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B.O. OSOTIMEHIN and A.O. UWAIFO

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Human immunodeficiency virus and the nervous system: some aspects of the molecular pathology.*

B. O. OSUNTOKUN

Neurology Unit, Department of Medicine, University of Ibadan, Ibadan.

Human immunodeficiency viruses (HIV-1, HIV-2), human T-cell lymphotrophic virus (HTLV-1, HTLV-2) which cause disease in human beings are retroviruses which belong to the group now referred to as lentiviruses, a sub-family of animal and human retroviruses capable of producing after usually prolonged incubation period, chronic diseases of the nervous system. The incubation period between HIV infection and the development of antibodies may be up to 6 months and during this period, the patient can transmit the infection while sero-negative. The mean incubation period between HIV infection and the development of AIDS is about 10 years. Probably about 10 million people world- wide are infected and over a quarter of a million AIDS cases including over 50,000 from African countries have been reported to the WHO. The neurological complications of HIV infection are very frequent and with a wide spectrum (see Table 1 according to a WHO consultation 1990)[1] and the timing of occurrence could vary from early to late in the course of the infection. HIV infects the central nervous system in 90% of patients dying of AIDS. The virus, and not intercurrent infection is the direct cause of the sub-acute encephalomyelities that produces the AIDS dementia complex found in terminally ill patients. The virus has also been found in the CNS of patients with myelopathy although the mechanism by which the myelophathy is caused is still unclear.

Table 1

HIV-associated cognitive motor complex
- HIV-1 associated dementia
- HIV-1 associated myelopathy
- HIV-1 associated minor cognitive motor syndrome.

HIV-associated mental and behavioural disorders
- Delirium
- Acute psychotic disorders
- Affective disorders
- Adjustment disorders
- Acute stress reactions
- Suicide.

Other HIV-associated central nervous system disorders
- Progressive encephalopathy of childhood
- Aseptic meningitis.

HIV-associated peripheral nervous system disorders
- Inflammatory polyneuropathy
- Predominant sensory neuropathy
- Myopathy.

Neuropsychiatric disorders due to opportunistic processes in HIV infected subjects.
- Progressive multifocal leukoencephalopathy
- Cerebral toxoplasmosis
- Cryptococcal meningitis
- Cytomegalovirus encephalopathy
- Cytomegalovirus neuropathy
- CNS tuberculosis
- Herpes zoster/simplex encephalitis
- Varicella zoster radiculitis
- Other syndromes due to opportunistic infections
- Primary CNS lymphoma.

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HIV has a particular tropism for the protein CD4 contained in receptors on T4 lymphocytes which are destroyed with consequent loss of cell-mediated immunity. However many cell lines of nervous system, liver and fibroblast origin do not express CD4, but can be infected albeit less efficiently with HIV-1. Apart from CD4 receptor, a galactosyl ceramide (Galc), a glycolipid that is typically found in association with myelin can serve as a receptor for HIV-1[2]. Entry of HIV-1 in neural cell lines can be inhibited by antibodies against galactosyl ceramide. The viral envelope protein, gp120 protein of the virus is the viral component that interacts with Galc; the gp120 is also the protein that binds to CD4 receptors. HIV antigen and nucleic acids are found in brain macrophages and endothelial cells and in cells morphologically and biochemically identified as astrocytes, oligodendroglia and rarely in neurones in brain biopsy of adult AIDS patient with encephalopathy. HIV can infect continuous human cell lines of glial origin as well as low passage neural cell population isolated from human nervous tissue.

In HIV encephalitis, there are loss of cortical neurones and synapses (synaptosin immuno-reactivity), vacuolation of dendritic processes, in addition to the predominantly subcortical multiple foci of multi-nucleated giant cells, macrophages and microglial cells[3,4] with relative sparing of the cortex. The cortical changes may be an indirect effect of HIV infection as they may not be associated with the presence of HIV antigens.

