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Chronic inflammation mediates brain injury in HIV infection: relevance for cure strategies.

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Abstract

Purpose of review: Chronic inflammation is a major component of HIV infection, the effects of which can be devastating in the central nervous system (CNS). Protecting the brain is therefore critical as efforts proceed to cure HIV infection by reactivating latent viral reservoirs and driving immune responses. We review the clinical presentation and pathology findings of inflammatory processes in the CNS in patients managed with ART and the drivers of these processes.

Recent findings: Chronic inflammation is associated with increased mortality and morbidity and HIV infection increases the risk for chronic diseases, especially cognitive impairment. Latent viral reservoirs, including microglia and tissue macrophages, contribute to inflammation in the CNS. Inflammation is generated and maintained through residual viral replication, dysregulation of infected cells, continuously produced viral proteins and positive feedback loops of chronic inflammation. Novel therapeutics and lifestyle changes may help to protect the CNS from immune mediated damage.

Summary: As therapies are developed to cure HIV, it is important to protect the CNS from additional immune-mediated damage. Adjunctive therapies to restore glial function, reduce neuro- and systemic inflammation, and inhibit expression of viral proteins are needed.

Keywords

chronic inflammation; HIV; cure; HIV-associated neurocognitive disorders

Introduction

Six years ago, President Obama announced the HIV Cure initiative with the aim of HIV eradication or development of a functional cure, to eliminate the need for long term antiretroviral therapy (ART) (1). Potential curative approaches include activation of the viral latent reservoir (2), transfusion of viral specific or viral resistant T cells (3, 4), gene editing excision of proviral DNA (5, 6*, 7), and immune checkpoint inhibition (8, 9). The majority of these strategies involve activating the latent viral reservoir, which includes T cells (10), tissue resident macrophages (11**, 12), microglia (13), and astrocytes (14) with latency-

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Conflicts of Interest

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reversing agents (LRAs). Re-activated virus can then trigger proinflammatory processes involving immune antiviral responses as well as non-specific inflammation. Such inflammatory processes can also lead to unwanted collateral tissue damage and result in immune-mediated complications. Therefore, it is critical to consider the unintended immunological consequences of these curative approaches.

During a chronic inflammatory process immune responses are involved both in tissue destruction and in tissue repair (reviewed in (15*)). This results in a positive feedback loop of immune responses and damage. Chronic inflammation is a major contributor to the pathophysiology of neoplastic, neurodegenerative, autoimmune, and cardiovascular disease; conditions that persons living with HIV (PLWH) are at an increased risk for (16*). Having HIV increases the risk of developing a chronic illness by up to 80%, the risk being greatest for cognitive impairment and dementia (16). HIV-associated neurocognitive disorders (HAND) (17) are tightly associated with chronic inflammation (18–20) .

Because of the potential immunological consequences of curative approaches on the CNS, a detailed understanding of the contribution and mechanisms of inflammation-mediated damage to CNS during HIV infection becomes ever more important. This review highlights the most recent advances in our understanding of how HIV infection impacts the brain, focusing on the presentation and immunopathology of patients with CNS inflammation, the role of microglia in chronic inflammation, and the viral factors that contribute to inflammation. Additionally, the importance of protecting the brain while moving towards a functional cure will be discussed.

Clinical presentation of PLWH with chronic CNS inflammation

Even after therapeutic viral suppression has been achieved, the incidence of comorbid disorders including neurologic and psychiatric disorders, accelerated vascular disease, and frailty is very high, and it is increasingly apparent that much of this is linked to or exacerbated by chronic CNS inflammation (21).

HIV-associated neurocognitive disorders

Of all the conditions linked to CNS inflammation (Figure 1), the best studied is HAND (reviewed in (22)). HAND can be identified in 30–50% of individuals (17, 23–25) and encompasses impairments in memory, attention, processing and motor skills that can range from mild or asymptomatic to severely debilitating. The most common neurological manifestations in the era of ART are mild neurocognitive deficits (see Table 1). Importantly, once established, the deficits appear to persist even with successful ART. For example, HIV + virally suppressed women showed deficits in verbal learning, verbal memory, executive function, attention/working memory, and fluency that persisted over four years of follow-up (26).

