical manifestations of AIDS as documented in Africa at present. It is based on papers published or presented on the subject in Africa and among Africans and anecdotal experiences from various parts of the continent.

Neurological manifestations
The spectrum of neurological diseases reported in AIDS patients in Africa, like elsewhere in the world, is quite wide, ranging from the primary effects of HIV on the nervous system, to opportunistic infections and, rarely, psychiatric disorders. These neurological complications may occur before there is clinical evidence of immunosuppression and the HIV infection is revealed.

Primary effects of HIV
HEADACHE
Case report
A Malawian 46-year-old male senior police officer presented with generalised headache described as heaviness of the head. It was continuous, severe and associated with episodes of crying with pain. He was fully conscious on admission to the Queen Elizabeth Central Hospital, Blantyre. He was rest-
less with pain but frequent changes of posture did not relieve his headache. There was no papilloedema. Neurologically there were no deficits. Blood pressure was normal. He was ELISA positive.

He was treated with large frequent doses of paracetamol-codeine preparations; reassurance; and amitriptyline 75mg at night. There was no relief, hence indomethacin was used instead of paracetamol; finally pethidine was administered. Lumbar puncture produced clear cerebrospinal fluid (CSF) under normal to moderate pressure. Prednisolone was added to his treatment regime. His conscious level deteriorated and he died in hospital four days after admission.

Comment
In managing-HIV related headache in Africa it is important to exclude tropical diseases such as malaria, syphilis and trypanosomiasis and local disorders which can also cause headaches such as sinusitis, migraine and dental abscess. The clinical assessment should take into consideration diseases like aseptic meningitis and intracranial space occupying lesions. With more imaging techniques becoming available on the continent, management of HIV related headaches should include investigating the patient with CT scan and MRI.

DEMENTIA COMPLEX
This is characterised by a wide spectrum of pathological disorders and clinical manifestations classified from normal (stage 0) to advanced (stage 4). The early features include personality changes with apathy and flat emotion. Next, impaired memory and concentration supervene. In the late stage the patient manifests ataxia with brisk tendon reflexes and Babinski response. In the late stage the patient manifests ataxia with brisk tendon reflexes and Babinski response. In Malawi, two forms of HIV associated dementia complex are recognized in the adult: the acute and chronic varieties. The acute type is characterised by confusion and the chronic one by behavioral disorders of apathy, personality changes and emotional flatness. The management employed consists in attempting to rule out treatable possibilities like malaria, syphilis and trypanosomiasis. The antiretroviral therapy (zidovudine) is not available in many parts of Africa.

In the developing regions of the world, including Africa, HIV infected children show delay in psychomotor development or the loss of already acquired physical and developmental abilities. Cognitive defects of speech and memory also occur. CT scan shows brain atrophy and ventricular dilatation in these children.

PERIPHERAL NERVOUS SYSTEM INVOLVEMENT
It is estimated that about 50% of AIDS patients will manifest evidence of peripheral nerve disease in the course of their illness. The various types encountered in Africa are herpes zoster; sensory painful peripheral neuropathy; isoniazid-related neuropathy, Guillain-Barre syndrome and cranial nerve palsy.

Herpes zoster has been found to be a clinical predictor of HIV infection in African patients. In Kinshasa, in Kigali and in Bangui, over 90% of patients with herpes zoster were found to be HIV positive. The clinical features were similar to those found in HIV-negative Africans except that recurrences were commoner in HIV patients. Whereas herpes zoster is traditionally found in patients over 60 years of age and those suffering from Hodgkin's disease, HIV-associated herpes zoster in Central Africa is a disease of young adults.

Axonal sensory painful peripheral neuropathy is estimated to affect about 30% of AIDS patients in the late stage of their disease. It presents with symmetrical intolerable painful paraesthesia and numbness in both feet which ascends to the knees. Muscle weakness is also associated and foot drop may occur.

