HIV Associated Eye Diseases: Existing Cognitive and Possible Mechanisms

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Abstract

The Human Immunodeficiency Virus-1 (HIV-1) envelope protein gp120 is the major contributor to the pathogenesis of retinopathy and uveitis in HIV-1-related eye diseases. Disruption of the structure and function of the Blood-Retina Barrier (BRB) is the major contributor of HIV-1-related eye diseases and the molecular mechanism remains unknown. Our mini review revealed that retinopathy and uveitis are required for gp120- induced inflammation and epigenetic changes and suggest that gp120 regulate tight junction protein. Keywords: GP120; Function; Retinopathy; Uveitis

Introduction:

The human immunodeficiency virus (HIV), the cause of acquired immunodeficiency syndrome (AIDS) has infected an estimated 33 million individuals worldwide{1}. HIV is a member of the lentivirus genus, part of the Retroviridae (retrovirus) family{2}. HIV is associated with immunodeficiency, neoplasia and neurological disease.

The development of an identifiable neurological syndrome in an HIV infected person is the culmination of a chain of events, determined by properties of HIV itself, genetic characteristics of the host, and interactions with the environment (including treatment). HIV-associated neurological syndromes can be classified as primary HIV neurological disease (in which HIV is both necessary and sufficient to cause the illness), secondary or opportunistic neurological disease (in which HIV interacts with other pathogens, resulting in opportunistic infections ((OI)) and tumors), and treatment related neurological disease (such as immune reconstitution inflammatory syndrome or IRIS).

HIV is neuroinvasive (can enter the central nervous system ((CNS)), neurotrophic (can live in neural tissues), and neurovirulent (causes disease of the nervous system){2}. Presumed mechanisms of CNS invasion include the "Trojan horse" mechanism in which HIV-infected monocytes are admitted by the blood-brain barrier and mature into long-lived, persistently infected perivascular macrophages; infection of the choroid plexus; and direct infection of capillary endothelial cells, among others. HIV-infected cells include capillary endothelium, microglia, monocytes, macrophages, astrocytes, and choroid plexus {3}. Neurons and oligodendrocytes are rarely, if ever, infected (although this is still under discussion), and "indirect" mechanisms are postulated to account for most damage {4}. There is a burst of viral replication in primary infection, followed by an aggressive immune response that declines over time, and by a long period of subclinical infection, followed by recrudescence of disease, and death {2}. Persistent infection and inflammation results in blood-brain barrier breakdown, neuronal and axonal injury, neurotoxicity, and clinical symptoms; damage to the immune system, particularly cell-mediated immunity, results in vulnerability to OI.

In addition to its importance as a cause of neurological problems, HIV infection of the CNS constitutes a serious barrier to management and eradication of the virus. The CNS is incompletely permeable to antiretroviral drugs, resulting in subtherapeutic levels of many antiretrovirals {5}; it is part of a protected reservoir {6} (along with the gut and several other organs), where HIV can evade the immune system; and it provides an environment where HIV can replicate, mutate, and re-infect the circulation. HIV stimulates a persistent inflammatory response that may activate pathways leading to other neurodegenerative diseases

Acute HIV infection is the period from initial infection to complete seroconversion. During this time 40-90% of individuals describe physical symptoms, similar to influenza, or mononucleosis. The most common features include a short period of fever, lymphadenopathy, night sweats, headache, and/or rash {8, 9}. Early CNS infection is usually asymptomatic, but cerebrospinal fluid (CSF) {10} and imaging studies {11} can detect abnormalities even during the "asymptomatic" period that presage later neurological events.

A minority of sero converters will experience a neurologic event that brings them to medical attention, such as aseptic meningitis, Bell's palsy {12, 13}, or inflammatory neuropathy. Individuals with symptomatic neurological disease tend to have higher CSF HIV levels than those without. Neurological symptoms may occur before an HIV diagnosis is suspected, e.g., before there are sufficient HIV antibodies to produce a positive HIV enzyme-linked immunosorbent antibody (ELISA, also called an HIV enzyme immunoassay). In such cases, a Western Blot or a polymerase chain reaction (PCR) test for HIV may lead to the diagnosis. Early diagnosis of acute HIV infection is important, as these individuals are at high risk to transmit the virus.

The most common neurologic syndrome associated with primary HIV infection is an acute aseptic (viral) meningitis or meningoencephalitis. The symptoms are similar to other viral meningitides, with fever, headache, stiff neck, and photophobia. Cerebrospinal fluid (CSF) shows a mild lymphocytic pleocytosis, normal or slightly elevated total protein, and normal glucose {14}. HIV may be detectable by antigen or PCR testing {15}. Most individuals will recover with supportive care. A few will have recurrent bouts.

Information on the management of HIV aseptic meningitis is limited to case reports. Initiating treatment with cART, or

changing and intensifying the regimen to include more CNS-penetrating drugs, may suppress the symptoms {16}. Others have recurrent meningitis when they stop combined antiretroviral therapy (cART), e.g. during structured treatment interruptions

Immune reconstitution inflammatory syndrome (IRIS)

The immune reconstitution inflammatory syndromes (IRIS) is a serious problem complicating the treatment of AIDS{183}. It refers to a group of syndromes characterized by paradoxical clinical worsening that usually occurs within the first four to eight weeks after starting cART {155}. The reconstituted immune system generates an inflammatory response, resulting in either a worsening of a known, underlying infection, or the unmasking of a subclinical, indolent infection. This exaggerated "dysregulated" inflammatory response is characterized by massive infiltration of CD8+ cells. Neuroimaging features include development of, or increase in, contrast enhancement, and unusual patterns of contrast enhancement {184}. Intracranial pressure may rise {185}, requiring the use of corticosteroids. Among the most common CNS infections reported to be involved in IRIS are HIV encephalitis {186-188}, TE {187, 189}, CM {185}, and PML {184} {155}. Risk factors for IRIS include taking cART for the first time, active or subclinical OI, CD4+ counts under 50 cells/mm3, high CD8+ cells, anemia, and a rapid decline in HIV viral load {190, 191}. There are relatively few biopsy or autopsy studies of IRIS, in part because most patients survive the syndrome. Some studies have reported both active lesions containing the pathogen (HIV-associated multinucleated giant cells, JCV, Toxoplasma parasites, etc.), and "sterile" lesions with inflammatory infiltrates. The treatment of CNS IRIS with corticosteroids has been advocated and remains controversial, as there are no formal studies, but should be considered if increased intracranial pressure is present.

The continuing evolution of the HIV epidemic has spurred an intense interest into a hitherto neglected area of medicine, neuroinfectious diseases and their consequences. This work has broad applications for the study of CNS tumors, dementias, neuropathies, and CNS disease in other immunosuppressed individuals.

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