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Recent Advances in HIV-Associated Neurocognitive Disorders

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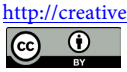

Abstract

HIV-associated neurocognitive disorders (HAND) are chronic complications of HIV infection in the central nervous system. Clinical presentations include asymptomatic neurocognitive impairment (ANI), mild neurocognitive impairment (MND), and HIV-associated dementia (HAD). In the era of combination antiretroviral therapy (cART), the prevalence of HAD has significantly decreased, but the rates of ANI and MND have increased, impairing patients' daily functioning, medical adherence, employment, driving abilities, risk of HIV transmission, overall quality of life, and posing challenges to society, economy, families, and public health. This article reviews the latest research findings regarding the pathogenesis, clinical diagnosis and treatment, neuroimaging, and neuropsychological assessment of HAND, aiming to provide insights into the prevention and management of HAND.

Keywords

HIV-Associated Neurocognitive Disorders (HAND), Pathogenesis, Clinical Diagnosis and Treatment, Neuroimaging, Neuropsychological Assessment

1. Introduction

HIV-related neurocognitive disorders (HAND) can be classified into asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) [1]. The prevalence of HAND ranges from 15% to 50% [2]. With the advent of combination antiretroviral therapy (cART), the incidence of HAD has decreased from 20% to 5%. A report from Kenya showed an overall incidence rate of 81.1% for HAND, with ANI and MND accounting for 78.6% and HAD for 2.5% [3]. In China, the prevalence of HAND is

37% in Beijing, 46.6% in Shenyang, 46.78% in Shenzhen, and 60% in Guangxi [4] [5] [6] [7]. Close correlations have been observed between HAND and factors such as disease duration, gender, age, race, education level, cardiovascular risk factors, drug use, smoking, hepatitis C, insomnia, malnutrition, and antiviral response. With the widespread use of cART in HIV treatment and extensive research, AIDS has transformed from a fatal disease to a preventable and manageable chronic illness [8]. Consequently, the life expectancy of individuals with HIV has significantly increased, leading to an increase in the incidence of non-AIDS-defining diseases. This includes an upward trend in the number of people affected by HAND, which impacts their daily functions, medical adherence, employment, driving ability, risk of HIV transmission, and overall quality of life. These challenges pose social, economic, familial, and public health concerns [9] [10]. This article provides a comprehensive review of recent developments in the etiology, clinical diagnosis and treatment, neuroimaging, and neuropsychological assessment of HAND.

2. Pathogenesis of HAND

The pathological changes in HAND result from extensive damage to the brain, spinal cord, peripheral nerves, and blood-brain barrier caused by HIV. Commonly affected areas include the basal ganglia, brainstem, deep white matter regions, frontal and temporal lobes, and hippocampal gyrus [2]. Although the mechanism of HAND is not fully understood, the main pathogenic mechanisms may be as follows [11] [12].

1) Direct neurocytotoxicity of HIV: During the early stages of infection, HIV infects CD14/CD16 monocytes as "Trojan horses" to cross the blood-brain barrier (BBB) and release the virus into the central nervous system. Infected cells activate and produce HIV proteins such as Tat, Gp120, Nef, Vpr, Env, Gp41, which bind to receptors (CCR5, CXCR4) on neuronal cells and astrocytes, leading to neurotoxicity.

2) Indirect immune-inflammatory response to HIV: HIV-infected monocyte-derived macrophages and glial cells in the brain produce cytokines like IFN-α, IL-6, IL-8, IL-1β, CD14, CD163, along with viral proteins, causing changes in BBB permeability and chronic neuroinflammatory responses that damage neuronal cells.

3) Neurotoxic side effects of anti-HIV drugs: Clinical observations have revealed that some antiviral drugs (e.g., efavirenz) have adverse effects on patients' cognitive functions. In vitro experiments have shown that these drugs can cause damage to neuronal cells [13]. Additionally, HIV can lead to central nervous system metabolic abnormalities and viral escape.

Recently, it has been discovered that cognitive impairment is associated with the gut microbiota-gut-brain axis. Alteration of gut microbiota can reduce the reservoir of HIV in the gut and potentially cure HIV [14]. The gut microbiota produces lipopolysaccharide (LPS), which causes an inflammatory environment

and damages the BBB, affecting central nervous system function [15]. HIV infection leads to changes in the diversity of gut microbiota in individuals, with enrichment or depletion of certain gut bacteria. Supplementation with probiotics can alter interferon response and improve cognitive function in HIV patients [16]. Therefore, balancing the gut microbiota to prevent inflammation can enhance cognitive abilities, which is an emerging field of research.