Adam from Nairobi, reported the good response of this disease to oral prednisolone 40mg daily. He reported a series of five women and two men seen in Nairobi, Kenya between 1988 and 1992, aged between 45 and 57 years. At presentation, three were known to be victims of AIDS and four were asymptomatic for HIV infection. One was an elderly male who was well except for severe burning sensation in his lower limbs and a painful band-like pain in the epigastrium referred to his lumbar spine. Investigations in general surgery and orthopaedic clinics and various endoscopic and radiological examinations were normal. He was found to be ELISA positive at the Neurology clinic and his painful leg was cured within one week of prednisolone at a daily dose of 40mg. He responded to the same treatment when his pain recurred a year later.
All the seven patients in the Nairobi study had axonal diffuse sensory neuropathy during nerve conduction tests. Most of them had treatment with tricyclic antidepressants (amytriptyline), anticonvulsants (phenytoin and carbamazepine), fluphenazine, alone or in various combinations without relief before they were placed on prednisolone. Non-steroidal anti-inflammatory drugs did not relieve their pain. The relief of pain from steroids was long lasting even after cessation of medication.

**Isoniazid-related peripheral neuropathy** has been seen in Malawi and attention is directed to the prevention or amelioration of the burning sensation that occurs in the feet. Since it is known that, when a TB patient starts isoniazid, his HIV associated neuropathy may worsen, all TB patients should receive pyridoxine 10mg daily as prophylaxis against isoniazid peripheral neuropathy. If resources are not buoyant to allow this, the pyridoxine prophylaxis should be reserved for the HIV-positive patients and TB patients who drink alcohol.

**Acute neuropathy of the Guillain Barre type** is also encountered in HIV-positive African patients. In Malawi, it occurs in young adults and rarely in children. It may occur at any stage of the disease although commonly it is seen at the early asymptomatic phase of HIV infection. The clinical features are similar to those of non-HIV infected subjects.

**Cranial neuropathy**, single or multiple cranial nerve palsy may occur during asymptomatic or early symptomatic HIV infection. In a series of apparently idiopathic acute peripheral facial palsy in Africans reported from Kenya, eight of the 32 patients were HIV positive; four of the eight had generalized lymphadenopathy; one had herpes zoster and another had generalized pruritic rash. Two were asymptomatic. The incidence of HIV seropositivity in patients with acute facial palsy is higher in other African countries than the 25% reported from Kenya.

**A chronic inflammatory demyelinating neuropathy** with episodes of clinical recurrences is also seen in the early stages of HIV infection. There is no known documentation of this variety in the African.

Between 10% and 25% of patients with AIDS suffer from **myelopathy** due to direct invasion of the thoracic portion of the spinal cord by HIV. The clinical manifestations are characteristic enough for a presumptive diagnosis to be made in the African. These consist of a short history of progressive difficulty in walking and the finding on physical examination of spastic paraparesis and ataxia, impaired vibration and joint position sense and the loss of sphincter control. Wadia of Bombay warned that peripheral neuropathy may overlap the myelopathy to such an extent that the increased tendon reflexes of the spastic paraparesis disappears but the Babinski response remains.

In Malawi, the last six cases of HIV myelopathy were aged between 25 and 45 years. There were four females and two males. The CSF was clear in all cases and myelography was normal. In South Africa, during a community-based seroprevalence survey in Kwazulu Natal 90 cases of HIV myelopathy presenting with spastic paraparesis were seen in the neurology unit of Wentworth Hospital up to December 1991. Harries has listed the various causes of spinal cord disease that must be differentiated from HIV myelopathy. These include TB spine, schistosomiasis of the cord, cervical spondylosis, prolapsed disc, epidural abscess and cord tumours like neurofibroma and meningioma.

There is no specific treatment for HIV myelopathy. Its similarity to subacute combined cord degeneration has lead some to treat cases with Vitamin B12 injections. Physiotherapy and antispasticity drugs are used to relieve the spastic limbs. Baclofen is not always available in parts of Africa, necessitating the use of diazepam. The usual measures are taken for treating neurogenic bladder.