There is some evidence that HIV strains infecting the brain are different in some features from those in other parts of the body (even in the same patient), for example, in reduced cytopathogenicity, efficient replication in peripheral macrophages, insensitivity to serum neutralization and agglutination by humoral antibodies, relative inability to infect established T-cell lines, and inability to modulate or reduce CD4 antigen expression on infected cells[5]. It is possible that such differences may be related to changes in the HIV regulatory genes (for example, as described for the nef gene) and differences in HIV gp120. It is speculative whether the differences in HIV strains could explain apparently lower frequency of neurological complications of HIV infection in the Africans.

Apart from the consequencies of imparied immunity such as opportunistic infections and neoplasm, the mechanism by which HIV infection directly causes nervous system lesions is not completely known. It is now well established that HIV is neurotropic and capable of replicating within the nervous system[6]. Some possible mechanisms for its pathogenicity are briefly described below:

(i) Demyelination is a prominent feature of the subcortical areas of the brain in HIV sub-acute encephalitis as found in AIDS dementia complex and in the long tracts of the spinal cord in AIDS myelopathy. Hypomethylation does occur due to inhibition of methyltransferase enzymes which are dependent on vitamins B12 and folate; but since levels of B12 and folate are normal in most HIV patients, the hypomethylation is probably due to some metabolic response to the virus or to secondary events it causes in the CNS[7]. It is also possible that the metabolism of B12 and folate is inhibited by excess of dihydroneopterin secreted by macrophages persistently activated by gamma-interferon. Malabsorption of B12 does occur in some, but not in all patients with HIV infection: in some it is corrected by oral intrinsic factor, in others it is not.

(ii) Some evidence suggest that HIV infected macrophages secrete heat-stable, protease-resistant neurotoxin molecules (with mass less than 2kd) which act through neuronal N-methyl-D- aspartate (NMDA) receptors and that the neurological consequencies of HIV infections might be reduced by suppressing macrophages, blocking synthesis of the neurotoxins or blocking the NMDA receptors[8]. Central nervous system damage has also been postulated to be related to cytokines released from infected immune cells or toxic product of the virus.

(iii) Neuroleukin, a 50kd protein promotes survival of foetal spinal neurones in CNS and immunoglobulin secretion in the immune system. It is partly homologous to the viral envelope or coat protein gp120 of the HIV and has led to the speculation that the HIV may interfere with the growth factor action of neuroleukin on nerve cells[9].

(iv) A particular sequence within the variable region of gp120 is partly homologous to a sequence of vasoactive intestinal polypeptide (VIP) known as peptide T. VIP influences the survival and growth of spinal motor hippocampal and retinal neurones and retinal

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ganglionic cells. HIV gp120 is lethal to cultured hippocampal and retinal ganglionic neurones and those neurones can be rescued from being killed by VIP.

(v) Neuronal death induced by HIV gp120 is mediated by an increase in intracellular calcium-dependent current, reminiscent of N-methyl-D-aspartate (NMDA) receptor-mediated neurotoxicity (which is believed to contribute to damage by stroke, trauma, epilepsy and several neuro-degenerative diseases) and is blocked by calcium channel antagonists and NMDA receptor antagonists[8,10].

The above imply that VIP and drugs like nimodipine, nifedipine, flunarizine and vitamin B12 and folate could be tried to prevent or ameliorate the CNS complications of HIV. In one report, the majority of patients with HIV-induced peripheral neuropathy but not those with myelopathy, who were treated with vitamin B12 had a therapeutic response[11].

(vi) As demonstrated by *in vivo* phosphorous 31 magnetic resonance spectroscopy to non-invasively assess brain energy and phospholipid metabolism, concentrations of adenosine triphosphate and phosphocreatine are reduced in the brain in HIV-seropositive patients, and particularly in the subcortical white matter in patients with AIDS dementia[12]. This suggests that HIV infection impairs brain cellular oxidative metabolism.

The investigations into the molecular pathology of HIV-induced neurological complications are important. They may open the way to effective prevention and treatment of the neurological complications of HIV infection which are not due to opportunistic infections and processes. This would be an important and remarkable achievement, especially as availability of a vaccine for prevention and treatment of HIV infection is as of now, nowhere in sight.

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