Although present in all patients across the spectrum of HIV infection, including the pediatric population (27**), HAND is more prevalent in older patients and in those with longer disease duration (28–30). This is particularly important as the age of PLWH is increasing. Indeed, approximately half of the PLWH in the United States are now over the age of 50

(31), suggesting a large proportion are at risk for HAND. Aging is also associated with enhanced immune activation that paradoxically results in a lack of appropriate immune response and is associated with mortality (32**). This inflammation may render older PLWH more susceptible to infections and loss of immune mediated clearance of cellular debris. Some have described this interaction of chronic CNS inflammation and aging as *"inflammaging"* (33, 34).

Other disease mechanisms

PLWH have substantial increased risks of cardiovascular disease (CVD) including acute myocardial infarction (35, 36), ischemic stroke (35), and heart failure (37) . CVD is strongly associated with inflammation and multiple mechanisms have been posited for how inflammation and virally driven processes accelerate atherosclerosis (38, 39). CVD risk factors including carotid intima-media thickness, central obesity and diabetes are important risk factors for the development of HAND (29, 40–42). As the cognitive profile of vascular cognitive impairment significantly overlaps with that of HAND (41), it remains to be seen whether CVD in PLWH leads to vascular cognitive impairment or accelerates more typical HAND, or some complex mix of the two. Concomitant drug use may add to accelerated CVD and drive neurological dysfunction (43). Further, given the known associations between CVD and Alzheimer disease (AD) it is also possible that HIV accelerates amyloid and tau protein deposition leading to AD and neurodegenerative processes.

CNS pathology during HIV infection and HAND

HIV infected cells enter the CNS shortly after systemic infection (44). In the CNS the virus infects tissue macrophages (11, 12), microglia (13) and astrocytes (14). Imaging studies have revealed ongoing CNS tissue loss in persons with HIV despite effective ART (45). In a recent longitudinal imaging study of 155 PLWH on ART, significant brain volume decreases, subcortical brain atrophy, ventricular expansion and white matter abnormalities were present despite undetectable viral loads (45). Brain atrophy is associated with neuroinflammation in HIV infection and HAND (19, 46–48) and recent studies utilizing magnetic resonance imaging coupled with metabolite spectroscopy have confirmed persistent neuroinflammation in individuals with HAND (49, 50). CSF biomarkers studies have also confirmed persistent inflammation and neural injury in virologically suppressed individuals (46, 51–61). Likewise, viral proteins, including the HIV transactivator of transcription (Tat) protein (62*, 63) and Nef (64), known to drive inflammation, have been found in the CSF of PLWH.

Histomorphological changes associated with HIV infection demonstrate evidence of ongoing immune processes and neuronal damage in the absence of viral replication. These include activation of infected and non-infected microglia and astrocytes (65), CD68+ cells in the white matter and vascular disease processes including infarcts, thickening of vessel walls, hemorrhage and atherosclerosis (66) as well as decreases in dendritic and synaptic complexity (67). Post-mortem studies have also revealed an increased accumulation of protein aggregates, especially Aβ, in individuals with HIV (68). This may reflect vascular damage as well as enhanced protein aggregate formation driven by Tat (69) . Biopsies from

patients with IRIS, the most fulminant and recognizable form of CNS inflammation in PLWH, demonstrated CD4+ and CD8+ T cells, including IL-17+ cells, and the viral protein Tat, in the parenchyma despite the absence of replicating virus (63, 70). Indeed, patients have persistent CD4+ and CD8+ T cell activation in both the periphery and in the CSF despite having undetectable viral loads (71). In particular, effector memory T cells are elevated (72) and expression of markers of T cell exhaustion are increased (73).

