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EVALUATING HUMAN IMMUNODEFICIENCY VIRUS (HIV) NEUROPATHOGENESIS ON HIV-ASSOCIATED NEUROCOGNITIVE DISORDER (HAND): ROLE OF VIROLOGY, CELLULAR AND IMMUNOLOGY ASPECTS

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Abstract

Human Immunodeficiency Virus (HIV) became a worldwide pandemic with a global prevalence of 36.9 million in 2014. One of the neurological complications of HIV infection is HIV-associated neurocognitive disorder (HAND). The administration of antiretroviral (ARV) therapy to HIV patients in general contributed to lowering HIV mortality and morbidity. However, ARV therapy did not provide complete protection for neurons. The cumulative prevalence of severe HAND in the lifetime of HIV patients is estimated to be 15%. HAND is classified into three categories: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). HAND remains a significant cause of morbidity in HIV patients. Recent findings on research using animal models have shown new concept development, both viral and cellular-related, on HAND neuropathogenesis, including other clinical factors contributing to HAND progression. Factors contributing to HAND neuropathogenesis consist of the cellular aspect, shown by the role of macrophages and astrocytes, and the viral aspect, shown by the role of neurotoxic HIV proteins and inflammatory molecules. HAND progression comprised chronic neuroinflammation, postsynaptic density decrements, and neurogenesis impairment. A better understanding of HAND neuropathogenesis will increase the optimization of HAND therapy.

Keywords: HIV-associated neurocognitive disorder, cellular, viral, inflammation

Introduction

Human Immunodeficiency Virus (HIV) infection had become a worldwide pandemic with a global prevalence of 36.9 million in 2014 (Estiasari et al., 2015; Organization, 2016). By 2009, an estimated 186,000 people in Indonesia live with HIV (Ministry of Health of Republic of Indonesia – Directorate General of Disease Control and Environmental Heath, 2011). One of the neurological complications of HIV infection is HIV-associated neurocognitive disorder (HAND). A cohort research found a 50% prevalence of HAND in Indonesia ART naive patients (Estiasari et al., 2015). HAND severely affects the quality of life and everyday functioning of HIV patients and remains a significant cause of morbidity (Saylor et al., 2016).

The current ARV therapy has not been particularly effective in lowering HAND prevalence. The blood-brain barrier (BBB) lowers ARV penetration to the central nervous system. Perivascular macrophages and microglia serve as HIV reservoirs, persistent replication locations, and HIV targets in the central nervous system (Lindl et al., 2010) (Rockstroh et al., 2016) (Zipursky et al., 2013). A comprehensive understanding of HIV-

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associated neuropathogenesis is required for satisfactory HAND management, which serves as the development basis of optimum HAND treatment in the future.

HIV-Associated Neurocognitive Disorder (HAND)

HIV-associated neurocognitive disorder (HAND) is used to describe the spectrum of neurocognitive dysfunction associated with HIV infection (Saylor et al., 2016). HAND is classified into three (3)

Neurocognitive dysfunction spectrums: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD), as shown in Table 1 (Hoffmann and Rockstroh, 2012; Saylor et al., 2016).

Table 1. Classification of HAND (Antinori, 2007)

HAND Type*	Prevalence in CART-treated HIV patients	Diagnostic xriteria
Asymptomatic neurocognitive impairment (ANI)	30%	Impairment in ≥2 neurocognitive domains (≥ 1SD) Does not interfere with daily functioning
Mild neurocognitive disorder (MND)	20-30%	Impairment in ≥2 neurocognitive domains (≥ 1SD) Mild to moderate interference in daily functioning
HIV-associated dementia (HAD)	2-8%	Marked (≥ 2SD) impairment in ≥2 neurocognitive domains Marked interference in daily functioning

Research Method

This study utilizes a descriptive, qualitative approach to explore the neuropathogenesis of HIV-associated neurocognitive disorders (HAND). The research focuses on understanding the virological, cellular, and immunological aspects contributing to HAND progression (Organization, 2018). By analyzing existing literature and recent findings, the study identifies critical pathways and mechanisms associated with HAND neuropathogenesis, specifically within the framework of inflammation, neuronal damage, and neurodegeneration (Tedaldi et al., 2015).

Literature Review, A comprehensive review of scholarly articles, clinical studies, and case reports on HAND pathogenesis is conducted. This review aims to gather insights into the roles of HIV virology, cellular mechanisms (macrophages, astrocytes), and immune responses (*cytokines and chemokines*) in HAND development. Identification of Key Factors, the study categorizes HAND-related neuropathogenic factors into three main aspects (Salawati, 2020). Virological Aspect: Examines the impact of HIV proteins, such as gp120 and Tat, which contribute to neurotoxicity by disrupting neuronal signaling pathways. Cellular Aspect: Investigates the involvement of macrophages and astrocytes in propagating HIV infection within the central nervous system, contributing to chronic neuroinflammation. Immunological Aspect: Focuses on the role of inflammatory molecules in exacerbating neuronal damage and synaptic dysfunction (Zayyad & Spudich, 2015).

Data collected from the literature are analyzed to identify patterns in the mechanisms underlying HAND neuropathogenesis. The analysis focuses on the interactions between virological factors and host immune responses, with an emphasis on how these interactions contribute to HAND progression. The study employs secondary data sources from peer-reviewed journals and clinical studies. The data collection process includes Document Analysis: Reviewing documented cases and studies to identify key elements of HAND pathogenesis. Comparative Analysis: Comparing data across studies to validate findings and recognize trends in HAND progression and neuropathology. Findings are synthesized through thematic analysis to illustrate the interplay between HIV virology, host cellular responses, and immune-driven inflammation in HAND. By focusing on the cumulative effects of these factors on neurodegeneration, the study provides a deeper understanding of the mechanisms driving HAND progression.

