International Journal of Infection
ISSN 1972-6945 / 2022 vol. 6, ISSUE N. 1, January-April

APPROACHING HIV-ASSOCIATED DEMENTIA: SYMPTOMS, NEUROLOGICAL AND LABORATORY EXAMINATION, AND TREATMENT

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ABSTRACT

HIV-associated dementia (HAD) is a severe mental disease caused by HIV-1 infection that usually occurs in the the advanced stages of AIDS. HAD affects cognitive, motor, and behavioral functions, and the symptoms have a varying range of severity, which is assessed by the use of neurological examination, laboratory testing, and imaging studies. Some electroencephalographic anomalies are considered an early marker of the disease. Widespread cerebral atrophy is seen in approximately half of HAD cases and is often present in the advanced stages, although this is not indicative of the severity of cognitive deficits. Studies have also demonstrated neuropsychological abnormalitis, especially regarding memory and language, and testing is necessary in order to assess the cognitive impact of HAD. Treatment is focused on managing the HIV-1 infection and alleviating the symptoms of HAD.

KEYWORDS: *HIV, HIV-associated dementia, virus, treatment, laboratory examination*

INTRODUCTION

HIV-associated dementia (HAD), also known as AIDS Dementia Complex (ADC), is a severe neurological complication of HIV-1 infection (1). In most patients, HIV-1 infection is already known before the onset of dementia symptoms but HAD can sometimes appear before other signs or symptoms of the infection (2). In the latter case, the onset of the disease is usually insidious and one of the first signs, psychomotor slowing, can be attributed to depressed mood. The onset is usually more abrupt in the later stages of HIV-1 infection.

HAD typically occurs in advanced stages of AIDS and can significantly impact cognitive, motor, and behavioral functions (3). HAD symptoms can vary in severity and may progress over time. They are generally categorized into cognitive, motor, and behavioral symptoms (Table I).

Received: 08 January, 2022
Accepted: 22 March, 2022

1972-6945 (2022)
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Table I. *Typical symptoms that present in HIV-associated dementia (HAD).*

Cognitive Symptoms:	Memory loss (especially short-term memory)
	Difficulty with attention and concentration
	Problems with problem-solving and executive functioning
	Impaired judgment and planning abilities
Motor Symptoms:	Poor coordination and balance
	Slowness of movements (bradykinesia)
	Tremors
	Weakness in limbs
	Gait disturbances
Behavioral Symptoms:	Apathy and lack of motivation
	Social withdrawal
	Irritability
	Depression or mood swings
	Psychosis (in severe cases)

HAD begins with apathy, psychomotor slowing, memory problems, and loss of interest in usual activities (4). Sometimes, however, the onset can be characterized by psychomotor agitation. Later, HAD is characterized by disturbances in recent memory, the slowing down of mental processes, and personality changes (5). Headache, gait disturbances, aphasia, hemiparesis, ocular disorders such as nystagmus and gaze paralysis, and, more rarely, compulsive seizures, may be present. As the infection progresses, there is further slowing of mental processes which can lead to a state of confusion, disorientation, hallucinations, stupor, and coma (5). Microcephaly and progressive psychomotor disorders may also be present in children (6). In the absence of therapy, the decline is rapid, and an average survival period of less than 6 months is generally reported.

DISCUSSION

Neurological examination, laboratory testing, and imaging studies utilizing computed tomography (CT), or magnetic resonance imaging (MRI) are all applied to assess the severity of HAD (7) (Table II).

Table II. *Neurological and Laboratory Examinations performed to assess the severity of HIV-associated dementia (HAD).*

Neurological Examination:	Detailed medical history and symptom assessment
	Assesses motor function, reflexes, coordination, and sensory perception
Laboratory Tests:	HIV viral load test: Measures the amount of HIV RNA in the blood
	CD4 count: Assesses the immune system's health
	Blood tests: Rule out other infections or metabolic conditions that could contribute to neurological symptoms
Imaging Studies:	MRI or CT scan: Can reveal brain atrophy, white matter changes, or other abnormalities associated with HAD

In the initial stages, the neurological examination is often within normal limits, although some difficulty in rapid eye movement and profound hyperreflexia may be noted. Subsequently, anisocoria, hypertonia, myoclonia, and tremor may appear (8). A scale of severity of the patient with HAD has been developed which ranges from normal stage 0 to terminal stage 4 (9) (Table III).

Table III. *Clinical staging of HIV-associated dementia (HAD).*

Normal Stage zero:	Mental and motor functions are within normal capacity.
Subclinical Stage 0.5:	Absent, minimal, or equivocal symptoms, without affecting daily activities or working life. Rapid eye movements may be present.
Mild Stage 1:	The patient can carry out all aspects of work and daily life, but with unequivocal disturbances of intellectual or motor functions and the patient can walk without assistance.
Moderate Stage 2:	The patient can perform essential self-care activities but is unable to work or perform most activities of daily living. When walking, there may be ambulation.
Severe Stage 3:	Severe intellectual involvement occurs. The patient is unable to hold complex conversations. There is severe motor impairment and the inability to walk without assistance.
End Stage 4:	The patient's life is vegetative with rudimentary intellectual and social activity, mutism, paraparesis or peraplagia, and urinary and fecal incontinence.

Cerebrospinal fluid (CSF)

The cerebrospinal fluid (CSF) does not present specific abnormalities, and a normal standard examination cannot exclude a diagnosis of dementia. An increase in total proteins has been highlighted in approximately 65% of cases and IgG in 38% to 80% of cases, while the presence of oligoclonal bands on CSF electrophoresis was found in 24% to 35% of cases examined. The number of cells in the fluid per mm^3 is usually within normal limits, but sometimes there may be a modest pleocytosis with a ratio between CD4+ and CD8+ that is similar to that in blood (10).

