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Online First Archive		Peer Review Policy	
Aims and Scope	<ol> <li>Glial Cells Involvement in Pathogenesis of Human Immunodeficiency Virus-Associated Sensory Neuropathy (HIV-SN): Literature Review</li> <li>Leutu Eka Widvadharma, Jimmy Barus, Putri Rossvana Dewi, Faldi Yaputra, LMade Oka Adavana</li> </ol>	Editorial & Peer Review Process	
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# GLIAL CELLS INVOLVEMENT IN PATHOGENESIS OF HUMAN IMMUNODEFICIENCY VIRUS-ASSOCIATED SENSORY NEUROPATHY (HIV-SN): LITERATURE REVIEW

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**ABSTRACT** Human Immunodeficiency Virus (HIV) infection has become an epidemic all around the world especially in developing countries including Indonesia. AIDS has so many comorbidities, and complications, one of them is HIV associated sensory neuropathy (HIV-SN). Distal sensory polyneuropathy (DSP) and toxic antiretroviral neuropathy (ATN) are the most common HIV-SN, disorders that characterised by peripheral nerve damage. These disorders have the same feature which is "dying back", a mechanism in which the long axon in the distal region degenerates. This mechanism is worsened by macrophages infiltration and loss of unmyelinated fibres in peripheral nerve and dorsal root ganglion (DRG). In recent studies, the pathogenesis of HIV-SN showed the involvement of glial cells (microglia and astrocyte). In this review, we will focus on the involvement of glial cells in the pathogenesis of HIV-SN.

KEYWORDS HIV Sensory Neuropathy, Glial Cells, Antiretroviral Toxic Neuropathy

# Introduction

Human Immunodeficiency Virus (HIV) infection is a disease caused by infection from immunodeficiency virus that attacks the immune systems. In 2015, approximately 735.256 people were living with HIV/AIDS in Indonesia, with 30.935 new cases of HIV and 6.081 new cases of AIDS [1].

The HIV consists of two types, HIV-1 and an HIV-2 virus, primarily HIV-1 is the cause of HIV infection in human. HIV-1 patients often have complications in nervous system, both cen-

tral and peripheral system which is about 35-63%. Peripheral sensory neuropathy is the most common neurological complications of HIV-1 infection [2,3]. Approximately, 30-60% of HIV-1 infection have peripheral neuropathy complication clinically. Moreover, there is some evidence showed the autopsy of all people who have died with AIDS suffered peripheral nerve abnormalities [4,5].

DSP is considered as the most comment complication of HIV-SN. It can be caused by the HIV or the antiretrovirals that are correlated to ATN. Nucleoside reverse transcriptase inhibitor (NRTI) especially stavudine (d4T), didanosine (ddI), and zalcitabine (ddC) are considered to increase the risk of ATN [5,6].

The primary symptom of HIV-SN is neuropathic pain that might be allodynia or hyperalgesia. Neuropathic pain is believed as a manifestation of neural plasticity which caused by peripheral or central sensitisation processes, leading to the formation and maintenance of neuropathic pain. The fundamental pathogenesis of HIV-SN is still not known. In recent, the current theories showed the involvement of glial cells (microglia, astrocyte, and Schwann cell), especially in the dorsal root ganglion

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(DRG) and spinal roots. Activation of glial cells by the HIV-1 virus will induce the release of pro-inflammatory cytokines, cyclooxygenases, and nitric oxide by the glial cells themselves which are potent mediators to produce HIV-SN [7,8]. Furthermore, glial cells involved in the pathogenesis of HIV-SN will be discussed in this review.

#### Pathogenesis of HIV-Associated Sensory Neuropathy

HIV-SN including DSP due to HIV infection and ATN are phenotypically identical to form neurological disorder that mostly found in HIV-AIDS patients. We will focus on discussing these the two most common neuropathies among HIV patients in clinical practice [9,10].

#### Distal Sensory Polyneuropathy

In HIV associated sensory neuropathy, the most common type is Distal sensory [11]. This disorder characterised by spontaneous or evoked pains that mostly found in AIDS stage [12]. Degeneration of long distal axon characterises DSP. This condition is often called "dying-back" because the degeneration of the axon is started from distal area of nerve fibres with centripetal development. This process causes the density of myelinated nerve fibres, and some of the unmyelinated nerve fibres are decreased. This process is similar to diabetic neuropathy and amyloidosis [9,10,12].

There is some evidence in the immunopathological study that demonstrated activation of macrophage that releases some local proinflammatory cytokines around the degenerated axon especially in DSP. Besides, the frequency of Nageotte nodule has been increased consistently. Nageotte nodule is a compact area of satellite cell proliferation that often accompanies the neuronal loss of DRG by any cause. DRG inflammatory infiltrate consist of activated lymphocytes and macrophage, with immunostaining for proinflammatory cytokines such as TNF- $\alpha$ , IFN- $\delta$ , and IL-6 [9,10,12].

