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VIEW AND REVIEW

Cerebrospinal fluid analysis in the HIV infection and compartmentalization of HIV in the central nervous system

Análise de LCR na infeção pelo HIV e compartimentalização do HIV no sistema nervoso central

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ABSTRACT

The nervous system plays an important role in HIV infection. The purpose of this review is to discuss the indications for cerebrospinal fluid (CSF) analysis in HIV infection in clinical practice. CSF analysis in HIV infection is indicated for the diagnosis of opportunistic infections and co-infections, diagnosis of meningitis caused by HIV, quantification of HIV viral load, and analysis of CNS HIV compartmentalization. Although several CSF biomarkers have been investigated, none are clinically applicable. The capacity of HIV to generate genetic diversity, in association with the constitutional characteristics of the CNS, facilitates the generation of HIV quasispecies in the CNS that are distinct from HIV in the systemic circulation. CSF analysis has a well-defined and valuable role in the diagnosis of CNS infections in HIV/AIDS patients. Further research is necessary to establish a clinically applicable biomarker for the diagnosis of HIV-associated neurocognitive disorders.

Keywords: HIV, AIDS, central nervous system, cognitive impairment, cerebrospinal fluid, viral load, biomarkers.

RESUMO

O sistema nervoso representa um papel importante na infecção pelo HIV. O objetivo desta revisão é discutir as indicações para análise do líquido cefalorraquidiano (LCR) na infecção pelo HIV na prática clínica. A análise do LCR na infecção pelo HIV é indicada para o diagnóstico de infecções oportunistas e co-infecções, meningite pelo HIV, quantificação da carga viral de HIV e compartimentalização do HIV no SNC. Uma série de biomarcadores no LCR foi investigada, na literatura, porém não apresentam aplicabilidade clínica. A grande capacidade do HIV de gerar diversidade genética, associado a características constitucionais do SNC propicia o desenvolvimento quasiespécies distintas no SNC das circulantes sistemicamente. A análise do LCR na infecção pelo HIV é bem estabelecida no diagnóstico de infecções no CNS, contudo mais pesquisas é necessária para estabelecer a aplicabilidade clínica dos biomarcadores no diagnóstico de desordens cognitivas associadas ao HIV.

Palavras-chave: HIV, AIDS, sistema nervoso central, alteração cognitiva, líquido cefalorraquidiano, carga viral, biomarcadores.

Almost forty years after it began, the HIV epidemic remains a challenging public health problem. The incidence of infection is increasing in some vulnerable groups, mainly young men who have sex with men (MSM) and older people[1,2]. The nervous and the immune systems are HIV target organs[3,4,5]. The introduction of highly active antiretroviral therapy (HAART) has changed the clinical situation for patients with AIDS, decreased the incidence of opportunistic infections, and thus lowered mortality. However, the incidence of neurological complications directly related to HIV has not decreased proportionally[6], probably because of the low penetration of antiretroviral (ARV) drugs into the central nervous system (CNS), the neuronal toxicity of ARVs, or the persistence of neuronal lesions caused by HIV before treatment[7].

The purpose of this review is to discuss the indications for cerebrospinal fluid (CSF) analysis in HIV infection in clinical practice. CSF analysis during HIV infection is indicated for the diagnosis of opportunistic infections and co-infections; the diagnosis of meningitis, acute or chronic, caused by HIV; the quantification of HIV viral load in CSF; and the analysis of HIV compartmentalization in the CNS[5]. Table 1 summarizes CNS complications in HIV infection.

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Table 1. Central nervous system complications in HIV infection.

Opportunistic infections	Co-infections	Directly related to HIV infection	IRIS
			After beginning treatment with ARV
a. *Cryptococcus neoformans* b. Toxoplasmosis c. PML (JC virus) d. Primary lymphoma	a. Tuberculosis b. Syphilis c.Community-acquired bacterial meningitis d. Cysticercosis e. Hepatitis C virus f. Chagas disease g. Schistosomiasis h. Malaria	a. Acute meningitis b. Chronic meningitis c. HAND d. Peripheral neuropathy e. Vacuolar myelopathy	a. Opportunistic infections b. Inflammatory disease

PML: progressive multifocal leukoencephalopathy; HAND: HIV-associated neurocognitive disorder; IRIS: immune reconstitution inflammatory syndrome; ARV: antiretroviral.

OPPORTUNISTIC INFECTIONS AND CO-INFECTIONS

CSF analysis is important for the diagnosis of opportunistic infections and co-infections in the CNS. Several diagnostic methods can be used. The operational characteristics of each method differ according to the etiological agents under investigation[8,9,10]. In AIDS, more than one opportunistic infection can co-exist because of immunosuppression.