Result and Discussion.

HAND Neuropathogenesis

HAND neuropathogenesis comprises three main aspects: cellular, viral, and proinflammatory molecules. From a cellular aspect, the brain's macrophage and astrocyte cells play the most significant role. Viral-related aspects mainly shown by the significant role of neurotoxic HIV proteins in triggering chronic inflammation of the central nervous system, such as gp120, Tat, and Vpr. Meanwhile, proinflammatory molecules manifested in chemokine and cytokine resulted from macrophage and microglia triggering a cascade of inflammation. All three factors will induce decrement of postsynaptic density and neurogenesis, resulting in neuronal apoptosis (Figure 1).

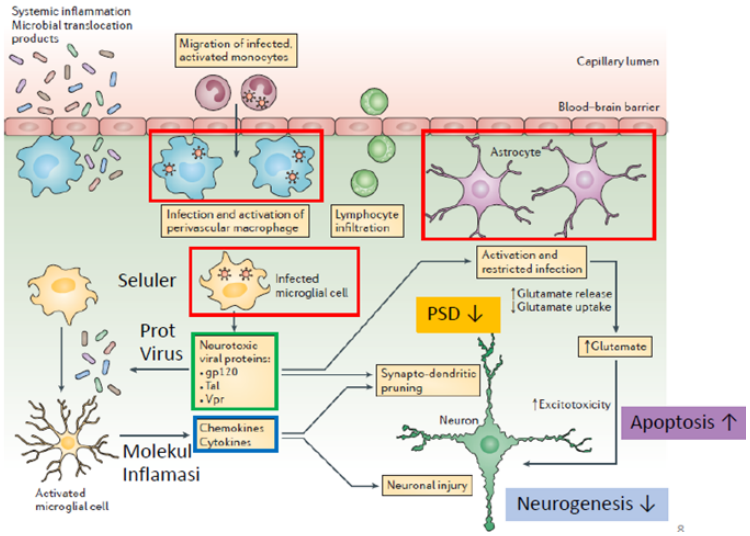

Figure 1. Neuropathogenesis contributing to HAND.

The role of cellular aspect, HIV serology, and pro-inflammatory molecules in HAND neuropathogenesis. Cellular factor (red box) was mainly played by macrophages and astrocytes in the brain. The HIV virology factor (green box) was played by the viral protein. The pro-inflammatory molecule factor (blue box) was mainly chemokines and cytokines. Those three factors would decrease synapse density and neurogenesis, resulting in neuron apoptosis (Saylor et al., 2016).

The Role of Cellular Aspect in HAND Neuropathogenesis

The virus infiltrates the central nervous system via infected macrophages, which occasionally migrate into the brain to replace the perivascular microglia (Harris & Harris, 2015). HIV-1 infiltrated BBB soon after initial infection using the "Trojan Horse" method, utilizing infected monocytes to invade the brain. HIV-1 infection then increases the adherence of monocytes to endothelial cells, increasing their transmigration across the BBB. The HIV-infected macrophages in the vicinity of the BBB secrete inflammatory cytokines and viral products that damage HBMECs, induce cellular oxidative stress and produce chemokines like CCL2 that facilitate the build-up of additional immune cells near the barrier. The interplay between the secreted cytokines, viral products, and HBMECs activates endothelial cells and increases surface expression of adhesion molecules on endothelial cells – which in turn accelerates the transmigration of infected macrophages across the BBB. HIV-1 proteins, both Tat and gp120, directly damage the BBB (Figure 3). Brain endothelial cells exposed to HIV-1 Tat have been shown to alter the expression and distribution of zonula occludens proteins (claudins & occludins). In vitro two-chamber models with HBMECs and astrocytes have also shown HIV-1 Tat causes dysregulation of nitric oxide production in brain endothelial cells and induces secretion of CCL2, a key chemokine responsible for migration of immune cells. Kanmogne et al. demonstrated, using a two-chamber BBB model, that the exposure of HBMECs to recombinant HIV-1 gp120 protein (from either X4 and R5 HIV-1 isolates) led to activation of proinflammatory and interferon-inducible genes, increased leukocyte adhesion, decreased trans-endothelial electrical resistance (TEER) and increased migration of monocytes across the barrier. Removal of gp120 resulted in complete restoration of TEER and significant improvement in permeability. Exposure of HBMECs to gp120 in vitro resulted in increased expression of adhesion molecules (ICAM and VCAM), damage to the barrier, and a consequent increase in monocyte migration across the monolayer of endothelial cells (Rao, Ruiz, and Prasad, 2014).

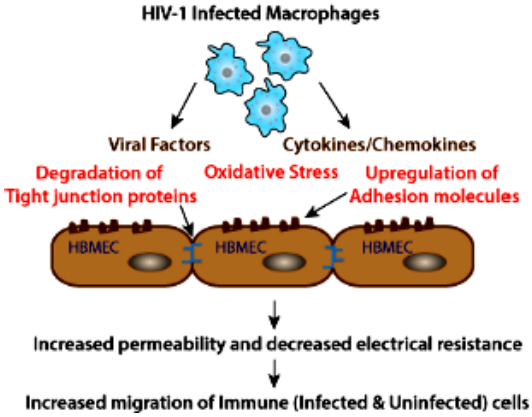

Figure 2. HIV invasion in the blood-brain barrier.

HIV-infected immune cells released viral, toxic products and inflammatory cytokines, causing degradation of tight junction proteins, oxidative stress, and up-regulation of adhesive molecules. This caused increased blood-brain barrier permeability and immune cell migration via blood-brain barrier (Rao et al., 2014).

