The AIDS-related demen

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Abstract

AIDS dementia complex or as it has more recently termed HIV associated dementia, is a subcortical dementing illness. It occurs in the advanced stages of HIV infection and develops over weeks to months. The authors review the pathophysiology, clinical picture, differential diagnosis and the therapeutic management of this situation.

Key words: AIDS Dementia complex, HIV associated dementia, AIDS.

Introduction

The existence of pathology of the central nervous system (CNS) during HIV infection, not related to opportunistic infections or tumor pathology, has been recognized since 1983. In 1985, the isolation of the virus in the cerebral parenchyma enabled its pathogenicity to be confirmed, and its role in the genesis of this situation to be determined.[1,2]

This entity has been known by various designations, such as HIV-related dementia complex (by Anglo-Saxon authors), HIV encephalopathy (by French-speaking authors), and more recently, it was classified by the WHO and by the American Academy of Neurology as cognitive-motor complex associated with HIV infection[1,2,3] (*Table 1*).

It is manifested as a subcortical dementia, constituting a non-focal alteration with more frequent preservation of lucidity in these patients. It evolves, from the diagnosis until the patient's death, over a period ranging from several weeks to several months, occurring in advanced stages of infection. The average survival time, according to some studies,[2,4] is six months from the initial diagnosis of dementia. Depending on the authors, the prevalence can range from 14 to 20% of the population with AIDS[4,5] or even from 15 to 40%.[1] It is currently being discussed whether the decrease in incidence of this pathology that is now being seen is related to AZT therapy. The average CD^4, in the works of Portegies and Brew, ranges from 109 to 94 cells per mm^3.

There are authors who defend the view that intravenous drug dependence is a cofactor in viral replication, as it can increase the incidence of encephalopathy in non-advanced stages of AIDS.[2,6]

Pathophysiology

The knowledge of the pathogenesis of this entity has recently undergone various changes. It is known that invasion of the central nervous system occurs in non-advanced stages of HIV infection, persisting until death, without any neurological manifestations in the majority of individuals. A considerable percentage of 20 to 30% of AIDS patients present dementia, and in 3%, this alteration establishes the diagnosis of the syndrome.[7]

The mechanism that occurs in the passage of the virus to the brain remains under discussion. "Trojan Horse" theory, whereby the virus is transported by infected peripheral monocytes, or the hypothesis that the agent crosses the haematoencephalic barrier, altered in infected T-cells, are currently believed to be the most likely possibilities.[4,8]

What appears to be certain, in light of current knowledge, is that the main infected cells are the macrophages and the microglia. The presence of virus in the astrocytes and oligodendrocytes continues to raise some doubts. The majority of studies agree that the neurons are not infected. However, there is a reduction in their number.[1,7]

The presence of numerous variants of HIV in the same individual is a constant factor, which leads to the hypothesis that some of them have a superior neurotropism, which would explain the existence of encephalopathy and neuropathies in just some patients (and not in all). The asymmetry that exists

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Received for publication on the 20th January 1997

TABLE I

AIDS Dementia complex – WHO and American Academy of Neurology Classification

AIDS Dementia Complex	Cognitive-motor complex associated with HIV
Stage 0 – Normal	There is no corresponding WHO classification
Stage 0.5 : Subclinical Minimum symptoms Mild neurological signs No alteration in day-to-day or work activities	There is no corresponding WHO classification
Stage 1 : Mild Alterations in motor or intellectual capacities Ability to perform all day-to-day and work tasks, except for more demanding activities	Minor cognitive-motor alteration associated with HIV Cognitive, motor and behavioral symptoms Neurological exam: Neurological or neuropsychological alterations Slight inability to perform in day-to-day activities
Stage 2 : Moderate Inability to work or perform day-to-day tasks Ability to take care of him/herself Outpatient, possibly requiring unilateral mechanical support	HIV Dementia and HIV Myelopathy Mild Inability to work and perform day-to-day tasks Ability to take care of him/herself Outpatient, possibly requiring unilateral mechanical support
Stage 3 : Severe Major intellectual inability or Inability to walk unaided	Moderate Inability to work or Inability to walk unaided
Stage 4 : Terminal stage Vegetative stage Rudimentary cognition Para- or tetraplegic	Severe Confined to bed or wheelchair Inability to take care of him/herself without assistance

Comparison of the classification of the AIDS dementia complex and those of the WHO and American Academy of Neurology (adapted from Price and Worley, 1995).

between the exuberance of the clinical symptoms and the sparseness of anatomopathological alterations, as well as the non-existence of neuronal lesion, have prompted the hypothesis that the mechanism of action of HIV is indirect, notably due to the inhibition of neuroleukin (trophic factor of the neuronal tissue) by glycoprotein gp 120.[1,8]

Neuropathology

The neuropathological alterations associated with HIV encephalopathy can take various forms, and are generally more exuberant at subcortical level.

The most frequent form is HIV leukoencephalopathy, which is characterized by alterations in subcortical white matter, with reactive astrocytosis, inflammatory infiltrations and the presence of multinucleated giant cells (now considered to be the principal marker of HIV infection).[1,4] Poliodystrophy is characterized by diffuse reactive astrocytosis and activation of the microglia, involving the gray matter. HIV encephalitis is manifested as inflammatory infiltrates of multinucleated giant cells, at subcortical level. In rare cases, alterations compatible with vacuolar leukoencephalopathy and cortical atrophy may occur, with neuronal loss.[12]

The presence of multinucleated giant cells and diffuse paleness of the white matter are the histological aspects most strongly correlated with the severity of the dementia.