There is still no evidence stated the causes of multifocal macrophage activation on the peripheral nerves and DRG in DSP. However, there are two hypotheses believed as the contributing factor in macrophage activation. The first theory noted that mild degeneration of distal axonal was occurred due to alcohol exposure, malnutrition, or drugs abuse. Even though, in HIV infection, these macrophages respond to axonal degeneration hyperactively, resulted from inflammation of the nerves and DRG. In the second theory, there is activation of monocytes and pro-inflammatory cytokines in an excessive amount that enters DRG and peripheral nervous system through leakage of blood-nerve barrier [10].

Brannagan et al. using PCR in situ hybridisation studies (ISH) reported HIV infected DRG neurons in both groups of HIVinfected patient with and without neuropathy. Other studies, in contrast, showed that Nageotte nodule and perivascular cells are infected predominantly [13].

The condition in which reduction of HIV replication and macrophage activation in DSP is similar to dementia-related HIV condition and vascular myelopathy, whereas the direct effect of pro-inflammatory cytokine is considered as the facilitator of neurotoxicity associated with HIV infection. However, some studies proved that HIV or the product of its gene might act directly as neurotoxic. Rat model study demonstrated that transcriptional neurofilament promotors controlled the entire HIV genome. Approximately 50% of sciatic nerve axonal degeneration was observed in rat embryos and showed no inflammatory infiltrate. Some studies proved that the pain intensity is related to systemic viral replication in DSP, especially the HIV-1 RNA. [9,10].

#### Antinucleoside Toxic Neuropathy

The incidence of HIV-associated neurologic complication has decreased dramatically after a combination of antiretroviral therapy was introduced in the mid-1990s. In the last decade, the prevalence of HIV-SN is increased simultaneously when the ddC first introduced to the community [14,15].

There is hypothesis stated that NRTI could cause mitochondrial toxicity. NRTI work as an inhibitor of mitochondrial DNA (mtDNA) polymerase. However, NRTI also inhibit mtDNA polymerase  $\gamma$  in human DNA because it has a similar structure with viral DNA. This inhibition can disrupt the production of mitochondrial protein. Accumulation of this dysfunction mitochondrial protein leads to oxidative phosphorylation and oxidation of fatty acid. Mitochondrial toxicity includes neuropathy, myopathy, lactic acidosis, and lipoatrophy [11]. Furthermore, some mitochondrial abnormalities that we can see in tissues are hyperlactatemia and muscle aches [11,14,15].

Direct inhibition of mitochondrial results in the cellular toxicity that caused NRTI. ZDV inhibits NADH-related respiratory activity and isolated NADH-cytochrome c reductase in mitochondrial of rat liver, brain, and skeletal muscles. Also, ZDV inhibits adenylate kinase, and an isolated ADP-ATP mitochondrial translocator in liver results from an early interruption of oxidative phosphorylation. ddC induces cardiac abnormalities in rats related to the reduction of respiratory activity, but there is no evidence showed this disorder related to depletion of mitochondrial DNA [15,16].

ATN is quite similar to DSP. ATN is always found in patients with DSP. It has led to the hypotheses that the development of ATN is clinically unmasking the actual nerve damage caused by HIV. HIV infection and peripheral neurons abnormalities are prerequisites of ATN development [14,15].

#### Other HIV-related neuropathies

There are several types of different HIV-related neuropathic pain, such as AIDP and CIDP, multiple mononeuropathy, and progressive radiculopathy. These four types of neuropathy are still rarely discussed including pathogenesis and role of agents that caused this neuropathic pain. Opportunistic pathogen and autoimmune activity are referred as a leading cause of this neuropathic pain [17].

#### The Role of Glial Cells in Pathogenesis of HIV-SN

As we know, the most common type of peripheral neuropathy in AIDS is HIV-SN, the prevalence is as high as 30%. The primary symptom of HIV-SN is neuropathic pain. The underlying mechanism of HIV-SN is remaining uncertain. Based on some kinds of literature, pathogenesis of HIV-SN involves glial cells such as the astrocyte, microglia, and Schwan cell [7].

Neuropathic pain is the condition resulted from injury or alteration in the nervous system, without evidence of tissue damage. [7]. Allodynia and hyperalgesia are the most common manifestations of neuropathic pain on HIV-SN. In physiological conditions, pain occurs due to activation of the afferent nociceptors fibres myelin (C nerves fibres) and thinly myelinated nerves (A $\delta$  nerves fibres) indicate tissue damage that could be caused by mechanical, thermal, and chemical stimuli [18].

Neuropathic pain is believed as a manifestation of neural plasticity that probably caused by sensitisation (an increasing of nociceptor excitability and sensitivity) that occurs in PNS and CNS leading to formation and maintenance of neuropathic pain.

#### Peripheral sensitisation

In peripheral sensitisation, there is an activation of nociceptors in the peripheral nervous system (capsaicin receptors and TRPV1) and glial cells in DRG as well as the phenotypic change in primary sensory neuron [7].