Collectively, clinical and pathology findings indicate that the immune responses in the CNS observed in people with HIV includes non-specific chronic inflammatory processes that are present even during viral suppression. As chronic inflammation is a key driver in many common diseases (15), and is tightly linked with neurodegenerative diseases (74, 75), it is important to evaluate what drives the neuroinflammation observed in PLWH and how the latent reservoir contributes to these processes.

Drivers of CNS inflammation during HIV infection

Residual viral replication from the latent reservoirs despite ART, and subsequent anti-viral immune responses, may account for some of the persistent immune activation noted in the CNS (76**, 77). However, because peripheral and CSF viral loads are often undetectable, factors other than viral replication likely also drive inflammation. These factors include skewing of immune trafficking, dysregulation of gene expression from infected cells, and the persistent expression of viral proteins from latently infected cells. Once initiated, positive feedback loops of immune-mediated tissue damage and repair processes result in self-sustained chronic inflammation. Key cells in these processes are brain macrophages and microglia.

CNS viral reservoirs mediate chronic inflammation

Microglia and tissue resident macrophages are the principal cells infected with HIV in the CNS (13) and recent work has demonstrated that these cells are an important reservoir of latent virus (11, 12, 78, 79, 80**, 81**). In an SIV model, infectious virus was produced from brain macrophages after the removal of ART (11). This suggests that the viral reservoir in the CNS might re-seed the periphery (11, 81). To underline this potential scenario, almost half of virologically suppressed individuals with over eight years on ART had HIV infected cells in the CSF, although very few participants had detectable viral replication (76). Additionally, there appeared to be enrichment of virally infected cells within the CSF as compared to the periphery which was correlated with neurocognitive impairments (76). However, this study could not discern if infected cells were trafficking into the CNS at increased rates or if uninfected cells were becoming infected from virus present in the brain.

Microglia are long-lived cells that are responsible for initiating immune responses, recruiting peripheral immune cells into the CNS, and maintaining CNS homeostasis (82). Microglia are likely the key cell for initiating and sustaining positive feedback loops of chronic inflammation in the CNS. Microglia undergo functional, morphologic and phenotypic shifts when activated and *in vivo* PET imaging has demonstrated microglial activation during HIV infection (83, 84). Once activated, gene expression changes result in increased proliferation and alterations in cellular communication, notably the synthesis and release of

proinflammatory cytokines, chemokines and effector molecules (85, 86). The release of these molecules, such as matrix metalloproteinases and reactive oxygen species, directly damage neurons resulting in loss of neuron function and neurotoxicity (87, 88). This, in turn, drives microglial activation. Additionally, the virally driven secretion of chemokines, such as CCL2 (53, 77, 89, 90), contribute to the propagation of chronic inflammation. CCL2 activates microglia, modulates their migration and encourages self-proliferation (91) as well as recruits peripheral macrophages and T cells into the CNS. These cells drive further immune-mediated damage, microglial activation, and immune cell recruitment. Viral infection early in life, as occurs in the pediatric population, may also generate an increase in proinflammatory brain resident T cells (92). These cells tend to cluster in regions of microglial activation and have also been shown to increase with age (93), promoting long-lasting proinflammatory CNS environments. The contribution of these cells during HIV infection is an area of current interest.

Astrocytes are the most common cell type in the brain (94). Although relatively few astrocytes are thought to become infected, and this infection is restricted and non-productive (14, 95) those that are may drive neuroinflammation by inducing apoptosis in uninfected astrocytes, secreting proinflammatory cytokines, altering synaptic integrity (96) and causing disruptions to the blood brain barrier (BBB) by impairing gap junctions (97, 98). In addition to the immune-mediated damage caused by activated glia, these same cells do not function in their normal role of synapse maintenance, glutamate uptake, BBB regulation, phagocytosis of dead cells and removal of protein aggregates such as Aβ (99–101), processes all critical for CNS health. Both the proinflammatory processes and the loss of brain homeostatic mechanisms contribute to CNS immunopathology. Therefore, not only eliminating HIV from the microglial and astrocyte populations, but restoring glial function is important to consider as cure strategies are implemented.