**Cerebrovascular disease**
AIDS patients appear to have an increased risk of cerebral infarction and transient ischaemic neurological deficits. These diseases may be the initial presentation of AIDS; they often signify the presence of treatable CNS infections such as opportunistic cerebral lesions, cryptococcal meningitis or neurosyphilis. Stroke in the young African, aged under 40 years, should evoke the suspicion of HIV infection.
Meningitis
This is commoner in HIV infected patients than in the general population, the various forms described in the literature being tuberculous meningitis (TBM); cryptococcal meningitis; acute bacterial; viral; syphilitic and the lymphomatous types. Non-Hodgkin's lymphoma is about 60 times more common in AIDS patients than in the general population, the various forms described with HIV associated meningitis admitted to the AIDS defining diseases in more than a quarter of cases. The authors predicted a rise in the incidence of TBM and cryptococcal meningitis in Africa.

The common forms of meningitis reported from HIV patients in Africa are the tuberculous, cryptococcal, acute bacterial and the viral varieties. In a report by Bergemann and Karstaed of 284 adult patients with HIV associated meningitis admitted to the Baragwanath Hospital in Soweto, Johannesburg, South Africa, the distribution of the disease was: TBM 25.4%, acute bacterial meningitis 22.5%; acute viral meningitis 14.1% and cryptococcal meningitis 13%. Strepococcus pneumoniae was the commonest organism found in acute bacterial meningitis. TBM and cryptococcal meningitis were AIDS defining diseases in more than a quarter of cases. The authors predicted a rise in the incidence of TBM and cryptococcal meningitis in Africa.

Cryptococcal meningitis
This is associated with the opportunistic infective agent Cryptococcus neoformans, a yeast first described in 1905 and which is universally present but seems more common in Africa than elsewhere in the world. The incidence of cryptococcal infection in AIDS patients in the UK is 3.6%; in the USA from 2% to 9% and in Africa, as high as 33%.

Cryptococcal meningitis is the third most common neurological presentation of AIDS after HIV invasion and toxoplasmosis. It is most common in sub-Saharan Africa, occurring in from 6% to 12% of AIDS patients, the increased incidence being due to the more common occurrence of the yeast or an increased genetic susceptibility of the African to cryptococcal infection.

Maher and Mwandumba reported a series of 31 cases from Malawi out of 30,000 medical admissions in an 18-month period. Headache, neck stiffness, fever and altered consciousness were the presenting features. In Zaire, serum cryptococcal antigen testing helped to predict a group of apparently healthy patients who are likely to develop cryptococcal meningitis but this was not so in the UK. The test was 95% to 100% positive for diagnosis in Central Africa where the specific drug treatment used was amphotericin B and fluconazole. The latter drug is not always available in hospitals in Africa; and not more than 10% of patients can afford to buy it. Under such circumstances treatment is symptomatic, consisting of the use of analgesia and sedation.

The prognosis of cryptococcal meningitis in Africa is poor, as shown by the report from Malawi. Without using the specific anti-cryptococcal chemotherapy, the mean survival time from time of diagnosis was four days. With treatment, it was some months. The problem of this meningitis is likely to increase in Africa as HIV infection becomes more widespread.

Neurosurgical aspects
Levy and Berger of the Department of Neurosurgery in Chicago reported that HIV infection can manifest as intracranial sepsis, cerebral...
mass lesions or as vascular disorders. The same experience is shared by neuroscientists at the King Edward Hospital, Kwazulu Natal, South Africa.