Clinical manifestations

HIV dementia is a diffuse cerebral pathology in which the state of conscience is maintained until more advanced stages of its evolution. Clinically, it takes the

form of a subcortical dementia.[1-6]

Currently, the definition of dementia covers a wide range of symptoms, characterized not only by intellectual deterioration, but also by alterations in previous behavior and personality. The mechanisms may vary, with degenerative diseases being a common cause, but not the only one. Subcortical dementias are related, as their name indicates, to disease of the basal ganglia, and are found in entities like Huntington's Chorea and Parkinson's disease. These are manifested by changes in motility, memory deficits, slowness of thinking, apathy and depression, unlike cortical dementias (such as Alzheimer's disease) in which changes in praxis, knowledge, language and calculation abilities are more evident.[9]

The symptomatology can be divided into three categories: cognitive, motor and behavioral changes. The motor changes are essentially motor difficulties involving fine movements (notably writing), tremor, and unbalanced gait. The cognitive functions initially affected are concentration and memory (particularly recent memory). The most frequent behavioral alterations are emotional blunted effect, with apathy and decreased libido; it can also manifest as depression or episodes of mania. In more advanced stages, where the association with myelopathy is common, patients are mute, with sphincteric incontinence, and bed-ridden (paraplegic or tetraplegic). The initial neurological exam may be normal, with alterations more commonly being observed a difficulty in eye-following movements (which is related to the severity of the dementia), difficulty walking in a straight line, and hyperreflexia.[2,4,8,10]

HIV myelopathy

This entity is associated with the dementia complex related to HIV, with around 60% of cases evolving, in a period of several months, from diagnosis to death.[11] There are studies that indicate a prevalence of this situation in 10% of cases of AIDS (47% in necropsy), with the majority of patients presenting the subclinical form.[11]

HIV myelopathy should probably be separated into two entities; vacuolar myelopathy (multiple vacuoles in the white matter of the posterior and lateral columns, more marked in the dorsal segments) and myelopathy of the multinucleated giant cells (without preferential localization) which are clinically manifested in similar form.[4]

Clinically, it is manifested as a spastic paraparesis, with evolution in several months, which determines a characteristic "scissor" gait. There is osteotendinous hyperreflexia, and the cutaneoplantar reflexes are in bilateral extension. Due to lesion of the posterior columns (as in Vitamin B12 deficit), the patient may present slight gait ataxia (worsening when the eyes are closed, due to alterations in postural sensitivity). The surface sensitivities are not significantly altered, the presence of a level of sensitivity being a rare finding. This myelopathy can evolve even to wheelchair dependence and in rare cases, it can acquire the form of tetraplegia with involvement of vital functions, such as respiratory function.[4,11]

Traditionally considered a neurological manifestation that is dependant on the HIV virus itself, the hypothesis is that the vacuolar variant is caused by an opportunistic infection, since it does not normally occur in infected children, and has been described in cases of immunosuppression not related to HIV.[4,5]

Diagnosis

The pathologies with which a differential diagnosis should be made are metabolic encephalopathies and depression, and opportunistic infections (in particular, cytomegalovirus in the case of encephalitis, and Cryptococcus in the case of meningitis). In principle, all these situations are treatable, and on being corrected, they considerably improve the patient's quality of life.[4,10]

In the LCR study, we can find a pleocytosis of mononuclear predominance, moderate hyperproteinorhachia and oligoclonal bands. Alterations suggestive of autoimmune activation, such as increased b2-microblobulin, neopterin (production of macrophage activation) and quinolinic acid (excitatory endotoxin) are related not only to the presence, but also to the severity of the encephalopathy. Other markers, such as tumor necrosis factor, remain controversial, while the interleukins 1b and 6 are related to the presence, but not the severity of the encephalopathy.[4,7] It is not always possible to perform these determinations in our laboratories. The culture of the virus in the LCR has proven to be of little use, and the core protein, the p24 antigen, is found in just 50% of patients with severe dementia. The detection of DNA in the HIV is now possible through the polymerase chain reaction (PCR).

The imaging methods reveal, in the majority of

patients, cerebral atrophy and MRE CE can reveal a hypersignal in the white matter and basal ganglia, in the proton density weightings and in T22.

Therapeutic

The role of HIV in the genesis of encephalopathy justifies the use of antiretroviral drugs in its therapy. The drug used must obey certain principles in order to be effective, namely:

• The penetration in the parenchyma and liquor must be satisfactory;

• Intracellular penetration, particularly intramacrophagic, must be sufficient to inhibit viral replication;

• The treatment must be given early, due to the irreversibility of the nerve cell lesions.[1]

Zidovudine is probably the most effective drug[11] and has been demonstrated, in various studies, to be superior to the placebo.[1] The dose to be used remains under discussion, but it appears to be higher than that recommended in the systemic disease.[1-5] Other nucleosides (other than Zidovudine), non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and other antiviral therapies have not yet been tested.

However, these drugs have secondary effects on the nervous system, notably as the cause of peripheral neuropathies.[11]

In the future, the optimum treatment should also include adjuvants that minimize the toxicity that leads to cerebral dysfunction, which may act as inhibitors of immunosuppressive action of the immunopathological mechanisms; it should also have neuroprotector action at the level of the target cells, and should exert compensatory action on the neuronal network.[2]

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