NEUROLOGICAL MANIFESTATIONS OF HIV-INFECTION AND AIDS

It has clearly been established that HIV in developed countries has neurotropic properties and that the nervous system may be invaded at the very onset of HIV infection.

Neurological complications are common in the HIV disease, occurring in 10% of AIDS patients as the initial manifestation and in as many as 70% of the HIV-infected subjects at some stage of their disease; it is found in up to 90% of the autopsy cases. Neurological disorders may result either from the direct or indirect effects of HIV itself or from opportunistic infections or malignancies arising in the central nervous system as a consequence of HIV-induced immunodeficiency (table 1).

Table 1: Neurological complications of HIV and AIDS infection

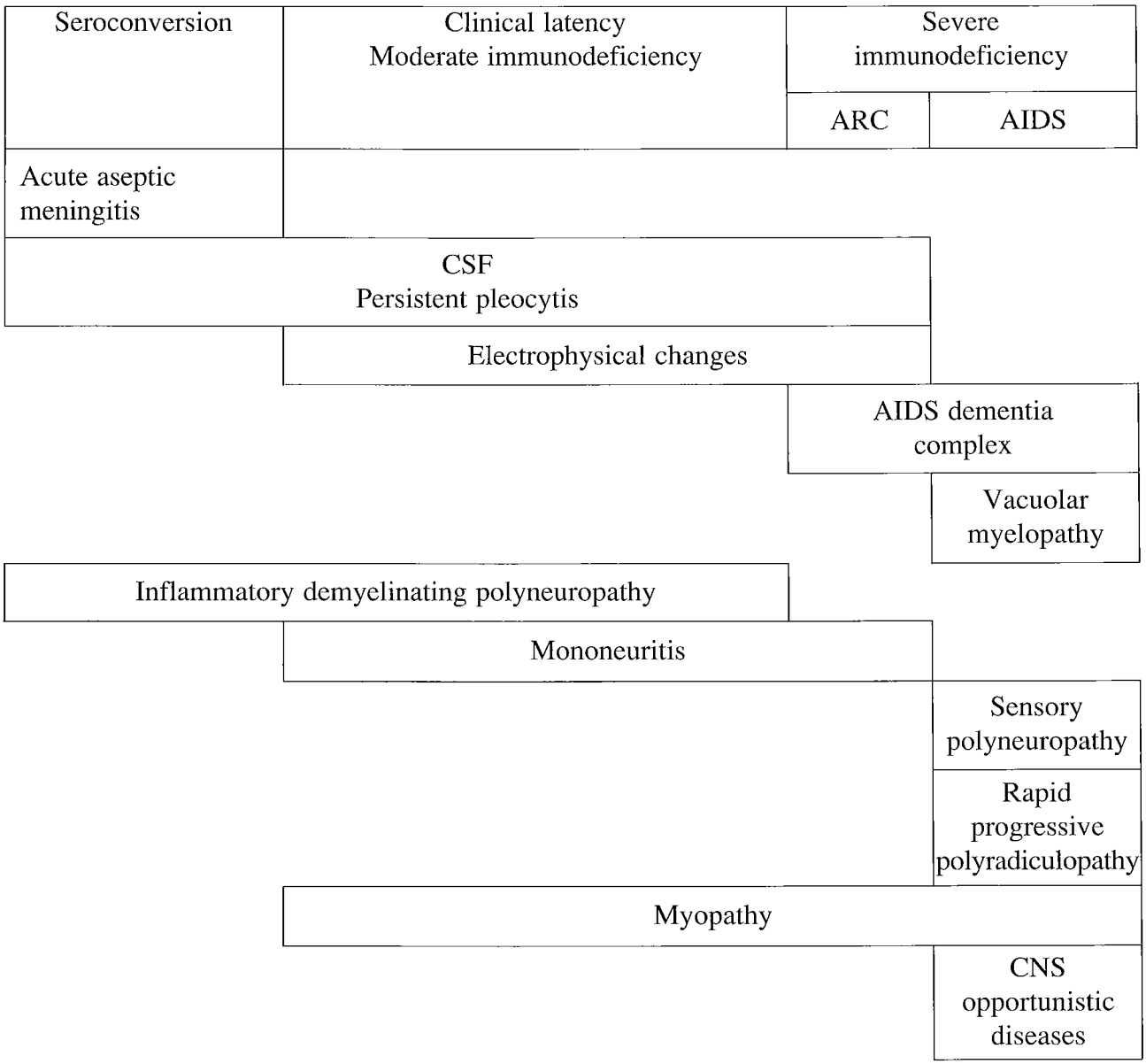
1. *HIV-related or associated*
Acute aseptic meningitis Silent chronic meningitis AIDS dementia complex Vascular myelopathy Peripheral neuropathies Myopathy
2. *Immunodeficiency-related*
Opportunistic infections: Cerebral toxoplasmosis Cryptococcal meningo-encephalitis Cytomegalovirus retinitis/encephalitis Progressive multifocal leuco-encephalopathy Tuberculous meningitis Other infections: varicella zoster virus herpes simplex virus listeriosis nocardiosis syphilis Opportunistic malignancies: Primary CNS lymphoma Metastatic systemic lymphoma

