Review Article

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Less Neuropathogenesis by HIV-1 C: Co-Operative Action of Viral Factors, Immune and CNS Cells

Mamata Mishra

Abstract

Among 34 million people living with HIV, genetic forms of HIV-1 differ significantly around the globe and sub type C infects highest population worldwide. Although disease severity has been reduced by the successful introduction of cART, complete assessment of therapy to CNS is not potentialy unbeaten. In post-HAART era, the predominance of HAND depends upon the likely effect of clade diversity. Neurological complication in HIV infection intimately related to virological, cellular and immunological factors which can either be beneficial or detrimental. Many experts report that immune system cells hinder the healing in subtype B which is somehow suppressed or eliminated in clade C. Other scientists claim that viral factors may mediate the stimulation and secretion of anti-inflammatory cytokines and neuroprotective factors which consequences less neuropathogenesis in subtype C infections. Hence less neurocognitive impairment in Indian subtype C is a dispute. This article reviews the co-operative action of viral, cellular and immunological factors involved in HIV-1 associated neurological complications in clade C and elucidate our knowledge in comparison to clade B.

Keywords: HIV-1 Clade C; Neuropathogenesis; Viral Factors; HAND; Cognitive Impairment.

Introduction

HIV-1 clade C is responsible for almost half of new HIV-1 infections worldwide [1] and more than 90% of HIV-1 infections in India [2]. Patients infected with HIV-1, if untreated, invariably experience frequent neurological complications which include decrease in memory, inability to concentrate, apathy and psychomotor retardation. Although the use of cART brought the disease severity down, HIV-associated neurocognitive disorders appear to be a major concern in the world. HIV-1 enters the CNS soon after infection, however the neurological complications appear in collaboration of viral factors, cellular factors [3]. Furthermore the magnitude of infection and immune activation within CNS yet not completely characterized. In India, sufficient amount of neuropathological data of HIV-1 C is not available due to various reasons such as inadequate medical facilities, social stigma and the burden of opportunistic infections 4. Existing reports suggest that India has an exceptionally low incidence of HIV Associated Dementia (HAD) cases [4, 5]. Among Indian clade C and South African clade C, the decline of neurovirulence Indian subtype is due to replacement of Serine at 31 positions that reduces monocyte chemoattractant protein 1 (MCP-1) secretion which in turn causes less direct neurotoxicity [6]. In CNS, neural cells are not productively infected by HIV and glial cells are rarely affected, which is why indirect neuropathogenesis by viral factors take the main lead. Regulated activity of immune cells required for homeostasis of healthy brain and maintenance of brain plasticity [7]. Infiltration of monocyte and monocyte mediated macrophages play immense role in producing anti-inflammatory cytokines, beneficial neuroprotective factors that modulate clade specific variation in neuropathogenesis. In pre-HAART era HIV-associated dementia (HAD) was most common (20-30%) worldwide among HIV infected AIDS people, especially subtype B predominant infections. However in post-HAART era the less severe form of neurological disorders consists of a spectrum of neurological complications ranges from mild

Author's Affiliation: Molecular Biology & Genetics Unit., Jawaharlal Nehru Centre for Advance Scientific Research, Bangalore, India.

Reprint Request: Mamata Mishra, Molecular Biology & Genetics Unit., Jawaharlal Nehru Centre for Advance Scientific Research, Jakkur, Bengaluru, Karnataka 560064, India.
E-mail: mmnbrc@yahoo.com

cognitive motor disorder (MCMD), HIV-1 associated neuro-cognitive disorder (HAND) and asymptomatic neurocognitive impairment (ANI) which are more or less equal among different subtypes [8]. On the other hand various clinical reports as well as cognitive studies implicate that clade C result a reduced amount of neurocognitive impairment while considering clade B. The question arises what happened to the damaged neuron. Are the neurotrophic factors give the healthy status to neuron or the new neurons formed in adult brain take over the job? Adult neurogenesis is a newly emerging area which enhances our understanding, how healthy neuron formation occurs in enriched environment where the burden of neurotoxicity decreases due to decline in protein aggregation, oxidative stress and mitochondrial injury. Blocking of excitotoxicity diminish the memory impairments occur during inflammation. Amusingly molecular mechanism of neural network and remodeling of new neuron with old ones are not yet clear [9]. Recently Madhavan Nair's group investigated that there were substantially affected synaptic genes at the post-synaptic density of clade B infections which is dissimilar from that of clade C spine morphology[10]. This finding apparently specifies that cognitive impairment in HIV infections closely imparted with synaptic plasticity and the expressed gene profile.