Viral proteins drive inflammation

Viral proteins produced during ART also drive inflammation. Even during ART pressure, provirus is capable of producing proteins, including Tat (62, 63) and Nef (64), which are secreted from infected cells. Tat is readily endocytosed by cells where it modulates gene expression and cellular function (102). Tat is directly neurotoxic and is potently neuroinflammatory, driving astrocyte, microglial and T cell activation as well as inducing secretion of inflammatory cytokines in both animal and *in vitro* models, and activating inflammasomes (63, 103–109). For example, Tat drives the production of CCL2, which recruits peripheral macrophages and T cells into the CNS and also activates these cells through chromatin remodeling. Not only does this facilitate further infection by HIV but it also causes aberrant secretion of cytokines such as granzyme B and interleukin (IL)-17 (63) which have been shown to be directly neurotoxic and to modulate the BBB (110, 111). Nef has also been shown to increase BBB permeability and drive neuroinflammation (112*, 113). Specifically, IL-1 dependent vascular changes and immune cell infiltration were noted in both the lung and the gut of animals expressing Nef in the hippocampus. These findings are of particular importance as they demonstrate that viral driven changes in the CNS can induce systemic immune responses that further damage the brain.

Protecting the brain while moving towards a cure

Neuroprotection and reducing neuronal inflammation will become even more important as cure initiatives move forward. Several LRAs are being developed to activate the viral reservoir prior to immune-mediated clearance and some consideration is being given to the use of Tat as an LRA during cure strategies (114). As discussed in this review, Tat is not only directly neurotoxic, but also drives substantial neuroinflammatory processes. Further, trials have already begun exploring the use of checkpoint inhibitor therapy in patients with HIV and have shown that some individuals have transient increased antiviral T cell responses (8). In an HIV+ patient treated with PD1 blockade for cancer, there was an increase in activation of antiviral T cells (115*). Lymphocytes transferred from elite controllers into patients with HIV also increased recipient CD8+ T cell activation with enhanced production of perforin and granzyme B (116). Importantly, antigen specific HIV responses in the brain can induce gliosis (117) and further contribute to neuronal injury. Therefore, strategies to monitor and protect the brain while activating HIV immune responses are needed.

Previous efforts at neuroprotection have been fraught with challenges. Anti-inflammatory strategies have been tested in over 20 clinical trials for HAND with few successes (22). None of these have entered mainstream therapy. However, recent work has demonstrated that protecting the CNS during HIV infection is possible. Intranasal delivered insulin reversed neuronal injury in an animal model of HAND (118), and is now being tested in PLWH. This benefit may be from a reduction in microglial activation and dampening of chronic inflammation (119). Other animal studies have shown that inhibiting JAK/STAT signaling reduces inflammation and reverses cognitive deficits (120). Further, pharmacologic inhibition of glutamate synthesis reduced the overproduction of glutamate from microglial cells and restored cognitive function in treated animals (121). Examples of targeting inflammation from outside the HIV field may also provide lessons for HIV. Immune-based therapies which lower inflammation, including IL-1β inhibition with the monoclonal antibody canakinumab, may reduce CVD in individuals without HIV (122). A recent pilot study in 10 PLWH on ART with viral suppression suggested that a single dose of canakinumab reduced plasma inflammatory markers and arterial inflammation. This finding suggests that attenuating inflammation may modulate atherosclerosis pathogenesis in HIV infection (123).

While these exciting developments suggest promising future therapeutics, some of the greatest benefits to patients are lifestyle changes. Moderate exercise improves learning and memory, which may be due to strengthening cardiovascular function, reducing inflammation and enhancing neurogenesis (124–128). Additionally, improving sleep, nutrition and social health have been linked to better cognition in PLWH (129), as has eliminating the use of drugs, alcohol and smoking (130). Importantly, these interventions are inexpensive and rapidly implementable (131).