Co-infections are prevalent in the population. They can occur in association with HIV infection, independent of immunosuppression[11]. Table 1 shows the most common etiologies of CNS co-infections that occur with HIV in Brazil.

CNS COMPLICATIONS DIRECTLY RELATED TO HIV INFECTION

Acute meningitis caused by HIV

Acute meningitis is present in 5%–10% of HIV-infected patients, usually before seroconversion, as well as during or after the observation of mononucleosis-like signs and symptoms. Its clinical evolution is self-limited. Acute meningitis can be asymptomatic or accompanied by focal neurological signs such as peripheral facial palsy.

The CSF has a biochemical and cellular pattern compatible with that of acute viral meningitis[6]. Anti-HIV enzyme-linked immunosorbent assays (ELISA) often yield negative results with blood and CSF samples. Because HIV/AIDS is a systemic infection, diagnostic tests (triage and confirmatory) must be performed using peripheral blood samples, not CSF samples[1].

Patients with a risk of HIV infection are advised to have a second serological diagnosis test for HIV after 4–6 weeks[1]. No specific biomarker in the CSF or blood helps diagnose acute meningitis caused by HIV. The p24 antigen test for early diagnosis of HIV using blood samples is neither sensitive nor standardized for CSF analysis.

Chronic meningitis caused by HIV

Chronic meningitis is present in 40% of infected individuals at any infection stage, while 59% are asymptomatic. Because it is an exclusion diagnosis, other causes of chronic meningitis must be ruled out. The CSF presents with pleocytosis (5–50 cells/mm^3) and increased total protein level (50–100 mg/dL); glucose, the CSF/blood glucose ratio, and lactic acid are in the normal range[8,12,13].

Other neurologic complications associated with HIV

The use of CSF analysis for the specific diagnosis of HIV-associated neurocognitive disorders (HAND), HIV myelopathy, and immunological recovery inflammatory syndrome (IRIS-HIV) is of limited clinical importance. Specific biomarkers for the diagnosis of these diseases have not been identified, although several have been studied.

HAND is the main neurologic complication directly associated with HIV infection[14]; it is a clinical diagnosis[6,7,15]. CSF analysis is important for ruling out opportunistic infections and co-infections. Several biomarkers in CSF with the potential to diagnose HAND have been studied. However, they are not clinically applicable[16,17,18,19,20] and are only used in research. With the aging of the HIV population, other biomarkers have become important and have been investigated[21,22,23,24]. The same can be applied to polyneuropathies and myelopathy associated with HIV. HIV vacuolar myelopathy occurs in 10% of patients with AIDS; it is an exclusion diagnosis. Other frequent causes of myelopathy, such as neurosyphilis, HTLV, CMV, and specific endemic etiologies, must be ruled out.

Neurons do not have a CD4 receptor, the main receptor involved in HIV cell invasion; consequently, HIV does not infect neurons. Neuronal injury in HIV infection results from an indirect mechanism due to the complex interaction of anions, inflammatory and neuronal injury proteins and also constitutional HIV proteins[4]. These proteins are investigated as biomarkers in CSF or serum for CNS HIV infection and are summarized in Table 2. It is possible that pyroptosis plays an important role in neuronal lesion and death. Pyroptosis markers in the CSF of patients infected with HIV have not yet been studied. The mechanism of cell death, namely, apoptosis, which here can be described as the death of cells with a productive infection caused by HIV, does not depend on the inflammatory process; it is associated with the activation

of caspase-3. Recently, a mechanism of cell death in HIV-infected cells, called pyroptosis, has been described. The term pyroptosis refers to proinflammatory programmed cell death, a form of cells death intermediate between apoptosis and necrosis. Pyroptosis is dependent on caspase-1, which in turn depends on inflammatory processes. Caspase-1 is not involved in apoptotic cell death, and caspase-1-deficient cells respond normally to most apoptotic signals. The HIV-1-induced death of CD4 T lymphocytes is mediated by pyroptosis. The two mechanisms of programmed cell death, apoptosis and pyroptosis, are not exclusive[25,26,27].

The CD4 and CD8 lymphocyte counts in the peripheral blood and the CD4/CD8 ratio are valuable biomarkers for immunological status in HIV/AIDS. In the CSF, they are of limited value because their changes reflect the changes in the peripheral blood[28]. For CSF analysis, some authors have suggested combining biomarkers for different conditions, such as neopterin to assess immunoactivation and light neurofilaments to evaluate neurodegeneration[29].

IRIS-HIV is characterized by the occurrence of opportunistic infections or non-infectious inflammatory disease within weeks of initiating or changing ARV treatment, despite improvements in immunological status. About 15%–25% of patients that receive ARV treatment develop IRIS-HIV within the first few months of therapy. The nervous system is a frequent target. Biomarkers in the CSF that diagnose IRIS have not yet been identified; the diagnosis is based on clinical criteria[30,31].

