HIV in Cerebrospinal Fluid and Central Nervous System

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Introduction
It is believed that HIV in humans originated in Congo basin in 1920 when it crossed from chimpanzees to humans. In 1981 first few cases of AIDS were reported from New York and California with presentation of PCP pneumonia and Kaposi sarcoma. Since then patients presented with all sort of signs and symptoms and amongst them neurological clinical features dominate. It includes HIV-associated neurocognitive disorders (HANDs), and HIV-sensory neuropathy (HIVSN). These patients are also prone for various CNS infections like tuberculosis, cryptococcal meningitis, cytomegalovirus infection and primary CNS lymphoma.

Transmission
HIV-1 traverses the blood brain barrier (BBB) within few days of primary infection, and it replicates within macrophages, perivascular microglia and astrocytes. One study reported CNS invasion in 18 patients by HIV as early as 8 days after infection with mean duration of transmission of 14 days. 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 inflammation of the choroid plexus. Although HIV does not directly invade neurons, it can be affected indirectly through HIV-infected macrophage and microglia cells with release of pro inflammatory cytokines. Basal ganglia, frontal cortices, and subcortical white matter are the main injury sites of HIV.

Furthermore, CNS suffers volume loss despite the use of ART, suggesting irreparable damage or ongoing injury. This CNS damage occurs irrespective of immunosuppression.

The BBB is composed of endothelial cells that selectively restrict the transport of cell components and macromolecules from the systemic circulation to the CNS. CNS cells do not have proteins with immunological properties such as MHC class I and II. And it lacks a lymphatic system.

ART and Neurocognitive Function
Determining the HIV viral load in the CSF is important for monitoring the therapeutic effects of ARV treatment and for identifying patients with CNS escape (compartmentalization). With the introduction of ART, there is decreased CNS-related morbidity and mortality but neurologic disease still remains a persistent burden for many patients. In one large study from Alberta, Canada, 24.5% of 1653 HIV positive patients had neurologic complications of HIV (distal-sensory polyneuropathy in 10% and HIV-associated neurocognitive disorders in 6.2% of cases). 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. Nadir CD4 count and current viral load are the risk factors for the development of HAND. And sometimes HAND may be refractory to ART. In Italian cohort, after a mean of 63 months of ART, 62.8% patients had persistent neurocognitive impairment, despite the good virologic suppression.

Few infections like neurosyphilis increases the HIV viral load in the peripheral blood and CSF.

Compartmentalization
Blood-brain barrier (BBB), rapid mutation, recombination of HIV, and poor ARV drugs penetration in CNS contribute to the compartmentalization of HIV. CNS penetration-effectiveness (CPE) score is different for different ART regime and the drug with higher CPE scores are associated with good HIV-1 viral suppression in CSF and improved neuropsychological performance.

CNS is an immunologically privileged site and it serves as an important reservoir for HIV. Other than CNS, genital tract, and gastrointestinal lymphoid tissue are also site for HIV viral reservoirs that allow HIV to persist despite good and active ART regime which may eliminates the virus from the peripheral blood. Despite the effective suppression of viremia with ART, HIV can still replicate

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in the CNS, with the development of resistant strains in the CNS with or without neurological manifestations. CSF Viral load of >200 copies/mL and plasma viral load is <50 copies/mL in a same patient is accepted as compartmentalization 

**Mutations**

The neurological symptoms of HIV changed with the introduction of highly active ART. The main objective of ART is to suppress HIV replication in all cells and tissues. Incomplete suppression of the virus in the CNS is mainly due to poor penetration of ART drugs in the CNS and it promotes resistance to ARV drugs. Both these mechanisms allow the resistant virus to redistribute to CNS and non-CNS tissues. Mutation with high error rate (0.2–2 mutations per genome per cycle) and recombination are the factors responsible for genetic diversity of HIV and the HIV-1 pandemic.

Article published in this issue by A.D. Mathur and, Devesh S. also suggest that neuropsychological manifestations are associated with high CSF viral load.

**References**