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Mechanisms of neuropathogenesis in HIV and HCV: similarities, differences, and unknowns

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Abstract

HIV and hepatitis C virus (HCV) have both been associated with cognitive impairment. Combination antiretroviral therapy (cART) has dramatically changed the nature of cognitive impairment in HIV-infected persons, while the role of direct-acting antivirals (DAA) in neurocognition of HCV-infected individuals remains unclear. Also, whether HIV and HCV interact to promote neurocognitive decline or whether they each contribute an individual effect continues to be an open question. In this work, we review the virally mediated mechanisms of HIV- and HCV-mediated neuropathogenesis, with an emphasis on the role of dual infection, and discuss observed changes with HIV viral suppression and HCV functional cure on neurocognitive impairments.

Keywords

HIV; HCV; Neuropathology; Neuroradiology; Neuropathogenesis; HAND

Introduction

For almost two decades, neurological manifestations ranging from poor sleep to cognitive impairment have been reported with chronic hepatitis C virus infection (Monaco et al. 2015). For almost twice that amount of time, patients with HIV infection have experienced symptoms ranging from cognitive impairment to severe dementia (Clifford and Ances 2013). Our understanding of the role of each virus and the mechanisms underlying these neuropathologies is evolving. While a significant amount of work has been done in HIV neuropathogenesis, there is a paucity of data about HCV neuropathology. This review will

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Compliance with ethical standards

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focus on the current understanding of virally mediated mechanisms of central nervous system (CNS) damage in HIV and HCV, and the similarities between them.

Overview of viral involvement in the CNS

HIV

Many of the neurological abnormalities in HIV infection center on cognitive impairment, initially described as very severe in the 1980s, then largely changing to milder and asymptomatic forms with the advent of combination antiretroviral therapy (cART) (Harrison and Smith 2011; Kranick and Nath 2012; Tan and McArthur 2012). The antecedents of these neuropsychological deficits are unclear with numerous possible sources, including persistent central nervous system viral reservoirs, chronic inflammatory cascades from the periphery, accelerated aging, vascular disease, substance use, or neurotoxic cART effects (Clifford 2017; Fauci and Marston 2015; Kranick and Nath 2012).

HIV entry in the CNS typically begins 1–2 weeks after systemic infection by crossing into the blood-brain barrier (BBB) via migrating infected peripheral blood monocytes (Gray et al. 1993; Haase 1986; Meltzer et al. 1990; Peluso et al. 1985). While the CNS is typically described as “immune-privileged,” the BBB is selectively permeable: peripheral blood mononuclear cells (PBMC), particularly monocytes, routinely cross the BBB and later differentiate into macrophages in the brain, replenishing the resident population (Strazielle et al. 2016). Cell-free HIV can also enter the CNS, where it can then infect macrophages (Churchill and Nath 2013). Additionally, HIV-infected lymphocytes can enter cells within the brain by cell-cell communication and has been shown in astrocytes in vitro (Russell et al. 2017).

Once in the CNS, the HIV-infected macrophages secrete pro-inflammatory chemokines and cytokines like monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interferon- γ (IFN- γ); this chemokine cascade promotes increased permeability across the BBB, prompting further translocation of monocytes (Gonzalez-Scarano and Martin-Garcia 2005). Of the five major CNS cell types (neurons, astrocytes, oligodendrocytes, perivascular macrophages, microglia), all are theoretically susceptible to HIV infection, however, perivascular macrophages and microglia are the most commonly infected by HIV (Cosenza et al. 2002; Wiley et al. 1999). Astrocyte infection by HIV has been described and is mostly restricted or latent, but can cause widespread damage, as it is the most abundant cell type in the brain (Churchill et al. 2009). Oligodendrocytes are susceptible to HIV per one study (Albright et al. 1996), but this finding has not been reproducible in the literature. HIV does not infect neurons (Gonzalez-Scarano and Martin-Garcia 2005).

Neuronal loss throughout the brain then occurs over time through two proposed mechanisms. The first is a direct, virally mediated effect through secreted viral proteins binding to neuronal cell surface receptors and causing calcium cytotoxicity in neurons (Eugenin et al. 2003; Haughey et al. 1999; King et al. 2010; Nath et al. 1996). The second is an indirect model, which suggests that neuronal death as a consequence of inflammatory

response of glial cells against HIV infection (Eugenin and Berman 2007; Eugenin et al. 2011; Gonzalez-Scarano and Martin-Garcia 2005).