HIV-related neurological disease may affect any part of the nervous system and includes pathologic processes such as meningitis, encephalitis, myelopathy, polyneuropathy, myopathy.

However, the *pathogenic mechanisms* by which HIV produces tissue lesions remain uncertain. Evidence for a direct infection of the neurones is lacking, but macrophages and monocytes of the brain are predominantly infected by HIV and could act as the source of infection for other brain cells — the Trojan's horse theory (Ho et al., 1987). HIV could cause neuronal damage indirectly through the release of cytokines (tumour necrosis factor alpha), enzymes and free radicals or HIV proteins from infected cells. Synergy between HIV and opportunistic viruses (such as herpes simplex, CMV), alteration of the permeability of the blood-brain barrier, modification of antigenic determinants of the nervous system leading to an auto-immune response, are other hypothetic pathogenic mechanisms.

The nature of neurological disorders varies during the course of HIV infection and is strongly dependent of the degree of immunodeficiency (Table 2).

Table 2: Neurological complications according to the stages of HIV disease



(Adapted from Howlett et al., 1989)

Few studies have generated from Africa. However, *Howlett* et al. (1989) have reported their findings on 200 AIDS patients from northern Tanzania. Focal neurological disorders including cranial neuropathies, hemiparesis and paraparesis were present in 10.5% of the patients and other neurological signs were detected in 76% of them. In Bangui, the Central African Republic, neurological manifestations were found in 12% of 93 AIDS patients (Belec et al., 1989) while in Kinshasa, Zaire, cognitive impairment was reported in as many as 33% of 43 HIV-seropositive patients at stage 4 of the HIV disease, behavioural changes in 62%, motor system dysfunction in 58% and frontal lobe release signs (polmomental reflex) in 38% of the cases (Perriëns et al. in 1992).

1. HIV-related neurological disorders

Recently, neuro-electrophysiological investigations have shown altered electrophysiological tests in 67% of HIV-seropositive subjects compared with 10% in carefully matched HIV-seronegative individuals.

1.1. *Meningitis*

Acute aseptic meningitis with headache, meningeal signs, sometimes transient encephalopathy and cranial neuropathies may be one of the manifestations of the mononucleosis-like syndrome characterizing primary HIV infection and coinciding with HIV seroconversion. Rarely the condition may precede HIV seroconversion (Hollander, 1988; Koralnik et al., 1990; Colon, 1989). It is seen in no more than 5% of HIV-infected individuals (Evans et al., 1991). However, CSF abnormalities without clinical expression — a silent form of meningitis — have been detected in up to 30% of otherwise healthy HIV-infected subjects.

