A REVIEW OF NEUROLOGICAL COMPLICATIONS IN AIDS

K V Ratnam, C K Tan

ABSTRACT

Involvement of the central nervous system is now being recognized as an important aspect of HIV infection. Acting as a sanctuary site, it may pose problems to effective therapeutic strategies. HIV-induced AIDS dementia complex is the commonest mode of presentation. Other causes include opportunistic infections and, more infrequently, malignancies. The precise diagnosis is often difficult to make and requires the judicious use of the CT scan. Treatment has been disappointing and is characterized by frequent relapses.

Key words: AIDS, CNS complications, Neuropathy, Management.

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INTRODUCTION

Since the advent of the AIDS epidemic, it is becoming increasingly apparent that the causal agent of AIDS, i.e. HIV, is able to penetrate the nervous system. This has profound implications. As a sanctuary site in the central nervous system, HIV may escape detection and elimination by antivirals. Its presence produces neurological deficits which impair cognitive function, resulting in greater difficulty for the AIDS patient in adjusting to the environment. The recent 1987 revision in the CDC Surveillance case definition of AIDS (1) included HIV encephalopathy (HIV dementia), HIV wasting syndromes in the presence of serological evidence of HIV infection. Even without serological data, Toxoplasmosis of the brain, Cytomegalovirus retinitis with loss of vision, progressive multifocal leukoencephalopathy and primary lymphoma of the brain are indicative of AIDS. Some 60% of AIDS patients have neurological symptoms (2). The array of neurological problems associated with HIV are many and are listed in the Table below. This does not include the complex psychological problems associated with the disease. This brief review will summarize the major neurological problems encountered in this disease.

PSYCHOLOGICAL PROBLEMS

There is a vast array of psychological disturbances associated with AIDS. Since it is not very clear how early the virus penetrates the CNS in the natural course of the disease, it may be speculated that many of the psychological phobias could be the result of actual HIV infection.

Middle Road Hospital
250 Middle Road
Singapore 0718

K V Ratnam, MRCP (UK), MBBS, MSc (Stanlord)
Senior Registrar

Department of Anatomy
National University of Singapore
Kent Ridge
Singapore 0511

C K Tan, PhD, MBBS, CBiol (UK), MIBiol (UK)
Senior Lecturer

Correspondence to: Dr Ratnam

Data have suggested that homophobia, stigmatization, guilt and rejection, discrimination, anxiety or depression, low self-esteem, anticipatory grief and sexual fears are some of the problems. However, as progress from ARC, or AIDS-related complex (which is the state where significant non-inguinal lymph node enlargement is accompanied by non-specific symptoms and signs like fever, weight loss and night sweats), to frank AIDS occurs, it is likely to be complicated by either opportunistic infections, malignancies or the AIDS dementia complex.

VASCULAR COMPLICATIONS

HIV has been shown to infect endothelial cells; hence it is not surprising for AIDS patients to experience haemorrhagic or bland cerebral infarction. Sometimes this occurs secondary to non-bacterial thrombotic endocarditis.

OPPORTUNISTIC INFECTIONS

These are usually either viral, bacterial, fungal or protozoal and their severity in general is inversely proportional to the depletion of the T-helper lymphocytes. The relative frequency of the pathogens depends to some extent on the peculiarities of the community from which the sample is based. In a recent series (3), 32% had Toxoplasma gondii, 17% had Cytomegalovirus, and 13% had Cryptococcus.

VIRUSES

The predominant opportunistic viruses include cytomegalovirus, papovavirus and herpes virus. Cytomegalovirus presents with a subacute encephalitis which is slowly progressive over the course of several months with only rare symptomatic remission. Treatment remains ineffective. Sometimes patients with this virus have aseptic meningitis with involvement of cranial nerves, most commonly the 5th, 7th and 8th. The papovavirus infection results in progressive multifocal leucoencephalopathy which is an unusual demyelinating disease in which affected patients present with mental aberrations, blindness, aphasia and focal deficits which slowly progress until death (4). Characteristic CT scan finding has been low density lesions. Both herpes virus (5) Types I and II

have been recognized as opportunistic viruses in AIDS patients. Patients may present with subacute progressive encephalomyelitis and other clinical manifestations including headache, seizures, aphasia and other focal findings. Diagnosis is made reliable only by temporal lobe biopsy.

BACTERIA

Of the known opportunistic bacteria, Mycobacterium avium intracellulare group has been a major cause (6). It is expected that in areas like Haiti, M. tuberculosis would be more prevalent. But it is all the more surprising that despite the high rate of pulmonary tuberculosis, CNS TB is much less frequent compared to other infections. Reports of pyogenic bacteria affecting the CNS in AIDS patients have been surprisingly rare.

FUNGI

Cryptococcus neoformans is the most common fungal infection of the CNS even in association with other systemic illnesses. Due to the minimal inflammatory response to this infection, patients may present with headache, confusion and seizures but is often atypical. Other rarer fungi include Candida albicans, Coccidiodomycosis (in endemic areas) and Aspergillus fumigatus.

PROTOZOA

The obligate intracellular protozoa, Toxoplasma gondii, is by far the most common infection in these patients. Their presentation usually involves focal deficits often with an altered level of consciousness. This pathogen should be one of the first to be excluded in any patient with CNS deficits.

NEOPLASMS

While systemic lymphomas frequently invade the meninges, primary cerebral lymphoma more frequently involves the brain parenchyma. Although Kaposi's sarcoma has been a primary feature of AIDS, CNS presentation of this neoplasm has been remarkably rare.