The Role of Macrophage/Microglia

The process of HIV-1 infection begins by HIV-1 binding to the CD4 receptor on the target cell surface through the viral envelope protein gp120. This binding induces a conformational change in gp120 that exposes a CD4-binding induced (CD4i) co-receptor binding site, subsequently binding to either CCR5 or CXCR4 co-receptor. The binding of gp120 to a co-receptor then exposes the fusion peptide in viral protein gp41, which is inserted into the cell membrane and drives fusion of the viral and cell membranes. HIV-1 can productively infect both CD4+ T lymphocytes and monocytic cells/macrophages. Infection of monocytic/macrophage cells is primarily by M-tropic viruses driving fusion through the CCR5 co-receptor. Still, infection by T-tropic viruses through the CXCR4 co-receptor has also been observed. While HIV-1 can also infect dendritic cells, these cells do not support robust HIV-1 replication. However, they do play a crucial role in the systemic spread of HIV-1 due to their strategic presence in lymph nodes. HIV infection leads to a progressive decline in the population of CD4+ T cells, which is due to the loss of both infected CD4+ T cells and uninfected cells (bystander killing) (Rao et al., 2014).

HIV-1-infected macrophages and microglia release neurotoxic host factors contributing to neuronal injury. The proinflammatory cytokines induced by HIV-1 infection of macrophages include TNF-α, IL-1β, IL-6, IL-8, and IFN-α. TNF-α has also been shown to inhibit glutamate uptake by astrocytes, leading to an extracellular buildup of glutamate that can lead to neuronal excitotoxicity. IL-1β is released from macrophages in response to protein kinases induced by gp120, and both IL-1β and TNF-α were found to dysregulate glutamate production in neurons through the induction of glutaminase. IL-6 is also directly induced in macrophages by gp120, leading to large cytoplasmic vacuoles in neurons that disrupt neuronal function. Excess levels of IFN-α have been correlated with the severity of HIV dementia. In addition to inflammatory cytokines, small molecules released by HIV-1-infected macrophages, such as platelet-activating factor (PAF) and quinolinic acid, play a key role in neurotoxicity via NMDAR dysregulation (Rao et al., 2014).

The Role of Astrocytes: no longer a passive, non-participating component

Astrocytes play a dynamic role by integrating neuronal inputs and modulating synaptic activity. It has been recently shown that HIV-1 can infect astrocytes in vitro and, additionally, that, infected astrocytes can impair BBB function. Recombinant Tat protein is responsible for the induction of chemokines, cytokines, and nitric oxide synthetase in cultured primary human astrocytes. Furthermore, Tat has been shown to induce astrocytes to produce platelet-derived growth factor BB (PDGF-BB), which in turn causes the production of CCL2. HIV-1 Tat can also up-regulate the expression of MMP-9 via the MAPK-NfκB-dependent mechanism, and MMP-9, in turn, disrupts the BBB (Rao et al., 2014).

Exposure of astrocytes to gp120 causes upregulation of IL-6 and TNF-α and increases the release of glutamate and potassium, which leads to toxic increases in calcium in neurons and astrocytes. Using Affymetrix microarray analysis, Wang et al. showed that primary human astrocytes when exposed to HIV-1 or gp120 in vitro, have an impaired ability to transport L-glutamate, and the authors ascribed this defect to transcriptional inhibition of the EAAT2 glutamate transporter gene. More recently, Fernandes et al. have used an animal model to show that gp120 prevents the uptake of extracellular glutamate by astrocytes, leading to a disruption of glutamate-glutamine homeostasis and a consequent impairment of memory. Release of toxic cytokines,

inability to take up excess glutamate, and damage to the BBB make astrocytes a central offender in the pathogenesis of HAND (Rao et al., 2014).

The Role of Viral Aspect in HAND Neuropathogenesis: Neurotoxicity mechanism of gp120 and Tat

The two main viral proteins that interact with receptors causing neuronal injury are gp120 and Tat. HIV-1 gp120 directly binds NMDAR on human embryonic neurons and can cause a lethal influx of calcium ions (Figure 4). HIV-1 gp120 can bind to either CCR5 or CXCR4 and induce death in neuroblastoma cells. This apoptosis takes place through a p38-MAPK-mediated signaling cascade. The natural ligands of both CCR5 (eg. CCL5, CCL3) and CXCR4 (CXCL12) were neuroprotective against gp120 neurotoxicity. However, CXCL12 displays neurotoxicity after the N-terminal cleavage of a tetrapeptide in CXCL12 by MMP-2. Another factor upregulated by the interaction of gp120 with CXCR4 is the neuronal nicotinic receptor α7, which increases cellular permeability to [Ca^{2+}] influx and contributes to cell death (Rao et al., 2014).

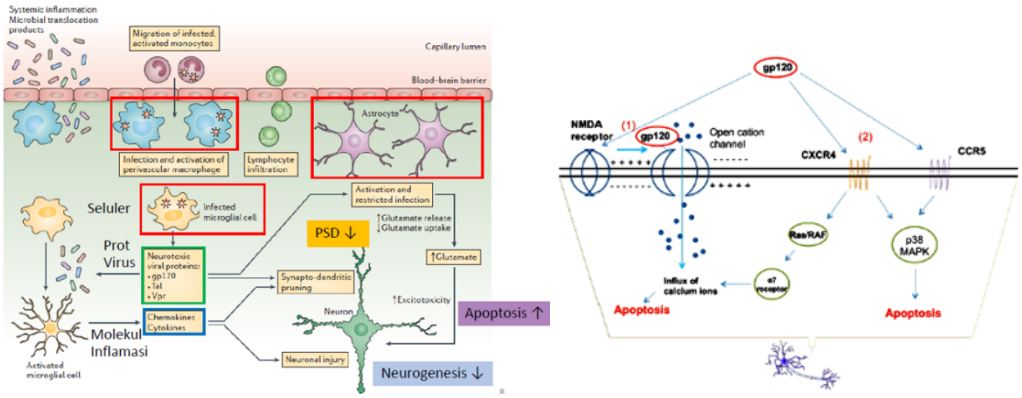

Figure 3. Gp120 neurotoxicity mechanism.