Several biological parameters have been found to increase during HAD. Among other things, there is an increase in some cytokines such as tumor necrosis factor (TNF), IL-1, IL-6, and GM-CSF (11). In addition, there is an increase in ferritin, beta-2-microglobulin, the beta-2-microglobulin ratio, liquor/serum microglobulin, neopterin, and quinolinic acid (12). In particular, beta-2-microglobulin, which comes from the first class major histocompatibility complex (MHC 1), is present in high concentrations in activated T lymphocytes, and can therefore be considered an index, like neopterin, of immune system activation (13). Quinolinic acid, a metabolite of tryptophan, may reflect macrophage activation within the central nervous system (14). Occasionally, an increase in CD3 TCR gamma/delta lymphocytes has also been found in both CSF and peripheral blood of patients with HAD (15).

Electroencephalogram

A generalized slowdown in cerebral electrical activity has been reported, with the appearance of theta (τ) or delta (δ) rhythms (16). However, approximately a third of patients have normal traces of these rhythms. The appearance of certain electroencephalographic anomalies has been considered an early marker of the disease.

Imaging examinations

In approximately half of cases, widespread cerebral atrophy is evident, especially in the more advanced stages of the disease (17). More rarely, focal or hydrocephalic lesions are found. It is hypothesized that there is no parallelism between the evolution of cerebral atrophy and the clinical picture of HAD. However, a correlation was found between the presence of lesions and white matter damage. Several parameters have been proposed for the evaluation of atrophy (18). One of these is the extension of the ventricular area of the third ventricle (19). In one study, the presence of supratentorial atrophy was found in 14 out of 19 patients with HAD through examination with CT or MRI. However, no correlation was noted between the degree of atrophy and the severity of the cognitive deficit. Very often, the CT examination was sufficient to establish the degree of atrophy. In addition, a significant correlation was highlighted between the presence of brain atrophy and average survival (20). After examination with CT or MRI, there is a normal survival in normal patients, while in patients with cerebral atrophy, survival was reduced by 50%.

Psychological tests

Some studies have demonstrated a higher frequency of neuropsychological test abnormalities in asymptomatic HIV-1-positive individuals compared to HIV-1-negative controls (21). It has been noted that in the disease state, the first deficits are in memory and language (22). Memory and language disorders seem less important in the initial stages of HAD than in Alzheimer's disease (AD) (23). However, in a multicenter study on asymptomatic seropositive patients, no cognitive alterations were highlighted. Often, the neuropsychological abnormalities found in HIV-1-positive patients are due to alcohol or drug use and not to the effects of the virus (24).

Neuropsychological testing is crucial for assessing the cognitive impact of HAD. These tests evaluate various aspects of cognitive functioning (25) (Table IV). Commonly used tests include the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Digit Span Test, the Trail Making Test (Parts A and B), and the Wisconsin Card Sorting Test.

Table IV. *Neuropsychological tests that are utilized to assess the cognitive impact of HIV-associated dementia (HAD).*

Memory Tests:	Assess both short-term and long-term memory capabilities.
Attention and Concentration Tests:	Evaluate the ability to focus and sustain attention.
Executive Functioning Tests:	Measure planning, problem-solving and organizational skills.
Language Tests:	Assess verbal fluency, comprehension, and language production.
Motor Skill Tests:	Evaluate coordination, speed, and precision of movements.

Diagnosis

Patients with HAD are frequently tested for HIV-1 positivity by ELISA and confirmed with Western blot analysis (26). In children, there may be false positives in the first 12 to 15 months of life due to the presence of maternally derived anti-HIV IgG (27). The polymerase chain reaction (PCR) technique can be helpful in indicating the presence of infection in the child (28). HAD can be diagnosed clinically in HIV-1 seropositive patients with progressive dementia when other causes of dementia have been excluded. At autopsy, there may be leukoencephalitis with modest astrocytosis and the presence of giant multinucleated cells (29).

Treatment

The primary goal of HAD treatment is to manage HIV-1 infection and alleviate symptoms (30).

Nucleoside analogous antiviral agents are frequently used for therapy and include zidovudine, didanosine, and dideoxycytidine (31). These drugs are useful in inhibiting the activity of reverse transcriptase and have demonstrated a notable increase in survival times, even in subjects with advanced HAD. Furthermore, in patients with HAD, the treatment also causes an improvement in the neuropsychological state.

In addition, treatment with nimodipine, a calcium channel blocker, may also have a positive effect by inhibiting viral proteins that cause neurotoxicity (32). Patients often present agitation, and in these cases, could be treated with modest doses of neuroleptics (33) (Table V).

Table V. *Treatment options for managing HIV-associated dementia (HAD)* .

Antiretroviral Therapy (ART):	Highly active antiretroviral therapy (HAART) is the cornerstone of treatment. Effective ART can reduce HIV-1 viral load, improve immune function, and slow or prevent the progression of HAD.
Symptomatic Treatments:	Psychostimulants (e.g., methylphenidate) for apathy and cognitive slowing Antidepressants for mood disorders Antipsychotics for severe behavioral disturbances Medications for motor symptoms, such as antispasmodics
Supportive Therapy:	Cognitive rehabilitation and occupational therapy to improve cognitive and motor functions Psychological counseling and support groups for emotional and social support Physical therapy to enhance motor skills and coordination

CONCLUSIONS

HAD is a serious neurological condition that requires comprehensive management, including antiretroviral therapy, symptomatic treatments, and supportive care. Early diagnosis and intervention are crucial to improving outcomes and quality of life for individuals affected by this condition and regular monitoring and follow-up are essential to address the evolving needs of patients with HAD.

Conflict of interest

The author declares that they have no conflict of interest.

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