HCV

The spectrum of neurological manifestations in chronic HCV include cognitive impairment, fatigue, sleep disturbance, and quality of life reduction (Monaco et al. 2015). Cognitive impairment occurs frequently in patients with HCV, regardless of viral load, genotype, or presence of cirrhosis. Impairment of executive function, sustained attention, working memory, verbal learning, and recall has all been described (Forton et al. 2001; Forton et al. 2002).

HCV sequences were first reported in the brain in 1996 (Bolay et al. 1996). RT-PCR analysis of a post-mortem brain in a patient with encephalomyelitis detected the HCV genome in the brain and brainstem, but not in the CSF (Bolay et al. 1996). Shortly after, HCV RNA was found in the cortical and subcortical white matter of post-mortem brain samples of two patients who underwent liver transplantation, developed recurrent HCV, and subsequently died from multi-organ failure and bacteremia (Vargas et al. 2002). The findings were thought to be part of a biological mechanism for HCV-associated neurological disorders. In another case series, HCV negative-strand RNA sequences were detected in six post-mortem samples, two of which had differing serum- and brain-derived HCV sequences (Radkowski et al. 2002). Immunohistochemical stains of post-mortem brain tissue of 12 HCV infected patients showed co-localization of HCV RNA with specific markers for microglia and rarely astrocytes (Wilkinson et al. 2009). Despite these findings suggesting HCV presence within the CNS, it remained unclear how HCV entered the CNS, as well as further details on its replicative capacity and inflammatory cascade once it passed the BBB.

Growing evidence from studies done by several groups suggested a number of key host cell molecules enable HCV entry, including low-density lipoprotein receptor (LDL-R), tetraspanin CD81, scavenger receptor class B member I (SR-B1), claudin-1, and occludin (Samreen et al. 2012). All of these major host cell molecules were found to be present in human brain endothelial cells, a key component of the BBB. Further experiments on primary derived brain microvascular endothelial cell lines (brain microvascular endothelial cells isolated from human brain) supported HCV entry and replication in vitro, providing a potential mechanism for HCV entry into the CNS (Fletcher et al. 2012). In another study, unique viral variants were found in the CSF of two cognitively impaired patients with HCV when compared to their peripheral blood samples, and compartmentalization was absent in infected patients without neurocognitive impairment (Tully et al. 2016).

Similarities and differences in virally mediated HIV and HCV neuropathogenesis

Neuroinvasion and compartmentalization in CNS

HIV is thought to enter the BBB while inside monocytes via a “Trojan horse” model, while HCV is thought to penetrate the BBB through uptake by the brain microvascular endothelial cell. HIV preferentially infects CD4+ T cells and HCV preferentially infects hepatocytes.

Despite the well-known tropism of each virus, HIV and HCV RNA have been found in other tissue compartments. HCV RNA has been detected in peripheral blood mononuclear cells (non-T cells), lymph nodes, ascites fluid, CSF, and brain matter (Table 1) (Antonucci et al. 2017; Morgello 2005; Weissenborn et al. 2009). HIV has been described in brain matter, lymph nodes, reproductive organs, lungs, and spleen (Costiniuk and Jenabian 2015). While viral copies have been demonstrated in all of these compartments, their replicative capacity and functional significance remains unclear.

Across various compartments, tissue-specific differences are found in HIV and HCV viral RNA. These findings suggest that viruses in the CNS may have more relation to each other than viruses in the blood, raising questions about when the virus entered this space and whether there is ongoing extrahepatic replication (Epstein et al. 1991; Forton et al. 2004; Radkowski et al. 2002; Reddy et al. 1996; Shimizu et al. 1997). While these studies have introduced the possibility of a latent reservoir for HCV in the brain through experiments on post-mortem brain samples, many of them were conducted in scenarios of uncontrolled infection. No cases of latent virus in the brain have been reported in patients treated and cured for their HCV. In contrast, once inside the brain, HIV is able to productively infect perivascular macrophages and microglia. Prior work by Fletcher et al. suggests that HCV co-localizes with microglia and sometimes astrocytes. Recent work also suggests that microglial activation as measured by neuroimaging markers in HCV-infected patients may be related to cognitive impairment (Pflugrad et al. 2016). The ability to determine replicative capacity of HCV in brain cells has been hindered by a lack of small animal models.

Chemokines and biomarkers

Chemokines and their receptors have been detected by many groups and are thought to have a role in HIV and HCV neuropathogenesis (Table 2). α - and β -chemokines have altered expression and are commonly found in the background of HIV encephalitis (Lavi et al. 1998; Zheng et al. 1999). CCR3 and CCR5 expressions have been reported in SIV-infected macaques, and CCR3 expression in microvascular endothelial cells was found in tissue samples of HIV-infected adult brains (Klein et al. 1999; Vallat et al. 1998). Despite clear patterns of abnormalities of chemokine expression in the HIV-infected CNS, the net effect of the expression profile has yet to be determined.