(1) Gp120 could bind to NMDA receptor and caused excess opeing of NMDAR-gated cation channels, causing calcium ion influx in toxic level. (2) Gp2 could bind to CCR5 or CXCR4 directly, activating p38-MAPK mediated signaling cascade that eventually result in neuronal apoptosis. The binding of gp120-CXCR4 could also up-regulate the nicotinic receptor expression α7, increasing the cellular permeability to Ca^{2+} influx and causing cell death (Rao et al., 2014).

(2) The viral protein Tat also causes neurotoxicity via multiple pathways. Like gp120, Tat can activate NMDA receptors and drive the toxic influx of Ca^{2+} ions. In addition to calcium dysregulation through the NMDAR, Tat can induce the phospholipase C-driven activation of inositol 1,4,5-triphosphate, which increases the intracellular levels of [Ca^{2+}] by mobilizing stores in the endoplasmic reticulum and contributes to calcium toxicity and cell death. Tat also binds LRP in neurons, causing LRP internalization and decreased uptake of natural LRP ligands such as amyloid-β peptide and Apolipoprotein E (Figure 5) (Rao et al., 2014).

The interaction of Tat with LRP can lead to the formation of an apoptosis-promoting complex, including postsynaptic density protein-95 (PSD95), NMDA receptors, and neuronal nitric oxide synthase (nNOS). Tat has been found to interfere with the expression of miRNAs in neurons, increasing the levels of CREB-targeting miR-34a and leading to neuronal dysfunction. Tat can also interfere with the ability of dopamine transporter to reuptake dopamine. This likely contributes to the particularly severe damage rendered to dopaminergic-rich regions in the brains of patients with severe HAND (Rao et al., 2014).

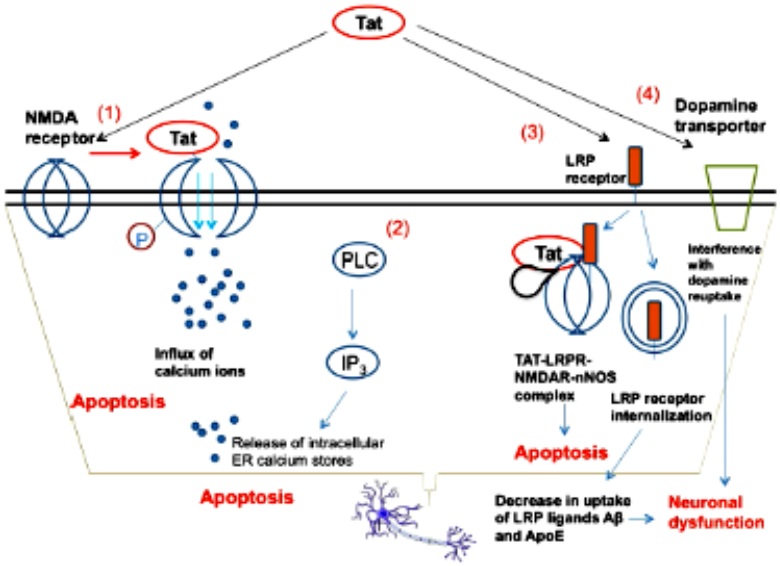

Figure 4. Tat neurotoxicity mechanism

(1) Tat bound with NMDA receptor and caused fosforilaztion of intracellular NMDAR subunit, causing excessive opening of cation canal and calcium accumulation. (2) In neurons, Tat could induce PLC activation and cause intracellular calcium release mediated by IP3 from endoplasmic reticulum, causing calcium toxicity and apoptosis. (3) Tat could bind to the LRP receptor and joint to be a part of the macromolecular complex, including NMDAR and neuronal nitric oxide synthase (nNOS) that induce cellular apoptosis. Tat could also cause internalization of LRP receptor, decreasing the uptake from LRP receptor ligands amyloid-β peptide and apolipoprotein E, which could contribute to systemic neuronal dysfunction. (4) Tat inhibited dopamine transporter activity, prevented dopamine reuptake by pre-synaptic neurons, and altered signal transmission (Rao et al., 2014).

Other toxic viral proteins that have been found to activate caspases in neurons include Vpr and Nef. Vpu has been found to form cation-selective ion channels in a lipid bilayer membrane, though this effect has not been observed in neurons. Recently, stress pathways and accumulation of amyloid beta (Aβ) fibrils have been reported to be important in causing neuronal dysfunction. It has been suggested that an integrated stress response (ISR) pathway involving specific ISR proteins may underlie the neuroinflammatory processes observed in HAND. It has also been reported that individuals with HIV encephalitis display higher levels of intraneuronal Aβ accumulation in comparison with controls, suggesting that HIV impacts the clearance of Aβ in the brain (Rao et al., 2014).

The Role of Immune-Related Aspect in HAND Neuro-pathogenesis: Inflammation-Induced Neuronal Damage

In general, inflammation induces neuronal damage in three (3) pathways: chemokine/ cytokine effects, excitotoxicity, and oxidative stress.

Chemokine/cytokine effects

Studies have found elevated levels of the α-chemokines, CXCL10/P-1o and CXCL12/SDF-1α, in the brains and CSF of HAD patients. α-chemokines, which are expressed in many types of CNS cells even under normal conditions, bind CXCR

chemokine receptors, can have both neuroprotective and neurotoxic effects. CXCL12 can act to either enhance synaptic transmission or activate caspase-3. When cleaved by matrix metallic proteinases, CXCL12 changes its receptor specificity from CXCR4 to CXCR3, enhancing this chemokine's neurotoxic functions. Similarly, CXCL10, which acts through CXCR3 without prior proteolytic cleavage, induces an increase in intracellular calcium and activation of caspase-3 upon binding to its receptor (Lindl et al., 2010).