Description:

Activity of Viral Proteins

Accumulating evidence suggest that viral proteins mainly Tat, gp120, Vpr and Nef have been implicated in neuropathogenesis [11, 12]. That has been detected in the autopsy brain samples of patients with HIV-1 associated dementia[13] and causes neuronal death via activation of the intrinsic apoptotic pathway that involves disturbances in mitochondria, release of cytochrome-c, calcium overload and subsequently the activation of caspase cascade in neurons[14,15]. Interestingly, the neurotoxic effect of Tat has been reported to be HIV-1 clade specific as differential neurotoxicity was observed in Tat derived from HIV-1 clade B and C by our studies and some other investigators [16, 17, 18]. For the development of HAND, dicystein motif at 30 and 31 positions is important determinant and clade C Tat is less neurotoxic due to absence of cystein at 31 positions which causes less monocyte migration to brain [6] and less hippocampal neuron cell death [17]. The neurotoxicity is through the cys-cys interaction between the NR-1 subunit (cys-744) and cys at position 31 of Tat which activate NMDA receptor, which perhaps do not happen in clade C Tat [19]. Primary monocyte treated with clade C Tat showed significant decrease of IL-6 and TNFα, cytokines that are pro-inflammatory [20]. In addition, clade C Tat appears to up regulate anti-inflammatory cytokines such as IL4 and IL-10 in comparison to clade B and is less disruptive to BBB [21] which is why clade C Tat less likely to develop HAND. Along with the effect of Tat protein, in neuro-AIDS, envelop protein gp120 contribute foremost role in hindering the neuronal function. The sequence variations and distinct structure of clade B gp120 differentially regulate the dopaminergic pathway and enhance neurotoxicity [22]. Clade C gp120 induces lower level of expression of neuropathogenic molecule such as COX-2 mediated arachidonic acid by-products which suggest clade C gp120 causes less neuropathogenic than clade B [23]. As illustrated by Prasad's group gp120 of Indian clade C HIV-1 isolates cause less neurotoxicity than both US clade B and the South African clade C [24]. In addition to Tat, gp120 other viral regulatory components such as Vpr and Nef have been implicated in "indirect" mechanism of neuronal injury which are likely responsible for majority of the neuronal damage in HIV-1 infection [25]. Moreover, HIV-1 induces apoptosis in HBMEC and disrupts the BBB [26] and Nef recruit leucocyte to CNS in vivo as well as in vitro [27]. HIV-1 Nef expression in microglia disrupts immune function, induces CCL2 expression and disturbs dopaminergic functions. In in vivo transgenic model, Vpr expression induces neurobehavioral deficits and neural loss [28]. So far, due to lack of research report, it is not clear whether Nef shows clade specificity.

Responsibility of CNS Cells

Healthy neurons in CNS have the self protection supremacy in any damage circumstances. Nonetheless imbalance in molecular events such as apoptotic cascade, antioxidant defense, enhanced trophic support consequences neuropathogenesis or neuroprotection [29]. Neuronal, non-neuronal and immune cells co-operate with each other to maintain the healthy status of brain in any altered or hazardous situation. In monocyte derived macrophages (MDM), primary isolates of HIV-1 clade C shows slower replication kinetics and lower level of neurotoxicity [30]. Microglia cells are highly adaptable immune cells in CNS who respond to delicate environmental changes and actively maintain the homeostasis. Although activated microglia cells release harmful neurotoxic components in HIV infection and other neuro-pathological states of CNS, they act as immune-modulator and potentially protect neuron from

dangerous infections and traumatic CNS injury by expressing neurotrophins and protective cytokines [31]. Astrocytes, the supporting glia, take the responsibility to uptake of neurotransmitters; modulate synaptic transmission, BBB maintenance, neuronal-glial intercommunication and synaptic activity. In primary astrocyte production of CCL2 is lesser in clade C Tat treatment than clade B indicate that lower amount of HAND in Indian subtype C[16].