3. Clinical Diagnosis of HAND

Diagnosis and differential diagnosis are based on clinical manifestations, laboratory tests, neuroimaging, and primarily on the results of neuropsychological assessments. Formal neuropsychological testing is considered the gold standard for confirming a diagnosis of HAND. HAND is a primary central nervous system damage caused by HIV and is a chronic complication of the central nervous system in HIV patients. The onset is insidious and progresses slowly. Early symptoms include short-term memory impairment, slowed reaction time, lack of concentration, reading and comprehension difficulties, apathy or emotional instability. As the disease progresses, patients may experience long-term memory decline, decreased ability to recognize objects, poor expression and comprehension of language. In the later stages, symptoms such as slow hand movement, unstable gait, difficulty walking, impaired coordination, and urinary and fecal incontinence may occur [1] [17]. These nonspecific clinical manifestations are often reported by patients during the diagnostic and treatment process. Laboratory tests such as viral load and nadir CD4 count are prognostic factors for HAND [18]. Biological biomarkers such as NF-L, sCD14, sCD163, NDE, and monocytic cell HIV DNA load may also indicate the presence of HAND.

4. Neuroimaging Examination

The findings of Magnetic Resonance Imaging (MRI) in HAND include brain atrophy, enlarged ventricular volume, and increased signal diffusion in T2-weighted images in the brain's white matter. However, early and mild HAND changes may not be easily detected, making it difficult to identify ANI and MND using MRI alone. In recent years, metabolic (Magnetic Resonance Spectroscopy Metabolic Imaging, PET), structural (Diffusion Tensor Imaging, 3D T1-weighted Imaging), and functional MRI (fMRI) techniques have been used for the diagnosis and treatment assessment of HAND. These techniques provide imaging-based evidence for early diagnosis and potential mechanisms of HAND, as well as monitoring disease progression and evaluating treatment efficacy [19]. Magnetic Resonance Spectroscopy Metabolic Imaging measures the ratio of neuronal metabolites (such as N-acetyl aspartate) or inflammatory metabolites (choline or myo-inositol) to a reference metabolite (creatine), reflecting neural damage. PET can detect focal glial cell activation in the cortical regions of asymptomatic HAND patients, and quantitatively analyze the degree of glial cell activation in the brain to reflect the level of inflammation. Diffusion Tensor Im-

aging describes the microstructure of the brain's white matter by measuring the diffusion of water molecules. It is highly sensitive to detecting subtle changes in white matter microstructure, even in cases where conventional MRI appears normal. DTI has revealed widespread white matter damage in HIV patients, primarily in the corpus callosum, corona radiata, and centrum semiovale. 3D T1-weighted Imaging is another common structural imaging method that is mainly used to observe the microstructure of brain gray matter and obtain structural information about local brain regions and connectivity. It can also perform cortical thickness analysis, and in early stages of HIV infection, cortical atrophy and dilation of the third ventricle can be observed. Despite receiving cART treatment, ongoing brain volume reduction still occurs [20], and even HIV-infected individuals with normal cognition show changes in brain volume [21]. Resting-state functional Magnetic Resonance Imaging (rs-fMRI), which reflects spontaneous neural activity and activation patterns and levels in the brain during a resting state, can provide information about functional connectivity. In HIV patients, there is a decreased functional connectivity between the striatum and frontal cortex, as well as reduced functional connectivity between the precuneus and prefrontal cortex. However, HIV patients receiving cART show enhanced functional connectivity between the striatum and default mode network. Although MRI examinations have the advantages of being non-invasive, radiation-free, objective, and highly patient-compliant, there is a lack of systematic MRI studies on HAND, with small sample sizes. Further research is needed to reach a consensus.