β-chemokines are found at increased concentrations in the CNS following HIV infection: CCL2, MIP-1α, MIP-1β, and RANTES/CCL5. β-chemokines act through CCR receptors, and, as with α-chemokines, they are capable of both neuroprotective and neurotoxic functions in the brain. CCL5, MIP-1α, and MIP-1β all protect against gp120-induced neurotoxicity in vitro. Contrarily, CCL2 is associated with an increased risk of HAND, which may be due to the role of this chemokine in the brain as a monocyte chemoattractant. Furthermore, microglia activated by interferons and astrocytes activated by IL-1β and TNF-α express CCL2. Thus, β-chemokines may contribute to neuronal toxicity via existing pathways that are overstimulated by higher-than-normal concentrations of these factors (Lindl et al., 2010)

Elevated levels of fractalkine/CX3CL1 have also been observed in the CSF of HAND patients. CX3CL1, a member of the CX3C family of chemokines, binds to endothelial cells and mediates monocyte attachment, potentially increasing monocyte migration across the BBO and into the CNS, further increasing inflammation in the brains of patients with HIV infection (Lindl et al., 2010).

Excitotoxicity

Excitotoxicity is a process where excess levels of an excitatory neurotransmitter or other agent evoke prolonged periods of neuronal membrane depolarization, thereby increasing calcium (Ca^{2+}) levels and consequently activating proteases, endonucleases, and other enzymes that damage cellular components. The most common form of excitotoxicity in the CNS is glutamate excitotoxicity, mediated by the NMDAR, a voltage and ligand-gated calcium ion channel that generates excitatory postsynaptic currents through calcium influx into the neuron. In the HIV-infected brain, activated and infected macrophages release excitotoxic molecules that act upon the NMDAR, including released glutamate, QUIN, and the neurotoxic amine, N-Tox, and, therefore, may evoke damaging periods of NMDAR activation. Furthermore, activated macrophages release factors that act paracrine to stimulate reactive CNS cells (Lindl et al., 2010).

Outwardly rectifying currents shape the action potential, interspike interval, and afterhyperpolarization, and act to determine overall membrane excitability. Prolonged exposure to glutamate evokes NMDAR-mediated excitotoxicity, but how outwardly rectifying channels are modulated in response to such stimuli is not fully understood. These changes in ion channel biophysics are ultimately damaging to the neuron in the long term because equilibrium likely favors a more depolarized voltage, thus depleting energy stores and maintaining continual activation of ion channels and calcium-dependent enzymes (Lindl et al., 2010).

Oxidative stress

Oxidative stress is a specific effect of both inflammation and excitotoxicity. Changes in cellular lipid metabolism that occur due to oxidative stress produce characteristic molecules, such as ceramide, sphingomyelin, and hydroxynoneal, all of which are found in patients with HAND. HIV proteins may directly increase oxidative

stress to neurons by inducing mitochondrial dysfunction and through interactions with membrane or cytosolic-bound proteins. This finding implicates oxidative stress as an essential mode of neuronal death in the indirect model of HAND neurodegeneration

Consequences of Chronic Neuroinflammation on HAND Neuropathogenesis

The pathways of neuronal damage described above are often considered the "classical" or "central" pathophysiologies of HAND. However, new studies have highlighted other consequences of neuroinflammation in HIV-infected and HAD patients that, when observed in the light of physiological mechanisms, become increasingly important in the study of disease progression. The two main types of chronic neuroinflammation in HAND neuropathogenesis are synaptic disruption and impairment of neurogenesis (Lindl et al., 2010).

Synaptic Disruption

Activation of calcium-dependent proteases that disrupt the postsynaptic density (PSD) is a likely mechanism by which synapses may be altered in the HIV-infected CNS. The endoplasmic reticulum, which extends into the dendritic spine, contains IP3 receptors that are tethered to mGluR and NMDARs by a complex of adaptor proteins, including Shank, GCAP, Homer, and PSD-95. IP3-mediated calcium influxes are thought to play a role in LTP. However, prolonged synaptic depolarization and IP-mediated signaling can also activate calpain proteases that can cleave PSD-95, releasing it from NMDAR. This could cause a large-scale decoupling of the postsynaptic complex from IP3-receptors. Interestingly, PSD-95 loss is also a distinctive sign of neurodegeneration.

Hence, uncoupling or disruption of the PSD may be an important step in synaptic dysfunction and damage. Thus, inhibition of IP3-mediated calcium currents may prevent calpain or other protease activation and block kinase enzymes from phosphorylating and modulating Kv channels (Lindl et al., 2010). A summary of synaptic/cellular neurotoxic pathways and synaptic damage is presented in Figures 6 and 7 to illustrate the complexity of the pathological mechanisms evoked by CNS HIV infection.

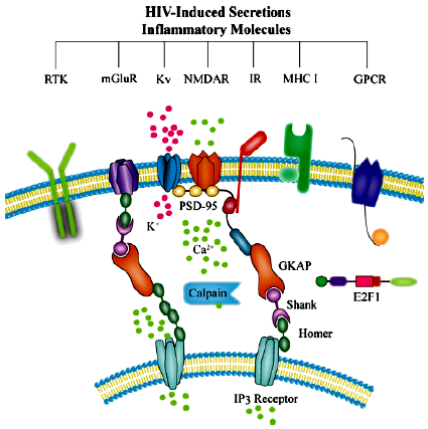

Figure 5. Toxicity pathway induced by HIV-related factors

Inflammatory molecules released by microglia or macrophage and astrocyte-triggered NMDAR activation, metabotropic glutamate receptors (mGluR), receptor tyrosine kinases (RTK), voltage-gated potassium channels (Kv), G-protein-coupled receptors (GPCR), and major histocompatibility complex subtype 1 (MHC-1) receptor. Excessive calcium influx caused by the intracellular release by IP3 receptor caused

activation of calpains and the other calcium-dependent protease, which could divide post-synaptic proteins such as PSD-95, causing synapse dysfunction (Lindl et al., 2010).