Recruitment of Beneficial Immune Cells

More than a decade ago, scientific advances lead to change the view of the prevailing notion that immune cells are detrimental to the CNS. The revised concept, the functional plasticity of healthy brain, neurogenesis and hippocampal dependent cognitive abilities are intimately involved with immune cells and neurotrophic factors. Studies from experimental animal model suggest that in healthy brain, immune cells are excluded out from the brain[32] which strongly emphasizes that tight regulation of immune cells directed by signaling molecules from CNS. The regulatory T-cells present at Choroid Plexus controls the local as well as remote health of brain [33]. In neurodegenerative conditions, either effecter T-cells declines or suppressor T-regulatory cells elevated in circulation[34]. Choroid Plexus is the only epithelial interface of brain, through which CNS parenchyma deliver the signal indicating the need and the circulation provide signal recruiting help. Hence, CP dysfunction may be modulated in well advance through the circulating immune milieu of the cerebrospinal fluid (CSF), to protect the CNS from neurodegeneration. In HIV infections less monocyte migration could be a tightly regulated action of immune system at CNS, due to which clade C shows less neuropathogenesis [6].

Adult Neurogenesis for Rejuvenation

Neuronal health depends upon the genetic as well as sporadic condition and their changes. Being lymphotropic as well as neurotropic, pathological manifestation of HIV get modulated by both host genetic as well as physiological environmental factors. In spite of tremendous attempt, successful vaccination not yet attained for HIV elimination. Persistence of the HIV mediated CNS complications may be due to either development of resistance to HAART or inadequate permeability of ART drugs through blood-brain barrier to reach the target reservoir cell. Over 20 years of surveillance, HAART failed to provide complete protection and complete eradication of HIV-1 from its reservoir, central nervous system (CNS) is an impossible tax yet. During HAND, the decrease of cognitive ability is believed to be the reason of reduced proliferation, differentiation and integration of adult born neural precursor cells. In subtype C infection, it could be possible that rewarding factors get improved and facilitate the potential of resident neural stem cells of hippocampus for synaptic modulation. Cellular mechanism by which specific synapses get eliminated and subset of synapse are maintained and strengthened are remain elusive [35]. The synaptic genes get affected by clade B and clade C shows differences as reported by Nair's group[10]. More detailed experiments as well as animal model studies are needed to provide more insight into critical elements that cause less neuropathogenesis in clade C infected patients. From our recent study, we found that subtype C allocates in different compartments of brain especially in hippocampus and basal ganglia [36]. Uneven distribution of glia in different compartment of brain and their role in synaptic plasticity may provide the cue; how glutamate mediated neurotransmitters hold the key in clearance of unwanted stuffs from the brain and help in strengthen the neural plasticity and memory [37].

Evaluation of Neurocognitive Impairment

Mental health function or status of neurocognitive ability is commonly screened by using a common tool, the international HIV dementia scale (IHDS). In HIV-infected individuals screening for possible cognitive impairment is important and the accuracy of screening tests depends upon various factors. The neurological disabilities shown in HAND are neurophycological impairments, neurobehavioral abnormalities and motor deficits. Unfortunately, neurocognitive impairment has been less extensively studied in subtype C. One of the recent reports specifies that in India, neuropshycological tests are heavily influenced by educational [38]. The evaluation of neurocognitive impairment rates in Indian clade C point out that cognitive dysfunctions likely occur in greater proportion than previously reported [39]. A study from south Indian clade C infected patients show that patients did not have any clinically identifiable impairment. However, prevalence of cognitive deficits is similar to that of clade B [40]. Report from South Brazil indicates, the neurocognitive performance among clade B and C did not differ [41]. During the screening of cognitive impairment, maximum care should be taken in the parameters like executive function, motor skill, language fluency and verbal learning which may

provide the most likely HAND status.

Experimental Approaches & Future Prospective

The missing links between the chronic neurodegenerative disorders including HIV neuropathogenesis and the immune network need to be explored. In HIV- C infections, more protective signal that protect neuron form injury and facilitate adult neurogenesis, yet to be established. In response to disease progression, the molecular approach of adult neurogenesis, formation of network with old new neuron and interaction of neuroglia in strengthening the neuronal plasticity may enhance our knowledge to keep the neuron fit at the adverse conditions. Additionally, future studies are required which will validate the findings so far and give direction to discover some more beneficial effect of immune cells in CNS and the role of immune cells in enhancing the potential of adult neural precursor cells to form new neuron.

Abbreviations

BBB: Blood brain barrier; CNS: Central nervous system; cART: combined antiretroviral therapy; CP: Choroid plexus; HAND: HIV-1 associated neurocognitive disorder; HAART: Highly active antiretroviral therapy;

Key Messages

Less neuropathogenesis in HIV-1 subtype C infections in India has multiple causes. Immune cells may not be detrimental. Anti-inflammatory cytokines have protective effect. Self protection potential of neuron could be enhanced. Rewarding factors get improved to facilitate residential neural precursor cells to form new neuron in adult (adult neurogenesis).

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