Similarly, in HCV, some clear patterns have emerged. Serum levels of IL-2 and IL-8 are increased with increasing liver fibrosis. TGF- β levels are also elevated, but levels decrease in cirrhosis (Neuman et al. 2007). In brain microvascular endothelial cell cultures, HCV infection induces CXCL10 elevation, likely through the phosphorylation of NF- κ B, which was subsequently blocked with neutralizing antibodies for HCV (Liu et al. 2016). In the HIV-associated dementia brain, CXCL10 is found in astrocytes, is induced by HIV tat, and is also found in microglia and brain endothelial cells (Williams et al. 2009). Its receptor, CXCR3, is found predominantly in microglia, as well as some neurons and astrocytes (Asensio et al. 2001). One proposed neuropathologic effect includes this chemokine and its receptor pair being involved in changing synaptic plasticity in the hippocampus (Vikolinsky et al. 2004). It was also hypothesized that the pair was responsible for inducing leukocyte infiltration in the brain, but that does not seem to be the case (Eugenin et al. 2006).

Neuropathologic mechanisms

The HIV-infected brain is not hallmarked by widespread infection, as neurons do not express CD4. Mechanisms driving neuronal loss in the brain depend upon active infection of perivascular macrophages and microglia disrupting CNS homeostasis. The two major mechanisms proposed in the literature involve a direct effect, through production of viral proteins, and an indirect effect, where neurons are damaged by HIV-induced inflammatory response.

Several in vitro experiments have shown that HIV gp120, through its interaction with chemokine receptors, leads to neuronal injury (Hesselgesser et al. 1998; Meucci et al. 1998; Meucci et al. 2000; Ohagen et al. 1999; Zheng et al. 1999). The majority of these experiments, however, involve CXCR4 as a co-receptor. While CXCR4 is present in microglia, neurons, astrocytes, and endothelial cells, many of the described isolates in the literature show CCR5 as the much more dominant receptor, making the in vivo relevance of gp120 unclear. Two other proteins, Tat and Vpr, have also been suggested to cause direct injury to neurons in vitro (Chang et al. 1997).

Another possibility is that increased expression of pro-inflammatory cytokines like TNF and IL-1 β from the HIV-infected CNS recruit virus-specific T cells into the CNS (Kim et al. 2004; Marcondes et al. 2001) and activate “bystander” cells (Kaul and Lipton 1999; Williams and Hickey 2002). The increasing insult to the CNS upregulates expression of activation markers in macrophages (Glass et al. 1995), further increases production of TNF (Wesselingh et al. 1993), production of free radicals (Adamson et al. 1999; Blond et al. 2000), and apoptosis of astrocytes (Thompson et al. 2001). Increased TNF levels promote high levels of glutamate release, which, around neurons, can promote toxic levels of Ca²⁺ influx leading to their apoptosis (Foos and Wu 2002).

Research on HCV-mediated neurotoxicity began much more recently and the exact mechanisms are still being unraveled. In one study, primary human astrocytes were inefficiently infected by HCV despite expressing all necessary receptors for viral entry. However, HCV exposure to astrocytes induced a robust IL-18 expression and led to direct neurotoxicity (Liu and Zhao 2014). The HCV core protein may be linked to sustained ERK/STAT3 activation through TLR2-IRAK1 signaling, leading to neurodegeneration (Paulino et al. 2011). In another study, HCV core protein exposure in the CNS induced higher expression levels of IL-1 β , IL-6, and TNF- α in microglia, but not in astrocytes. Levels of HCV core protein levels in the CNS during physiologic infection are unclear. CXCL10 expression was also increased in microglia and astrocytes, and these pro-inflammatory effects were potentiated by the HIV Vpr protein (Vivithanaporn et al. 2010). HIV tat, when added to PBMCs, can potentiate replication of HCV through induction of CXCL10 (Qu et al. 2012). PBMCs are known to cross the BBB on a periodic basis.

Neurologic manifestations in patients

Over half of HIV patients suffer from some form of cognitive impairment detectable by neuropsychiatric testing (Table 3) (Heaton et al. 2010). Often coupled with this impairment is a notable functional decline, by self-report or from family members. This may involve

requiring significant assistance with activities of daily living, being unable to maintain former employment, or having greater difficulty with aspects of cognition (Antinori et al. 2007). The profile of neuropsychological deficits in HIV-infected persons has evolved since the advent of cART, however, it is confounded by comorbidities commonly seen in HIV-infected persons. Nevertheless, there are consistent reports of motor slowing in the cART era suggesting that basal ganglia damage may be the underlying pathogenesis (Heaton et al. 2011).