Impairment of Neurogenesis

Recent studies have shown that adult neurogenesis (ANG) disruption is significantly involved in HAND and other neurodegenerative diseases. HIV infection induces several processes by which ANG could be interrupted. HIV-induced alteration of general astrocyte function, including the trophic support these cells provide for both mature and immature neurons, may impair the proliferation and migration of NPCs and immature neurons along their migratory route (Figure 8). Under this hypothesis, the olfactory bulb (OB), the most distant structure along the RMS, would be affected first in the earliest stages of the disease. Not surprisingly, cell cycle machinery plays a role in regulating the fate of NPC. Interestingly, cell cycle proteins, such as the transcription factor, E2F1, and its regulator, the retinoblastoma gene product, exhibit increased levels and altered expression patterns in Alzheimer's Disease (AD), Parkinson's, and HAND postmortem tissue (Lindl et al., 2010; Sereia et al., 2012).

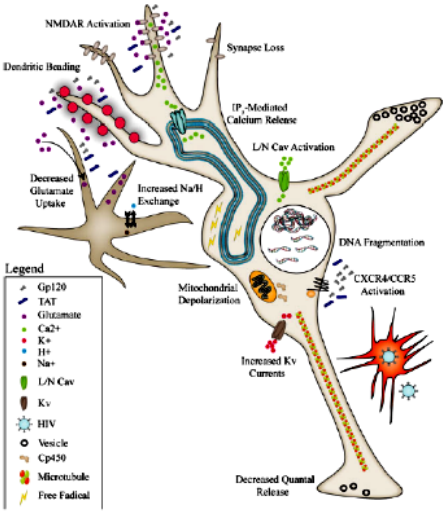

Figure 6. The process caused by HIV infection in the brain which alters the functions and survival of neurons

Glutamate excess from extracellular fluid released from astrocytes caused excitotoxic mechanisms, such as dendritic breading, continuous NMDAR activation, increased calcium influx, and increased intracellular calcium release. In the end, this process altered the post-synaptic density and synapse loss. Viral protein (gp120 and TAT) activated chemokine receptors (CXCR4 and CCR5) and increased voltage-gated calcium channel (Cav) and potassium channel (Kv), causing the activation of cellular death pathway that resulted in mitochondria depolarization, cytochrome p450 release, and DNA fragmentation related to apoptosis. Viral protein also increased Na+/H+ exchange, which resulted in astrocyte pH incline, glutamate release, and glutamate reabsorption decline, which in turn caused excitotoxic damage (Lindl et al., 2010).

Similar with the role of these proteins in altered neurogenesis, mice carrying a gene-targeted deletion of E2F1 display substantially reduced ANG in the OB and hippocampus. Furthermore, doublecortin (DCX), a microtubule protein expressed in immature neurons, has several promoter sites regulated by cell cycle proteins, including the E2F consensus

site. Thus, altered E2F1 function and consequent disruption of DCX in HAND may cause an interruption in ANG, thereby contributing to the pathogenesis of these HIV-associated disorders. The CNS relies heavily on plasticity. Hence, the disruption of ANG and its molecular regulation could yield devastating consequences for circuits and brain regions assaulted by HIV-induced toxicity (Lindl et al., 2010).

Another mechanism by which HIV could impair ANG is the perturbation of metabolism and associated insulin signaling pathways. Insulin in the brain enhances working memory, promotes neuronal survival, and regulates reproduction via the hypothalamic-pituitary axis. This hormone acts as a neuromodulator by affecting synaptic plasticity and neurotransmitter release. Several lines of evidence suggest that insulin and insulin-like growth factor (IGF) are very important in ANG. Hippocampal neural progenitor cells express the insulin receptor (IR) and IGF-1 receptors, and insulin and IGF-1 are known to stimulate ANG in the dentate gyrus. ANG, synaptic plasticity, and learning potential are significantly compromised in the rodent model of type 1 diabetes, suggesting that both endocrine and brain insulin play a substantial role in generating new neurons. A study by (Lang et al., 2009) also shows that ANG is severely impaired in the adult type-2 diabetic GK rats, demonstrating that aberrant insulin signaling or insulin resistance can disrupt ANG. IGF-1 also has received considerable attention in recent years as a potential modulator of ANG. In adults, peripheral IGF-1 mediates an exercise-induced enhancement of neurogenesis in the hippocampus and has a direct proliferative effect on adult hippocampal progenitor cells in culture. Intracerebroventricular infusion of IGF-1 also eliminates the modest decrease in ANG that occurs in advanced geriatric animals (Lindl et al., 2010).

HIV infection alters insulin signaling, glucose homeostasis, lipid distribution, and metabolism in patients with or without HAART therapy (Lindl et al., 2010). Mechanisms of metabolic disruption in HIV-infected patients remain unclear. Still, it is hypothesized that peripheral chemokine signaling is at least partially involved in the alteration of insulin and glucose homeostasis. In addition, patients on HAART therapy experience more pronounced metabolic disturbance, leading to aberrant lipid distribution. HAART and some medications used to treat behavioral perturbations in HAD are known to cause a prolonged form of insulin resistance. Some of these medications can bind the insulin receptor kinase domain and inhibit downstream phosphorylation of targets or reduce voltage-gated K+ channels and other anion currents, which are known to affect glucose sensitivity and insulin response signaling. Thus, altered signaling from the IR+ could potentially cause a form of insulin resistance and may be one of the factors by which HAND continues to progress in patients on HAART (Lindl et al., 2010).