1.2. *Dementia and brain damage*

AIDS dementia complex, also called subacute encephalitis, is one of the most important neurological complications of HIV disease and has been recognized in approximately two-thirds of the patients at the advanced stage of AIDS. Cognitive impairment (memory loss, poor concentration, mental slowing low), behavioural changes (apathy, depression, agitation) and motor dysfunction (unsteady gait, lower limb weakness, poor coordination, tremor) are the salient features of this subcortical dementia. At the final stage patients suffer from severe dementia, become mute, incontinent, paraplegic, develop seizures and tremors (Navia et al., 1987). Average survival from the first months of the disease to death does not exceed 6 months. In the Netherlands a striking decrease of the number of AIDS patients with AIDS dementia complex has been registered following the use of zidovudine (Schmitt et al., 1988).

Brain diagnostic picture tests techniques reveal cortical atrophy and widening of the ventricles. Although several CSF abnormalities have been reported in patients with AIDS dementia complex (pleocytosis, increased protein level, presence of specific HIV immunoglobulins and p 24 antigen), the diagnosis of the disease relies mainly on clinical symptoms and signs and exclusion of other diseases.

Post-mortem studies of patients dying with AIDS dementia complex reveal lesions consisting in macrophage and microglial cell infiltration of the perivascular space and in reactive astrocytosis located in the white matter of the frontal and occipital lobes, the cerebellum, the pons and occasionally the basal ganglia.

1.3. *Myelopathy*

Vacuolar myelopathy is depicted as a progressive spastic paraparesis with sensory ataxia and sphincter disorder; it is often associated with AIDS dementia complex and progresses in parallel with the brain involvement. It affects as many as 20% of the patients with AIDS. Histopathological examination of the spinal cord reveals vacuolation in the lateral and posterior columns of the thoracic spinal cord (Gray and Gherardi, 1990).

1.4. *Peripheral neuropathy*

Several types of peripheral nerve disorders have been found in association with HIV infection.

- The most common is the distal symmetrical painful sensory polyneuropathy, characterized by dysaesthesia, stocking-glove sensory loss, which affects 30% of the patients with overt AIDS. To produce these complications, HIV itself, nutritional or toxic factors may be involved.
- Inflammatory demyelinating polyneuropathy (Koralnik et al., 1990) appears to be an immune-mediated disorder occurring in an early stage of HIV infection; it manifests itself clinically as a profound distal motor weakness which resembles Guillain-Barré syndrome in its acute form. Corticosteroid therapy and plasmapheresis have proved successful.
- Mononeuritis consists in a necrotic vasculitis induced by circulating immune complexes, involving one or several peripheral nerves and is seen in patients at various stages of the HIV infection.

Peripheral facial paralysis associated with HIV infection has been described in Africa (Belec et al., 1989) and may correspond to one of those polyneuropathies or be related to herpes zoster.

- Rapid progessive polyradiculopathy presents as a progressive flaccid paraplegia with bowel and bladder dysfunction and affects some AIDS patients. Inflammation and necrosis of the dorsal roots' ganglia are the pathological substrate of this neuropathy. CMV has been implicated in some cases.

1.5. *Myopathy*

In addition to the muscle weakness associated with the wasting syndrome of AIDS, HIV-infected patients may also develop a distinct myopathy at any stage of HIV infection and characterized by a progressive proximal muscle weakness. An auto-immune phenomenon has been suggested as underlying the disease.

1.6. HIV may also be responsible for many kinds of *vascular cerebral haemorrhage* in the subarachnoid space, or in the intracerebral tissue. This happens through two main mechanisms: auto-immune thrombocytopenia, or vasculitis of several types, occurring specially in children (7 to 19% of children with AIDS suffer from cerebrovascular impairment due to vasculitis).