## Central Sensitization

Central sensitisation is the process of forming hyperexcitability state in the central nervous system. Central sensitisation will induce an overreactive response to nociceptive stimuli in the central nervous system. There are at least three fundamental mechanisms in the central sensitisation process, hypersensitivity process which mediated by glutamatergic neurotransmission/ N-Methyl-D-aspartate receptor, loss of tonic inhibition control (dis-inhibition) and glial-neuronal interaction. The last mechanism is the primary mechanism in central sensitisation process of HIV-SN [7].

### Glial Cells Involvement in HIV-SN

HIV-1 belongs to neurotrophic virus group that could penetrate blood-brain barrier or nerve barrier. After entered DRG and spinal cord, HIV-1 through gp120, a protein presented in its external sheath, will bind to glial cells such as microglia and astrocytes. This bond between gp120 and glial cells is facilitated by CXCR4 and CCR5 receptors on the glial cell surface. The next step of this process will induce glial cells activation. Activated glial cells will release several important pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6. Based on existing research data, TNF- $\alpha$  and IL-1 $\beta$  are likely continued their signalling through the cascade of p38 mitogen-activated protein kinase (p38 MAPK) in glial cells. A study by Miligan et al (2007) is supporting this theory which stated the inhibition of p38 MAPK by CNI 1439 (a substance which can penetrate the blood-brain barrier) might inhibit stages of pain that mediated by central propagation processes (mechanical allodynia and thermal hyperalgesia) induced by gp120 (mainly through inhibition of pro-inflammatory cytokines transduction signal [8].

The activation of p38 MAPK stimulates the synthesis of proinflammatory cytokines such as IL-6, IL-1 $\beta$ , and TNF- $\alpha$ . At low concentrations, these cytokines facilitate central sensitisation through different mechanisms. For example, TNF- $\alpha$  could increase the frequency of spontaneous excitatory postsynaptic currents (sEPSCs) and AMPA- or NMDA-induced currents amplitude by increased the excitatory synaptic transmission. Meanwhile, IL-1 $\beta$  can simultaneously increase excitatory synaptic transmission and decrease inhibitory synaptic transmission. IL-6 inhibits inhibitory synaptic transmission by reducing the frequency of sEPSCs, GABA amplitude, and glycine-induced current [19].

TNF- $\alpha$  is also known to be involved in the pathogenesis of HIV-AIDS, not only modulates neuropathic pain but also increases HIV replication in T-cells and lymphocytes in infected individuals. Serum TNF- $\alpha$  concentrations have a positive correlation with the progression of HIV-1 infection, which supports the hypothesis that TNF- $\alpha$  contributes to the progress of HIV infection.7

Also, activated glial cells also release nitric oxide (NO) and

cyclooxygenase (COX) products. Both act as potential inductors in neuropathic pain. NO might work through amplification of gp120 action on glial transcription factor and release proinflammatory cytokines by glial cells [8,20].

In addition to microglia and astrocytes, the Schwann cells, myelin-forming cells in the peripheral nerve axons, play a role in DSP. Activation of Schwann cells by HIV-1 occurs when it binds to the CXCR4 receptor on the surface of the Schwann cell with gp120. The activated Schwann cells release the five ligand chemokine (CCL5)/RANTES. RANTES (regulated upon activation, normal T-cell expressed and secreted) induces up-regulation of TNF- $\alpha$  production by DRG neurons. TNF- $\alpha$  activity facilitated by TNFR1 receptors is known to be potent hyperalgesia mediator and to some extent have neurotoxic effects on neurons in DRG [7,21].

The damage to neuronal cells due to TNF- $\alpha$  cause side effects of increased expression of CCL5 or monocyte chemoattractant protein-1 (MCP-1). MCP-1 played an essential role in the occurrence of macrophage influx in DRG and affected the spinal cord. This theory explains the accumulation of activated macrophages in DRG in the pathologic examination of DSP. In addition to macrophage influx, the enhanced expression of CCL5 in the superficial lamina in the dorsal horn of the spinal cord triggers the activation of microglia and spinal astrocytes. It is seen that is a dynamic interaction between microglia, astrocytes, and Schwann cells in inducing and modulating the neuropathic pain in HIV-SN [22].

# SUMMARY

HIV-1 belongs to a class of neurotropic virus that can penetrate the blood-brain or nerve barrier. After entering the DRG and spinal cord, HIV-1 via gp120, a protein present on its external sheath, binds to both glial cells, microglia and astrocytes facilitated by CXCR4 and CCR5 receptors on the glial cell surface and induces activation of glial cells. Activated glial cells will release some pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6. In addition to cytokines, activated glial cells also release nitric oxide (NO) and cyclooxygenase (COX) products. Both act as potential inductors in neuropathic pain.

Another mechanism of involvement of glial cells in HIV sensory neuropathic is shown in ATN. NRTI regiment for AIDS therapy resulted in up-regulation mRNA expression of the CXCR4 receptor in neurons as well as glial cells. The enhancement of this receptor expression will certainly facilitate the binding process between HIV-1 (via gp120) with neurons and glial cells.

#### Authors' Statements

## Competing Interests

The authors declare no conflict of interest.

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