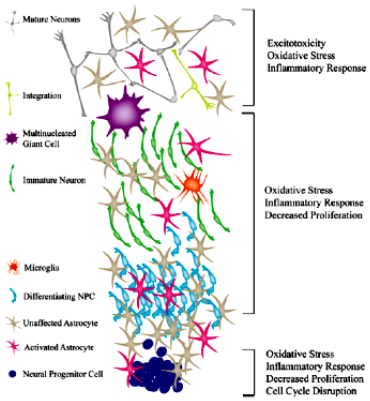

Figure 7. Schematic figure of adult neurogenesis area affected by HIV infection in the brain

Neuron progenitor cells and their supporting astrocytes could be destructed by HIV infection. Multinucleated giant cells and microglia also contributed to the toxicity and NPC damage, and immature neuron (Lindl et al, 2010).

HAND Neurodegeneration mechanism of

HIV-infected cells, especially microglia, can release not only HIV virion but also HIV protein some of them are neurotoxic, including gp 120 and Tat. gp120. Those proteins can cause neuron damage by activating macrophages and microglia to produce inflammatory cytokines and arachidonic acid. The proteins also have the potential to directly act in the neurons to induce apoptosis by changing Ca^{2+} metabolism. Gp41 was reported to be able to induce the production of nitric oxide (NO) by increasing the production of inducible nitric oxide synthetase (iNOS, NOS-2). iNOS is reacted with arginine to produce citrulline and NO. NO will react with superoxide ($O2^{-}$) to form peroxynitrite (ONOO-), a strong neurotoxin. Peroxynitrite stimulates the increase of neuronal Ca^{2+} and causes neuronal apoptosis (Reiss et al., 2008).

HIV tat was thought to increase Ca2+ in neurons, alter the glutamate absorption by astrocytes, and induce iNOS resulting increase in NO production, which all could cause neuronal apoptosis. Tat was also thought to increase astrocyte MCP-1 expression that would induce. Monocyte derivate cell lines to the brain and hasten neuron inflammation (Reiss et al., 2008).

Neuron inflammation could cause neuron damage and death by various mechanisms. Activation of microglia and gliosis is common in HIV, especially in HIV patients with dementia. Abnormal cytokine release, including IL-1, TNFα, and IL-6, was also reported and could affect glial normal functions. Microglia and astrocytes could be induced to express iNOS, whereas upregulation of IL-1β could also increase iNOS regulation. TNFα alters the glutamate absorption by astrocytes from the extracellular environment, which causes neuron damage. Combined with IL-6, TNFα could induce HIV replication by inducing nuclear factor expression that could act in HIV LTR, further damaging the neuron. TNFα blocks the astrocyte's ability to eliminate glutamate excess from the extracellular environment, which causes neuron damage. Figure 9 shows the association between various factors in neuron damage and CNS dysfunction (Reiss et al., 2008).

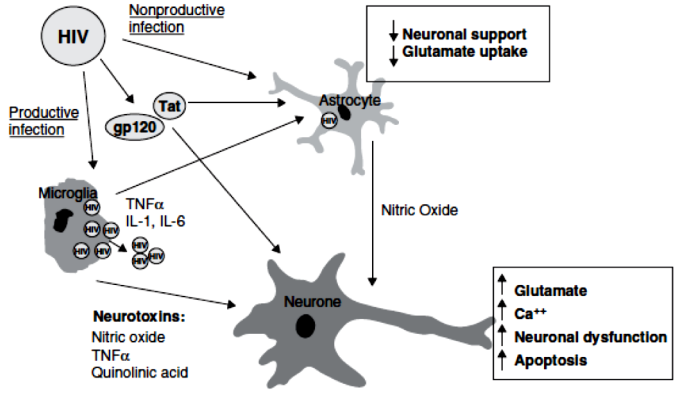

Figure 8. Central neuronal degeneration mechanism in HIV infection

Neurodegeneration of the brain in HIV infection is caused by several mechanisms, including the role of inflammatory cytokines, HIV virus protein, and immune cells (Reiss et al., 2008).

Neuroprotective factors

Platelet-derived growth factors (PDGF) have neuroprotective effects on gp120 toxicity by stimulating PI3K/Akt, and pretreatment of neuronal cells using PDGF-CC can save cells from the neurotoxicity process mediated by Tat by mitigating the apoptosis process and neurite loss. Astrocytes exposed to HIV-1 or chronically infected by HIV-1 will express tissue inhibitors of metalloproteinases-1 (TIMP-1), which also has been known to have a neuroprotective nature when primary human neurons are exposed to HIV-1. It was previously reported that HIV-1 gp120 exposure to astrocytes induces the expression of nuclear factor erythroid-derived 2-related factor (Nrf2), which has an essential role in stimulating antioxidant-defending enzymes (Rao, Ruiz, and Prasad, 2014).

Fractalkine (FKN/CX3CL1) is a chemokine produced by neurons, and this chemokine has an essential role in communication with microglia, which massively express FKN receptor CX3CR1 (neurons also express this receptor in lesser quantity). FKN has a vital role in the neuroprotection process and helps reduce gp120 toxicity via ERK1/2 and CREB activation (this effect is found in the presence and absence of co-culture glial cells).

Increased level of FKN is found in neuron cells of patients with HIV encephalitis, and this FKN is able to control monocyte migration across in vitro trans-well systems and also detain neurotoxicity effects of that protein in rats' cerebellum neurons. CCL3LI chemokine also protects cells from gp120 neurotoxicity via CREB fosforilaztion, which induces transcription of gene survival cell bcl-2. The action route of these host mediators in combating viral neurotoxin could give an insight into new therapeutic scope based on the neuroprotection pathway known today (Rao, Ruiz, and Prasad, 2014).