Table 2. Biomarkers of HIV and central nervous system (CNS) infection[15, 17, 18, 19, 59].

Blood brain barrier	CSF/ serum albumin ratio
Lymphocytes	CD4, CD8, CD4/CD8 β-2 microglobulin
Monocytes	Soluble CD14 Neopterin Quinolinic acid
Microglia*	
Astrocytes	S-100 Glial fibrillary acid protein (GFAP)
Interleukins	IL-1, IL-2, IL-4 IL-6, IL-7, IL-10, IL-17
TNF	TNFα
Interferon	IFNα and γ
Chemokines	MCP-1/CCL2 MIP-1α MIP-1β RANTES IP-10 Fractalkine Nitric oxide
Host toxins	
Neurons**	Light neurofilaments (NF-L) Total tau, phosphorylated tau Amyloid-β, amyloid-β precursor proteins

GFAP: Glial fibrillary acid protein; IL: interleukin; TNF: tumor necrosis factor; IFN: interferon; MCP-1/CCL2: monocyte chemotactic protein-1/ chemokine (C-C motif) ligand 2; MIP-1: macrophage inflammatory protein 1; RANTES: regulated on activation normal T cell expressed and secreted; IP-10: Interferon gamma-induced protein 10; NF-L: Light neurofilaments.

*There is no specific biomarker with which to assess lesions or functional changes in microglia. **Neuronal lesion proteins.

HIV VIRAL LOAD IN THE CSF

HIV particles present in the CSF can have different origins: they can drain from perivascular spaces or infected cells of the meninges, or they can originate in the plasma and pass through the choroid plexus during CSF production, particularly in the case of damage to or inflammation of the choroid plexus[12]. In clinical practice, determining the HIV viral load in the CSF is important for monitoring the therapeutic effects of ARV treatment, for identifying patients with CNS escape (compartmentalization), and for determining the differential diagnosis in psychiatric disorders[5].

The correlation between HAND and the HIV viral load in the CSF is dependent on the degree of immunosuppression. In cases with a CD4 count of > 200 cells/mm^3, the HIV viral load in the CSF correlates positively with that in the peripheral blood, but not with HAND. After the initiation of ARV therapy, the HIV viral load in the CSF and blood decreases. In patients with a CD4 count of < 200 cells/mm^3, the HIV viral load in the CSF correlates positively with cognitive symptoms, but not with the peripheral blood viral load. The initiation of ARV treatment leads to a decrease in the CSF viral load, although the decrease is slower than the decrease in the blood[32,33,34].

Opportunistic infections and co-infections increase the HIV viral load in the peripheral blood. Some opportunistic infections or co-infections in the CNS can increase the viral load in the CSF, as noted in patients with neurosyphilis[35].

Automated methods, commercially available, for quantifying HIV RNA in blood samples have not been standardized for CSF analysis.

COMPARTMENTALIZATION OF HIV IN THE CNS

Specific CNS immunological characteristics, the blood-brain barrier (BBB), rapid mutation and recombination of HIV, and poor ARV penetration in CNS contribute to the compartmentalization of HIV in the CNS.

Some organs, such as the CNS, genital tract, and gastrointestinal lymphoid tissue, are viral compartments and reservoirs that allow HIV to persist despite ARV therapy that eliminates the virus from the peripheral blood. Compartments are defined as anatomical regions that restrict the genetic flow of HIV, thereby enabling viral evolution and divergence from the virus circulating in the peripheral blood. On the other hand, reservoirs are cells or anatomical sites where HIV or HIV-infected cells survive because the viral kinetics is slower than that in the peripheral blood. Compartments and reservoirs protect HIV from specific immune responses,

ARV therapy, and biochemical changes, thereby providing an environment for pathogen-host interactions[36,37].

The CNS serves as an important reservoir for HIV[36,38,39]. Several constitutional characteristics specific to the CNS support the view that the CNS is an immunologically privileged site. The BBB is composed of endothelial cells that selectively restrict the passage of cell components and macromolecules from the systemic circulation to the CNS. CNS cells rarely express proteins with immunological properties, such as MHC class I and II. In addition, the CNS lacks a lymphatic system[40,41,42,43].

HIV can infect two types of cells in the CNS: cells derived from monocytes (microglia and macrophages) and astrocytes[3]. The neurological symptoms of HIV, which are the same as systemic symptoms, change dramatically after the introduction of ARV treatment.