Intracranial sepsis and HIV
The presentation of intracranial suppurative disease is different in HIV positive patients. Multiple brain abscesses and suppuration caused by multiple, mixed organisms are common in HIV-positive patients but are unusual in HIV-negative patients. The rest of the differences noted are shown in table I.

| TABLE 1 Brain abscess: experience in a South African hospital (Bhigjee 1996) |
|-----------------|-----------------|
| **HIV NEGATIVE** | **HIV POSITIVE** |
| Multiple abscesses | Unusual | Common |
| Multiple organisms | Unusual | Common |
| Location | Normal | Unusual |
| Number of procedures | One | 1.7/patient |
| Primary source | Common ones | Rare ones |
| Mortality | Low | High (over 55%) |

Cerebral mass lesions
Ten per cent of HIV-positive patients in Durban had mass lesions comprising toxoplasmosis, lymphoma and PML.

TOXOPLASMOSIS
Toxoplasma encephalitis, caused by the protozoan *Toxoplasma gondii* is the most treatable CNS complication of AIDS. It results from reactivation of latent disease and occurs in the advanced stage of HIV infection when the CD4 count is below 100. It is seen in about 3% to 10% of AIDS patients in the USA but here, in Africa, where seroprevalence of toxoplasma is high, it has been predicted the incidence maybe as high as 50%26. Whereas only 17% of AIDS patients from Africa treated in Europe some years ago had toxoplasma encephalitis1, a recent African study reported a prevalence of 53%27.

There are three main features of the disease. Generalised neurological symptoms develop over a few days to weeks characterised by severe headaches and altered mental status. Secondly, subacute encephalitis may develop. Thirdly, there are focal findings which result from involvement of the frontal and parietal lobes and the basal ganglia.

Involvement of the basal ganglia causes movement disorders of cerebellar ataxia and chorea. The latter, in AIDS patients, is almost always pathognomonic of toxoplasma encephalitis27.

Diagnosis of toxoplasma encephalitis is definitively and best made by stereotaxic brain biopsy. Lack of facilities for the procedure in many places in Africa or reluctance on the part of the neurosurgeon to do the biopsy, have led to the use of therapeutic diagnostic trial. The practice in Africa is to begin treatment on a presumptive diagnosis. In Durban, oral clindamycin and pyrimethamine therapy provide rapid clinical and radiographic improvement with 72% of patients responding on day seven of treatment. Steroids are to be avoided.

CT scan and MRI show multiple contrast enhancing lesions. These are not diagnostic of toxoplasma as they may mimic tuberculoma or lymphoma. Serum antibody test for toxoplasma is often positive.

Lymphoma
Primary lymphoma of the CNS is seen in about 3% of AIDS patients. Half of the cases present clinically and the other half are picked up at autopsy28. This incidence is similar to the experience in Africa29.

Progressive multifocal leukoencephalopathy (PML)
PML, due to reactivation of the JC virus, is seen in about 5% of patients. The clinical features depend on the site of demyelination.

Unrelated neurosurgical disease
HIV seropositivity may occur coincidentally with any neurosurgical disorder, notably in those with neurotrauma and with intracranial vascular anomaly. HIV positivity worsens the prognosis of these neurosurgical diseases.

Discussion
The incidence of CNS involvement in patients with HIV infection in Africa is not known for sure due to the paucity of reports on the subject. Given the widespread nature of HIV infection in Africa, it may be higher than the 79% and 85% incidence recently reported from India29 and France30 respectively. Like elsewhere in the world29, cryptococcal meningitis and toxoplasma encephalitis are invariably fatal in Africa. Lack of financial resources
to obtain appropriate but expensive chemotherapy contributes to the high mortality. The early deaths from opportunistic infection may explain the relative infrequency of CNS lymphomas in AIDS patients in Africa.

While the pathogenesis of the primary effects of HIV on the nervous system is unclear, experiences from Africa have established some valid information about HIV invasion of the peripheral nervous system. Thus reports from Central Africa have shown herpes zoster to be a clinical predictor of HIV infection and, in Kenya, prednisolone has been shown to be consistently superior to tricyclic antidepressants, anticonvulsants and non-steroidal anti-inflammatory drugs in the relief of axonal sensory peripheral neuropathy.

References
20 Murphy SA, Denning DW. Cryptococcal meningoencephalitis in AIDS. Hospital Update 1994; 151-156.