2. **Opportunistic diseases and malignancies**

Some of the opportunistic infections and malignancies of the AIDS-defining diseases' spectrum are located in the CNS and reflect the immunosuppression related to the HIV-induced depletion of CD4 cells. Rare in children, who are preferably infected by common germs, those opportunistic infections can affect meninges, cerebral parenchyma, the spinal cord or the peripheric nerves.

2.1. *Toxoplasmosis*

In Europe the most common opportunistic infection involving the CNS is toxoplasmosis, affecting between 20 and 40% of all the AIDS patients; this is different from the 8% frequency registered among the North American AIDS patients. This discrepancy reflects the geographic variations in the endemicity of the parasitosis.

The parasites produce necrotic and inflammatory multifocal abscesses, scattered in the cerebral hemisphere with a predilection for the basal ganglia. Diagnostic picture tests techniques clearly demonstrate multiple thrombo-necrotic lesions.

The disease is characterized clinically by fever, altered mentation, focal neurological impairment, developed over a few days.

Among 137 African AIDS patients diagnosed in Belgium, toxoplasmosis was documented in 17.5% cases which is significantly lower than 33% found in 93 European AIDS patients (Taelman et al., 1989; Lesbordes et al., 1986; Rogerie et al., 1987; Testa et al., 1988; Carme et al., 1988; Bissagnene et al., 1989; Lohoue et al., 1992).

In Africa, because of the non-available diagnostic picture tests techniques the diagnosis of cerebral toxoplasmosis rests entirely on clinical grounds and therapeutic response. Autopsy studies in Abidjan have revealed that this complication is a frequent cause of death in HIV-infected Africans. Its prevalence in Rwanda (Bogaerts et al., 1990; Taelman et al., 1991), Burundi (Laroche et al., 1990) and Zaire (Lamey and Melameka, 1982, Kapend and Odio, 1983) is particulary high (Batungwanayo et al., 1993; Taelman et al., 1988).

An empiric treatment is usually started and a definite diagnosis ultimately relies on the favourable response to pyrimethamine (50mg/day) and sulphadiazine (4-6g/day). Prompt specific treatment leads to rapid improvement for 90% of the patients. Side-effects consist in drug hypersensitivity and haematological toxicity; they occur in 40% of the patients.

Folinic acid 10 mg per day is strongly recommended to minimize the haematological side-effects. To prevent the relapses which are frequent, a maintenance therapy with lower regimens of the same drugs is required.

Primary lymphoma of the brain should be considered if the therapy fails to provide clinical improvement.

2.2. *Cryptococcosis*

The most common cerebral opportunistic infection diagnosed in sub-Saharan Africa is meningoencephalitic cryptococcosis. Its occurrence among African AIDS patients has been estimated between 12 and 20% contrasting with the 7 to 9% found in European and American patients. Environmental factors could play a role in the geographical variations in the prevalence of the yeast-like fungus (Swinne et al., 1991).

The disease typically appears as a subacute meningitis with severe headaches, meningismus, fever, altered mentation, nausea and vomiting; but symptoms may be mild and limited at headaches or confusion. Occasionally focal deficits are seen.

The single most useful diagnostic test is the lumbar puncture. In Kigali (Rwanda), it is carried out in each patient with unexplained neurological symptoms or

signs, particulary headaches. This allows a prompt diagnosis of the majority of the patients with this condition (Swinne, 1992).

CSF glucose and protein levels as well as white cell counts may be normal or moderately altered. A definite diagnosis is established by demonstration of the fungus by Indian ink staining of CSF which is positive in up to 85% of the patients. Various culture media may be used to detect the fungi (specially Sabouraud medium, Desmet et al., 1989). The cryptococcal antigen test is easy to apply for recognizing the disease, but it is more expensive compared to other methods.

Amphotericin B, fluconazole and itraconazole are all an effective treatment of the condition. Recurrences are common and can be prevented for some time by a suppressive treatment with one of the drugs.