Conclusion

Chronic inflammation is associated with mortality and significant morbidity and is a major complication in PLWH. While efforts are underway to cure HIV, a more nuanced consideration of the “unintended consequences” of further immune activation in the CNS are needed because the CNS is especially vulnerable to inflammatory processes. Residual viral replication, infected cell dysfunction, particularly long-lived microglia, and continuous expression of viral proteins all contribute to sustained chronic inflammation in PLWH. Importantly, activation of the latent viral reservoir, as part of cure initiatives, may well lead to further CNS damaging proinflammatory processes. Future research efforts should be focused on mitigating virally driven inflammation and preventing chronic inflammation.

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Key Points

- Tissue macrophages and microglia are functional viral reservoirs and contribute to chronic inflammation during HIV infection.
- Inflammation is a key mediator of CNS damage and is driven by residual viral replication, expression of viral proteins despite viral suppression, immune cell dysfunction and positive pro-inflammatory feedback loops.
- HIV cure strategies include activating viral reservoirs and triggering immune responses. Protecting the brain during these processes will be critical for their success.

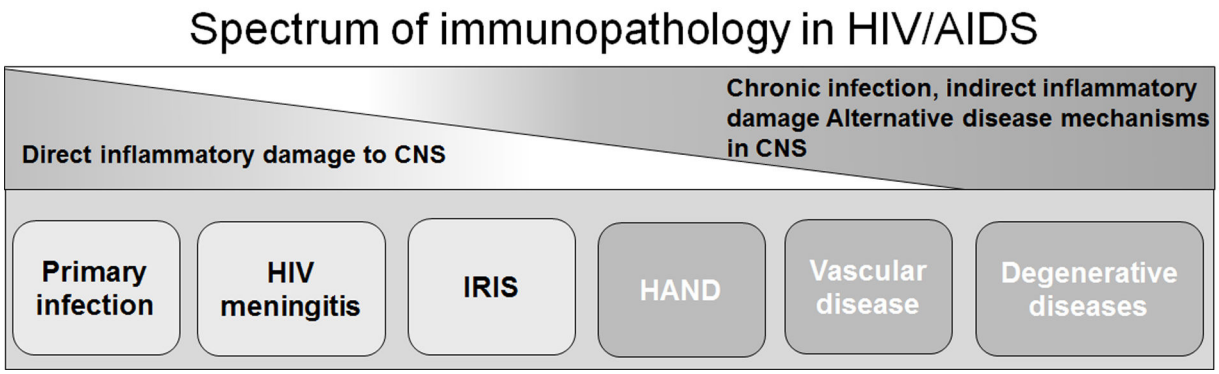

Figure 1. The immunopathology of HIV CNS disease.

The immune response during HIV infection can damage the CNS through direct and indirect mechanisms. Shortly after HIV infection, the virus enters the CNS and infects resident cells, inducing immune responses within this compartment that result in edema and bystander tissue damage. HIV infection is also associated with a lymphocytic meningitis, often occurring within weeks or months of initial infection (132). Encephalitis, primarily driven by CD8+ T cells can also occur in the absence of opportunistic infections (OIs) and is typically due to immune reconstitution inflammatory syndrome (IRIS). IRIS phenomena unrelated to OIs are relatively rare, but is the best direct example of a harmful effect of inflammation on neurological function (133). The immune system can also damage the CNS through indirect mechanisms. The best studied neurological complication associated with chronic inflammation is HAND. However, chronic inflammation within the context of HIV infection also contributes to the development of cardiovascular disease, a major contributor to CNS pathology in the era of ART, and neurodegenerative diseases.

Table 1.

HAND in the era of ART: Key Clinical Features.

• Dysexecutive syndrome with prominent disruption of attention, multitasking, impulse control, and judgment.
• Apathy and depressive symptoms
• Impairments in memory, specifically encoding and retrieval.
• Motor impairment ~ fine fractionated movements, mild rigidity, and imbalance