In treatments with a combination of ARV drugs, the main objective is to suppress HIV replication in all cells and tissues[7]. Effective treatment of HAND probably entails complete suppression of HIV replication in the CNS. Incomplete suppression of the virus in the CNS, caused by factors such as lack of ARV penetration in the CNS, can promote viral mutations and resistance to ARV drugs, both of which allow the virus to redistribute to non-CNS tissues. In this context, the CNS is considered a possible reservoir or sanctuary for HIV[44].

HIV exhibits high genetic and antigenic variability. Mutation and recombination are the main mechanisms that underlie the genetic diversity of HIV and the evolution of the HIV-1 pandemic[45,46]. The high genetic diversity of HIV can be attributed to the lack of a control mechanism for reverse transcriptase activity and the consequently high error rate (0.2–2 mutations per genome per cycle), in association with a high replication rate accompanied by rapid viral turnover[47,48]. Reverse transcriptase does not have 3′-exonuclease regulatory activity and therefore cannot ensure that the DNA transcribed is an accurate copy of the RNA[49].

The *env* and *gag* genes in the HIV-1 subtypes differ by approximately 20% and 15%, respectively[50]; fewer differences, greater than 1%, characterize quasispecies. The nucleotide sequences of different groups (M, N, O, and P) differ by 30%, and the nucleotide sequences of different types (HIV-1 and HIV-2) differ by approximately 50%[51].

The failure of some ARV drugs to penetrate the CNS contributes to persistent neurocognitive deficits and allows for slow replication in the CNS. The improvement of neurocognitive performance after 12 weeks of HAART is greater in those who receive ARV drugs with better CNS penetration[52].

Despite the limited CNS penetration of most ARV drugs, HAART is partially effective in suppressing HIV replication in the CNS. Although some HAART-based treatments are better than others with regard to CNS penetration [34], ARV drugs must be selected to prevent viral activity in the CNS, limit neuron dysfunction, and prevent or treat HIV-infected patients with HAND. In addition, these strategies may help prevent the development of ARV resistance[53]. Table 3 shows the ARV CNS penetration according to the index of ARV CNS penetration effectiveness (CPE)[53].

Despite the effective suppression of viremia with ARV therapy, HIV can still replicate in the CNS, with the development of resistant strains in the CNS in patients with acute and sub-acute neurological manifestations[38,39,54]. Disagreement between the HIV viral loads in the plasma and CSF is defined by detectable levels of HIV RNA in the CSF, indicative of a viral load of > 200 copies/mL, when the viral load in the plasma is < 50 copies/mL or by an HIV RNA viral load in the CSF that is ≥ 1 log higher than that in the plasma[55].

Different concentrations of ARV drugs have been found in the CSF. Therefore, the use of ARV drugs that penetrate the BBB is considered necessary to control infection in the CNS in patients at an advanced stage of the disease, particularly those with neurological problems. Compartmentalization of HIV-1 infection in the CNS can affect the response to

Table 3. Index of ARV central nervous system penetration effectiveness (CPE)[53].

	4	3	2	1
NRTIs	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
NNRTIs	Nevirapine	Delavirdine Efavirenz	Etravirine	
PIs	Indinavir-r	Darunavir-r Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir Atazanavir-r Fosamprenavir	Nelfinavir Ritonavir Saquinavir-r Saquinavir-r Tipranavir-r
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide
Integrase Inhibitors		Raltegravir		

ARV: antiretroviral; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

treatment, which can lead to the development of varying degrees of resistance to ARV drugs in both compartments. Although tests for HIV-1 resistance in the CSF are not recommended during routine treatment of individuals with ARV failure, the choice of treatment in patients with neurological problems requires knowledge of the resistance profile of the virus in the CSF[56,57].

Because lumbar puncture is an invasive procedure, researchers have attempted to develop a predictive model with which to estimate the risk of detectable RNA in the CSF (threshold of > 50 copies/mL) and help identify HIV-positive patients who would benefit most from CSF monitoring. The variables included in the predictive model are race, major depressive disorder (MDD), adherence to ARV, AVR CNS penetration effectiveness (CPE), plasma HIV RNA quantification, and duration of current antiretroviral therapy (ART). However, the CSF-HIV risk score for assessing HIV activity in the CNS requires further validation[58].

Final remarks, CSF analysis has a well-defined and valuable role in the diagnosis of CNS opportunistic infections and co-infections in HIV/AIDS patients. Although further research is necessary to establish a clinically applicable biomarker for HAND diagnosis, promising CSF biomarkers include neopterin, MCP-1, IP-10, and light neurofilaments.

Because of its constitutional and immunological characteristics, the CNS can act as a reservoir for HIV. HIV can replicate in the CNS, independent of HIV in the peripheral blood, and compartmentalization can occur, with the development of quasispecies. Determination of the HIV viral load in the CSF is important for assessing the compartmentalization of HIV in the CNS and for monitoring therapeutic effects.

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