2.3. *Opportunistic viral infections*

2.3.1. *Progressive multifocal leucoencephalopathy* affects 2 to 3% of AIDS patients. It is a subacute demyelinating disease involving the white matter of the hemispheres, particularly the occipital lobe, and is caused by a papovavirus, the JC virus. Patients with the disease are febrile and show a cognitive impairment and a sequence of variable focal deficits such as aphasia, blindness, hemiparesis or ataxia. Diagnostic picture tests studies show multiple hypodense lesions within the white matter. Biopsy examination is necessary to differentiate definitely the disorder from other cerebral opportunistic diseases. No treatment is satisfactory.

2.3.2. *Cytomegalovirus retinitis* is a rather common complication seen in profound immunodeficient patients, causing visual loss in 20% of patients with AIDS in developed countries and in Africa. *Cytomegalovirus encephalitis* is clinically similar to AIDS dementia complex and requires biopsy studies to be finally diagnosed. Ganciclovir and foscarnet have been used with success in active cytomegalovirus disease.

2.3.3. *Varicella-zoster virus* (VZV) infection represents the reactivation of latent varicella in immunodepressive patients and is present in a very severe form in HIV patients in Africa: it affects numerous dermatomes with particular aggressivity for thoracic and cranial nerves, specially ophthalmic and trigeminal nerve, but also vertebral dermatomes (see the chapter Dermatology, p. 872). This painful neuritis may remain active after the resolution of the skin lesions. Seldom VZV infection may involve the brain (encephalitis) or give hemiplegia, myelitis, radiculitis.

The treatment involves analgesics, even opiates, and the administration of intravenous acyclovir, which is unfortunately very expensive.

The main new aspect of VZV infection is its dramatic increase in most urban centres in East and Central Africa. As it is one of the earliest manifestation of AIDS, it appears in patients who feel healthy. More than 90% of patients going into hospitals with HZ are now proven to be HIV positive (Katabira, 1989).

2.3.4. *Herpes Simplex virus* type 1 infection may lead to a haemorrhagic encephalitis, while type 2 may lead to a self-limiting meningitis. Both types of these may result in acute and subacute encephalitis. This infection is very difficult to distinguish from other viral encephalitis in the absence of PCR (Polymerase Chain-reaction).

2.4. *Mycobacterial infection*

Although tuberculosis associated with HIV infection commonly occurs in Africa, tuberculous meningitis is rarely diagnosed (Taelman et al., 1992). However autopsy studies carried out in Abidjan indicate that among the HIV-infected patients dying in a general hospital 10% die with tuberculous meningitis (Bishburg et al., 1986). Tuberculoma of the brain has occasionally been reported.

2.5. Treponema pallidum *infection*

Although syphilis is very common in Africa, the prevalence of neurosyphilis is low. HIV associated cases are rarely described: it are meningovascular syphilis, acute syphilitic meningitis, and parenchymal neurosyphilis.

The treatment is procain-penicillin, in association with Probenacid to shorten the treatment.

The main role of syphilis, in fact, in Africa, is to increase the risk of contracting HIV infection through genital ulcer.

2.6. *Malignancies: lymphomas*

Primary CNS lymphoma is a B cell lymphoma occurring in 5% of the AIDS patients. It develops with slow neurological involvement which progresses inexorably to death within a few months. Metastatic systemic lymphoma is observed in over 50% of patients with systemic lymphoma and may produce meningeal, cerebral or spinal cord involvement and cranial neuropathies.

Conclusion

Neurological diseases occur frequently among HIV-infected/AIDS patients in Africa. Due to the lack of diagnostic facilities prevailing on this continent, a definite aetiologic diagnosis of the neurologic disorder is

difficult to establish. However, in areas where HIV is endemic, physicians should consider HIV infection in any adult patient showing unexplained neurological symptoms.

Africa is presently facing an epidemic of devastating proportions. Considering the impact of HIV on the nervous system it can be anticipated that Africa will be confronted with an epidemic of debilitating nervous diseases of which cryptococcal meningoencephalitis represents only a small part of the burden (Taelman, 1991).

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