Patients with HCV have reported a host of neurologic symptoms including memory loss, depression, fatigue, and sleep disturbances (Table 3) (Monaco et al. 2015). Cognitive impairment occurs frequently in patients with HCV unrelated to the levels of viral load, genotype or underlying cirrhosis, or genotype and in the absence of structural damage to the brain. Impairment of executive function, sustained attention, working memory, verbal learning, and recall has all been reported (Forton et al. 2001; Forton et al. 2002). An additive effect of HCV to cognitive impairment in HIV-infected patients is controversial. Some groups found that HCV likely further impairs cognition on a background of HIV infection (Cherner et al. 2005; Hinkin et al. 2008; Thiyagarajan et al. 2010), while others have not (Clifford et al. 2015). In a study in Southern Brazil, greater cognitive impairment was seen in HCV mono- and HCV-HIV co-infected groups as compared to healthy controls, but impairment was comparable between the mono- and co-infected groups (de Almeida et al. 2018). Similarly, no clear additive effect was seen with HCV in HIV co-infected patients with regard to white matter microstructural integrity (Heaps-Woodruff et al. 2016).

Neurologic manifestations in both viruses may stem from differing neurodegenerative processes. In HIV, the process likely occurs through entry of the virus into the CNS compartment, causing a pro-inflammatory cytokine cascade, disrupting CNS homeostasis, and driving neuronal loss. Early viral suppression has a dramatic impact on the extent of neurodegeneration in HIV-infected patients (Clifford 2017). In HCV, distribution of HCV RNA and NS3/5A proteins in cortical and subcortical telencephalic areas seem to activate glial cells. This activation causes alterations in brain metabolites such as reduced dopamine and serotonin levels, suggesting a role for glial cell activation leading to CNS dysregulation (Forton et al. 2001; Forton et al. 2002).

Treatment effects

The advent of cART and DAA has led to dramatic changes in the natural history of patients infected with HIV and/or HCV. In HIV, rates of AIDS-defining illnesses such as toxoplasmosis of the brain and primary CNS lymphoma have dramatically dropped (Lima et al. 2015). The epidemiology of neurocognitive disorders associated with HIV has largely shifted from the classical HIV-associated dementia (HAD) to asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disease (MND) (Clifford 2017). Despite this progress, however, over half of patients that frequent HIV clinics and are virally suppressed have neurocognitive abnormalities detectable by neuropsychological testing (Gisslen et al. 2011).

In HCV, the introduction of DAA was much more recent than cART, and subsequent follow-up is therefore less, but recent studies suggest that functional cure confers an improvement in neurocognitive function. In one study, sustained virologic response (SVR) was associated with improvement in verbal episodic memory, selective attention, and phonemic fluency (Barbosa et al. 2017). In another study, SVR did not improve neurocognitive performance compared to controls, but benefits were seen in a particular subgroup of responders who had improvements in their white matter integrity on neuroimaging (Kuhn et al. 2017).

Concluding remarks

Through similar routes of infection, up to a third of people with HIV are also infected with HCV (Alatrakchi and Koziel 2003; Chen and Morgan 2006; Operskalski and Kovacs 2011). Both viruses have been found in CSF and in brain matter, and many patients suffer from several different neuropsychiatric symptoms, ranging from poor sleep to severe dementia. The brain microvascular endothelial cell likely plays a critical role in HCV viral entry, and HIV likely enters through monocytes. Mechanisms of neurodegeneration in HIV are likely related to the inflammatory response generated by presence of the virus in the brain, whereas HCV-mediated neural damage may be caused by direct interaction of viral proteins with CNS cells. HCV and HIV viral proteins together potentiate expression levels of inflammatory cytokines and chemokines, and this likely occurs in the co-infected brain.

The proposition of neurological manifestations from HCV infection is not without controversy. A multicenter AIDS Clinical Trial Group (ACTG) study did not show any difference in neurocognitive defects between HIV/HCV co-infected patients when compared to HIV mono-infection (Kemmer et al. 2012). Other studies have not entirely clarified whether HIV/HCV co-infection creates an additive effect on cognitive impairment (Clifford et al. 2005; Perry et al. 2005). Prior trials have shown improvement in cognitive function between SVR and non-SVR subjects (Kemmer et al. 2012), but the reason behind that improvement is not known. It could potentially be linked to HCV eradication in the liver, but also be due to CNS penetration of DAA.