HIV-induced AIDS Dementia Complex

Subacute encephalitis or AIDS encephalopathy or AIDS dementia complex is the most common neurlogical problem in AIDS (2). Clinically, it is characterized by poor memory, inability to concentrate, apathy and psychomotor retardation. Focal motor abnormalities and behavioural changes may also occur. For the vast majority of patients, the symptoms progress rapidly with the full blown dementia complex developing within a year. Even in those without clinically apparent neurologic disease, HIV can be isolated from more than 50% of patients with AIDS or PGL (or persistent generalized lymphadenopathy in which a palpable lymphadenopathy greater than 1 cm in two or more extra-inguinal sites persists for more than three months in the absence of concurrent illness (7). Several workers have also demonstrated intrathecal production of HIV-specific immunoglobulins in patients with subacute encephalitis. It is very likely that HIV enters the CNS through infected monocytes and its envelope glycoprotein gp 120 acts by blocking neuroleukin-binding to neurons. Neuroleukin is a neurotropic factor which promotes the in vitro survival of embryonic spinal neurons, motor neurons and sensory neurons (8). This syndrome represents a real challenge for clinicians to treat although it has been reported that Azidothymidine is beneficial (9).

OTHER PROBLEMS

These include several types of peripheral neuropathies like distal symmetrical neuropathy, Bell's palsy, polymyalgias and polymyositis. It is speculated that these may be due to direct HIV infections.

NEUROPATHOLOGY

Detailed accounts of the neuropathological changes in the CNS in AIDS and dementia complex have been published in 1986 by Anders et al.3 and Navia et al.10.

The CNS involvement in AIDS affects selective sites in both the spinal cord as well as the brain. In the spinal cord, the sites of predilection are the major long tracts resulting in a myelopathy. The most common tracts affected are the dorsal columns and the lateral corticospinal tract. Histologically, these tracts show vacuolation and are infiltrated with lipid-laden macrophages. As a result, routine staining with H & E show pallor of these tracts. In the brain, only the subcortical structures are involved. Remarkably, the cerebral cortex is spared although its deeper layers may show evidence of astrocytosis; neuronal loss occurs only in very advanced cases of white matter involvement. The subcortical structures which are frequently involved are the basal ganglia and the pons. The nuclei in the basal ganglia which are involved are usually the putamen, caudate nucleus and claustrum; the globus pallidus is less often affected. In the pons, there is no particular nuclear group which may be involved.

The reactive cellular changes in the white matter and subcortical grey matter are manifested by (a) the occurrence of reactive astrocytes, (b) perivascular and parenchymal infiltration of lymphocytes and macrophages, and (c) nodules of microglial cells. Oligodendrocytic involvement is rare and when it occurs, the cells show degenerative changes. The perivascular infiltration of lymphocytes and macrophages occur mainly around small blood vessels and capillaries. The microglial nodules occur mainly in the white matter which is affected. At such sites, intranuclear inclusion bodies resembling those in CMV infection are a feature.

DIAGNOSIS AND TREATMENT

The most important investigation is the CT scan (5) which allows one, firstly, to exclude raised intracranial pressure and; secondly, to allow biopsy under CT scan guidance. When raised intracranial pressure has been excluded, it is rational to proceed to a lumbar puncture and analyse the fluid for evidence of common opportunistic organisms in the usual manner.

Serological tests should be interpreted with caution; for instance, there is usually no IgM response to cerebral Toxoplasmosis in AIDS patients on account of the patient's inability to mount a primary immunological response. Hence positive tests are helpful but negative tests do not exclude the infection. When infection has been rigorously excluded, CNS changes can then be ascribed to HIV encephalopathy. The treatment is poor with viral infections, but fungi respond to Amphotericin B and 5-fluorocytosine. Mycobacteria tend to be difficult to treat and second-line drugs are usually required. Toxoplasma gondii does respond to pyrimethamine and sulfadiazine. Neoplasms and vascular complications do poorly. There is a frequent tendency to relapse and therefore prophylaxis is frequently given after successful initial treatment. Overall, both the success rate and prognosis remain poor and in view of considerable diagnostic difficulties, it is recommended that treatment be commenced presumptively based on local experience.

CNS COMPLICATIONS OF AIDS

A. Infection

1) **Viral**
   Cytomegalovirus (retinopathy, encephalities)
   Herpes Simplex I and II (encephalities)
   Herpes Zoster (Zoster opthalmicus angiites)
   HIV (progressive dementia)
   Papovavirus (progressive multifocal leucoencephalopathy)

2) **Bacterial**
   Listeria monocytogenes
   Mycobacterium avium intracellulare (meningitis, abscess)
   Mycobacterium tuberculosis hominis (meningitis, abscess)
   Nocardia species

3) **Fungal**
   Aspergillus species
   Blastomyces dermatitidis
   Candida species (meningitis, abscess)
   Coccidiodes immitis
   Cryptococcus neoformans (meningitis, abscess)
   Histoplasma capsulatum

4) **Protozoa**
   Toxoplasma gondii (encephalitis abscess)

B. Non-infectious complications

1) **Neoplasms**
   Kaposi's sarcoma
   Metastatic lymphoma
   Primary CNS lymphoma

2) **Vascular**
   Cerebral haemorrhage
   Marantic endocarditis

3) **Peripheral neuropathy**

4) **Retinopathy**

SUMMARY

This brief review has looked at the problem of CNS complications of AIDS. These complications include opportunistic infections, neoplasms, vascular and peripheral neuropathies. There is growing recognition that the commonest cause of CNS problems is due to HIV encephalopathy or AIDS dementia complex. The problem this may pose to therapeutic strategies is obvious. The neuropathology of the various complications is being further classified by brain biopsies. Psychological problems experienced by AIDS patient further compound the challenge facing physicians and surgeons treating this aspect of HIV infection.

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