The role of host determinant genetic factors in neurotoxicity

Several important host polymorphic genes have been known to affect the HIV-1 transmission and/or the development of AIDS (e.g., CCR5-Δ32, CCL31). Several polymorphic genes have also been known to be associated with susceptibility to neurocognitive dysfunction. A mutation point found in the CCR2 gene (V64I), which is related to the deceleration of immunosuppressive diseases, is also known to slow down

the progression of neurocognitive dysfunction. Polymorphism in the TNFα gene increases the production of TNFα as a response to bacterial LPS, and now it is known that this allele has increased frequency in HAD patients. CCL2 allele, 2578G is related to 50% reduction of HIV-1 infection risk. However, the same allele that appeared after HIV infection is also related to a 4.5 times higher risk of HAD. This 2578G allele is the output of CCL2 transcription process in larger scale, which can exacerbate HAND progressivity by increasing monocyte cell influx as a response to CNS infection (Rao, Ruiz, and Prasad, 2014).

HAND pathologic description

Pathologic examination in HAND showed pale brain white matter. Myelin destruction was possibly caused by an early viral infection or as a result of an indirect immunologic response to the virus. Axonal destruction was very variable among cases, from focal deficit to large destruction of central white matter. Presymptomatic individuals showed low-grade lymphocytic leptomeningitis and perivascular lymphocytic cuffing, especially in central white matter. The main cell types found in these infiltrates were CD8 lymphocytes and also lymphocytes B CD20. In the advanced cases, there was a foamy macrophage cluster and multinucleated cells, indicating white matter thinning (Figure 10) (Reiss et al, 2008; Gorantla, Poluektova and Gendelman, 2012; Saylor et al, 2016).

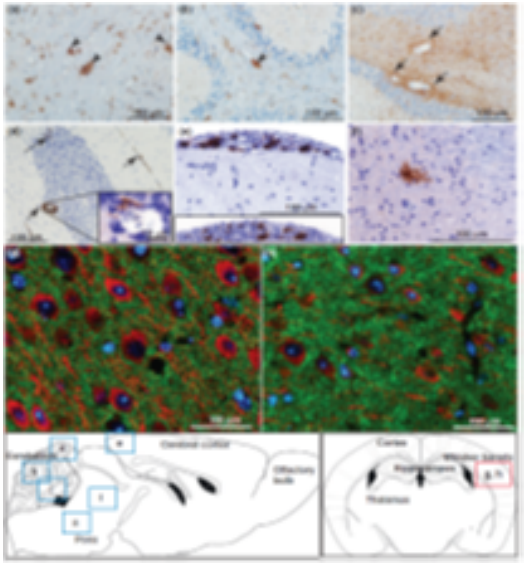

Figure 9. HIV-1 neuropathology in brain biopsy of experimental animal

HIV-1 chronic infection for 8 weeks decreased TCD4+ lymphocytes and acceleration of cellular migration to the brain. (a) Microglia activation and nodule formation in the cerebellum white matter tract was proved by immunohistochemical staining (brown) for calcium-binding adaptor molecule-1 (anti-Iba-1, arrow). (b) Macrophage accumulation and perivascular microglia (Iba-1 staining) in the cerebellum (arrow). (c) Astrocyte activation in cerebellum white matter surrounding vessels was proved by positive staining from glial fibrillary acidic glial (arrow). (d) The distribution pattern of immunocompetent cells was visualized with HLA-DR staining (MHC-II surface receptor, brown). Human cells in cerebellar fissure in the granular layer and perivascular (arrow). (e) HLA-DR staining showed leukocytes in the meningeal layer. (f)

Cells similar to microglia were rarely visualized in the parenchyma (Gorantla et al., 2012).

Pathologics described above were only found in several patients. A third of the patients had relatively mild pathologic conditions, not proportional to the disease severity. Mild changes were also found in half of the patients without dementia symptoms with subclinical conditions. In the CART era, the white matter changes were milder. Those changes were detected in diffusion tension imaging. More severe changes are commonly found in increasing age and infection duration (Saylor et al., 2016).

Neuroimaging in HAND patients showed a general decline of white matter and an additional decline of gray matter, especially in basal ganglia and posterior cortex. These findings were consistent with general neuropathologic findings in this case. Neuronal loss was already explained in HAND, and apoptotic cells were commonly found in basal ganglia and lower-level parts, such as the hippocampus and frontal cortex (Saylor et al., 2016).

Conclusion

HAND is classified into three (3) neurocognitive dysfunction spectrums: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). HAND remains a significant cause of morbidity; estimatedly, 15-55% of HIV/AIDS patients had HAND – a similar prevalence to the pre-CART era. Due to its effects on cognitive ability impairment, HIV is considered to induce neuronal damage, both directly and indirectly. HAND neuropathogenesis comprises three main aspects: cellular, viral, and proinflammatory molecules. IN general, the progression comprised of chronic neuroinflammation, postsynaptic density decrements, and neurogenesis impairment. A better understanding of HAND neuropathogenesis will increase the optimization of HAND therapy. Pathogenic models on neuroimmune damage are built based on the alteration of immune cells and CNS immunity molecules trafficking, cytokines and chemokines release, which accelerates the neuroinflammation process, and neurotoxic molecule production that aggravates neuronal damage. Recent research findings also show various specific mechanisms, such as the effect of oxidative stress on inflammation response and the role of Tat protein in neuronal transcription pathways. HIV influences normal neuronal activity through neuronal pathway alteration and neuroinflammation triggering. Neuroinflammation also serves as a neurotoxicity marker. In the advanced stage of infection, CNS immunity activation, such as monocytes, directly correlates with neurocognitive ability impairment. Astrocytes were also found to play a crucial role in HIV-related neuronal damage. On a cellular level, astrocytes are not only passively infected but also, in the effort to expel HIV from brain cells, these cells end up becoming HIV infection targets.

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