Further research is needed to elucidate the mechanisms driving neuronal loss and guide CNS-targeted therapies, as well as to investigate whether HIV and HCV cause an interaction versus an additive effect on cognitive impairment or whether HCV functional cure in HIV-infected patients leads to improved neurocognitive function, thereby expanding the use of DAAs for improving extra-hepatic outcomes.

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Table 1

HIV and HCV RNA detection in various tissue compartments. Check marks indicate presence of detectable RNA in the corresponding cell type/tissue compartment from previous patient cases and laboratory experiments with their associated references. *BMEC*, brain microvascular endothelial cell; *CSF*, cerebrospinal fluid; *HIV*, human immunodeficiency virus; *HCV*, hepatitis C virus.

	HIV RNA	HCV RNA
Lymphocytes	✓ (Haase 1986)	
Monocytes	✓ (Meltzer et al. 1990)	✓ (Morgello 2005)
Brain matter	✓ (An et al. 1999; Davis et al. 1992)	✓ (Bolay et al. 1996; Radkowski et al. 2002; Vargas et al. 2002)
Perivascular macrophages	✓ (Cosenza et al. 2002)	
Microglia	✓ (Wiley et al. 1999)	✓ (Wilkinson et al. 2009)
Astrocytes	✓* (Churchill et al. 2009)	✓ (Wilkinson et al. 2009)
Oligodendrocytes	** (Codazzi et al. 1995)	
Neurons		
BMEC	** (Liu et al. 2002)	** (Fletcher et al. 2012)
CSF	✓ (Patel et al. 2000)	✓ (Tully et al. 2016)

* Astrocyte infection by HIV is controversial.

** Cell is susceptible to infection in vitro

Table 2

Selected chemokines and receptors expressed in brains of HIV and HCV infected patients. *CCL*, CC-chemokine ligand; *CCR*, CC-chemokine receptor; *CXCL*, CXC-chemokine ligand; *CXCR*, CXC-chemokine receptor; *IP10*, interferon- γ -induced protein of 10 kDa; *MCP*, monocyte chemoattractant protein; *RANTES*, regulated upon activation normally T cell expressed and presumably secreted; *IL*, interleukin; *BMEC*, brain microvascular endothelial cell; *BBB*, blood-brain barrier; *HIV*, human immunodeficiency virus; *HCV*, hepatitis C virus. NT2.N Human Ntera-2 cell line (human neuronal cell line)

Chemokine	Receptor	HIV	HCV	Effect
CXCL10 (IP10)	CXCR3	Microglia, neurons, astrocytes (Asensio et al. 2001; Williams et al. 2009)	BMEC cell cultures (Liu et al. 2016)	Synaptic plasticity, leukocyte infiltration
CCL5 (RANTES)	CCR1, CCR3, CCR5	Microglia, neurons, astrocytes (Kaul and Lipton 1999; Meucci et al. 1998; Meucci et al. 2000)		Monocyte recruitment, macrophage migration
CCL2 (MCP1)	CCR2	Neurons, astrocytes, NT2.N cells (Andras et al. 2003; McManus et al. 2000; Park et al. 2001; Song et al. 2003)		Neuroprotective
IL-6	IL-6 receptor	BMEC (Tyor et al. 1992)	Microglia, astrocytes (Vivithanapom et al. 2010)	Neuroprotective
IL-8 (CXCL8)	CXCR1, CXCR2	Microglia, neurons, astrocytes, oligodendrocytes (McManus et al. 2000)	Serum (Neuman et al. 2007)	Synaptic plasticity
TGF- β	TGF- β receptor	Microglia, astrocytes (Wahl et al. 1991)	Serum (Neuman et al. 2007)	Neuroprotective

Table 3
Commonly reported neurologic manifestations reported in HIV and HCV infected persons

Abnormality	HIV	HCV
Cognitive impairment	(Clifford and Ances 2013)	(Fontana et al. 2005; Forton et al. 2001; Forton et al. 2002; Lowry et al. 2010)
Impaired executive function	↑↑	↑
Decreased attention	↑	↑
Memory impairment	↑↑↑	↑
Psychiatric abnormalities	(McIntosh et al. 2015)	(Carta et al. 2012; Ferenci and Staufer 2008)
Sexual dysfunction		↑
Emotional distress	↑↑	↑
Depression	↑	↑↑
Fatigue	(Low et al. 2014)	(Poynard et al. 2002)
Poor sleep quality	↑	↑
Increased nocturnal activity	↑↑	↑
Altered sleep patterns	↑↑	↑
Quality of life	(Cooper et al. 2017)	(Forton et al. 2002)
	↓	↓