5. Neurocognitive Psychological Assessment

Neuropsychological assessment is an important tool for diagnosing and studying cognitive impairments. There are three well-known diagnostic criteria for HIV-associated neurocognitive disorders (HAND) [11]: Frascati criteria (2007), Gisslén criteria (2011), and DSM-5 criteria (2013). The assessment covers 5 - 6 cognitive domains: attention, executive function, learning, memory, processing speed, and motor skills. Gisslén criteria are stricter than Frascati criteria, and DSM-5 criteria are more lenient than both Gisslén and Frascati criteria. The most commonly used is the Frascati criteria, which requires a clinical score in at least 2 cognitive domains to be 1 standard deviation below the mean for ANI/MND and 2 standard deviations below the mean for HAD. Conducting any of these assessments is time-consuming (about 3 hours) and requires skilled professionals, making it difficult to widely implement. There is a need to develop effective, easy-to-use, and practical screening measures for HAND, such as the HIV Dementia Scale (HDS), International HIV Dementia Scale (IHDS), Mini-Mental State Examination (MMSE), Cogstate test, Montreal Cognitive Assessment (MoCA), and Kaufman Assessment Battery for Children (KABC). Overall cognitive functioning assessment scales include Wechsler Intelligence Scale and Alzheimer's Disease Assessment Scale. For daily and social functioning assessment, there are the

Social Functioning Questionnaire and Activities of Daily Living Scale. HDS is used to differentiate HIV dementia, IHDS is suitable for MND and HAD but not ANI, MMSE is used for screening HAND, Cogstate test is sensitive for MND or HAD with sensitivity of 100% and specificity of 98%, MoCA is a screening tool for mild cognitive impairment and for evaluating HAND and its antiviral effect, as patients with cognitive dysfunction have a significantly lower immune recovery ability compared to those with normal cognitive function [5]. KABC/KABCII is used for assessing pediatric HAND [22].

6. Treatment of HAND

Treatment of HAND in HAND patients is an individualized approach based on identifying and controlling relevant high-risk factors, followed by antiviral and causal therapies. If a cure is not possible, efforts are made to delay disease progression. Currently, cART is the mainstay of HAND treatment. Research has shown that HIV-infected individuals who have undetectable viral loads for two years do not experience any cognitive or brain volume damage. Early treatment not only limits the size of the HIV viral reservoir but also slows down the progression of HAND. However, it has been observed clinically that about 10% of HIV-infected individuals achieve virologic suppression in the blood but still have low-level replication in the brain. Antiviral drugs cannot fully penetrate the blood-brain barrier (BBB) and as a result, the HIV viral reservoir persists, making it difficult to completely prevent HAND. Some approaches to address this challenge include intensified cART regimens, the establishment of Central Nervous System (CNS) penetration effectiveness (CPE) scoring systems for drugs, and Monocyte Efficacy (ME) scoring systems. High CEP scoring cART has been found to effectively reduce viral load in brain tissue, but it also increases the risk of HAND. Balancing this dilemma is crucial. It has been discovered that there is a treatment time window between HIV infection and the onset of HAND, during which cART and other interventions can achieve the maximum therapeutic effect and preserve cognitive function. This finding has significant implications for the prevention and treatment of HAND. Other adjunctive therapies include pharmacological interventions such as cholinergic drugs, excitatory amino acid receptor antagonists, antioxidants, brain metabolic enhancers, traditional Chinese medicine, and antipsychotic drugs. Minocycline, with its anti-inflammatory and neuroprotective properties, is used in the treatment of HAND. Rivastigmine can improve motor nerve speed and alleviate HAND symptoms [23]. Sodium valproate, an antiepileptic drug, improves cerebral cell metabolism and reduces cognitive impairment symptoms. Lithium therapy can improve brain imaging abnormalities in HAND. Recent analysis of pharmacological and non-pharmacological strategies suggests [24] optimizing HIV and comorbidity management. Non-pharmacological strategies, including neurostimulation techniques, exercise interventions, and computer-assisted cognitive neurorehabilitation strategies, can alleviate cognitive impairment.

7. Summary and Recommendations

HAND has become a common complication of the central nervous system in the era of cART despite advancements in HIV treatment. The pathogenesis of HAND involves the neurotoxicity of HIV proteins as well as the inflammatory response caused by the virus within the nervous system. The neurotoxicity of antiretroviral drugs and the disruption of the gut-brain axis by gut microbiota also play a role in its development. Neurocognitive testing is currently the gold standard for diagnosing HAND, and there is a need to develop simple and practical screening tools for widespread use. Diagnosis and differential diagnosis should be based on clinical manifestations, laboratory tests, neuroimaging, and other relevant tools. Identifying and controlling the high-risk factors associated with HAND is crucial, and antiretroviral therapy remains the mainstay of treatment. Individualized, early initiation of cART within the therapeutic window is the best management approach. Further research is needed to evaluate the potential benefits of adjunctive therapies in delaying disease progression.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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