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Neuromuscular complications in HIV: effects of aging

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Abstract There has been speculation that chronic HIV infection is a condition of accelerated aging that may lead to early onset of disease in multiple organ systems. The neuromuscular disorders of HIV, in particular distal symmetric polyneuropathy and myopathies, are also seen in the general population among older patients. As the HIV-infected population ages, there may be deleterious synergistic effects of age and chronic HIV infection on the brain, peripheral nerve, and muscle. In this review, we explore commonalities between the clinical features and putative mechanisms of neuromuscular disorders and HIV.

Keywords HIV · AIDS · Aging · Neuropathy · Myopathy · Neuromuscular

Introduction

HIV-positive patients are living longer due to highly active antiretroviral therapy (HAART). However as a consequence of this longevity, individuals are accruing multiple comorbid illnesses, many of which are typically associated with older age such as cardiovascular disease, cancer, and osteoporosis. This phenomenon has led to speculation that HIV and its treatment may cause accelerated aging. The lay press has referred to the phenomenon as "the new AIDS epidemic" (*New York Magazine*; November 1, 2009). Neuromuscular disorders, such as peripheral neuropathy, are common in both HIV-infected individuals and the elderly and are associated with aging within the HIV population. This epidemiologic data suggests the potential for common mechanisms underlying these disorders (Table 1). In this article, we review the neuromuscular complications of HIV with an emphasis on the potential role of aging.

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Peripheral neuropathy

Clinical characteristics

Distal symmetric polyneuropathy (DSP), also referred to as HIV-associated sensory neuropathy, is the most common neuromuscular complication of HIV. Prevalence estimates vary based on the definition of DSP used and the overall health of the population but usually fall between 30–60% (Evans et al. 2011; Ellis et al. 2010). Primary HIV-associated DSP (HIV-DSP) and antiretroviral therapy-associated toxic neuropathy (ATN) are the two most common etiologies; however, they are not readily distinguishable (McArthur et al. 2005). Most commonly, ATN is associated with dideoxynucleoside analogues (d-drugs), including stavudine, didanosine, and zalcitabine (McArthur et al. 2005; Cornblath and Hoke 2006). While the use of d-drugs has dramatically declined in the developed world due to the availability of less toxic alternative antiretroviral therapy (ARV), they remain in common use in the developing world.

While many individuals with DSP are asymptomatic, most present with bilateral numbness, paresthesias, and dysesthesias in the distal lower extremities. It is unknown why some patients have painful symptoms and others do not. In DSP related to diabetes, local hemodynamic changes are under study (Quattrini et al. 2007). Neurologic examination reveals decreased vibration, temperature, and pinprick sensation in a stocking distribution, reduced or

Table 1 Potential mechanisms of neuromuscular disorders common to HIV infection and aging

	Mechanism
Distal symmetric polyneuropathy	Mitochondrial dysfunction
	Greater burden of comorbidities (e.g., diabetes, renal impairment)
	Polypharmacy
	Immunosenesence
Metabolic disorders of muscle	Medication toxicity
	Hormonal changes
	Chronic Inflammation
	Accumulation of visceral adipose
	Autonomic changes

absent ankle reflexes, and relative preservation of motor function (Cornblath and McArthur 1988; Schifitto et al. 2002). In more severe cases, signs and symptoms may extend further up to the legs or involve the hands. However in many patients, the symptoms are mild and do not progress. Some patients may even show signs of improvement (Simpson et al. 2006). While the diagnosis of DSP is usually apparent based on history and neurological examination, the diagnosis can be confirmed by nerve conduction studies/electromyography (NCS/EMG) and skin punch biopsy evaluating epidermal nerve fiber density (ENFD) (Zhou et al. 2007). Common abnormalities include decreased or absent sural sensory nerve action potential on NCS and decreased ENFD.

In the pre-HAART era, risk factors for HIV-DSP included age, nutritional deficiencies, alcohol exposure, and lower CD4 count (Childs et al. 1999). In the HAART era, the risk factors include age over 40 years, history of diabetes, nadir CD4 count of <50 cells/mm^3 and viral load of >10,000 copies/ml (Lichtenstein et al. 2005). In addition, concurrent use of protease inhibitors in conjunction with dideoynucloside analogues has been associated with higher odds of ATN (Evans et al. 2011).

Pathophysiology

HIV-DSP is a length-dependent degeneration of large myelinated and small unmyelinated nerve fibers consistent with a "dying back" phenomenon (Cavanagh 1964). However, unlike most other peripheral neuropathies, there is also some evidence of cell death at the neuronal level (Cornblath and Hoke 2006) and degeneration of the rostral gracile tract (Rance et al. 1988).

Proinflammatory cytokines, including tumor necrosis factor-α, interferon α, interleukin 6, and inflammatory mediators like nitric oxide, have been found in dorsal root ganglia of some patients (McArthur et al. 2005). Animals and in vitro models seeking to explore the role of neuronal damage in HIV-DSP have shown that the HIV envelope protein, gp120, induces inflammation and indirect neuronal injury via perineuronal Schwann cells in dorsal root ganglia (Keswani et al. 2003), leading to neuronal cell death and secondary axonal degeneration (Melli et al. 2006). However, recent work supports a localization of the primary pathology to the distal axon. In a study of peripheral nerves taken at autopsy from HIV-positive individuals with and without DSP, increased levels of mitochondrial DNA mutations were seen in those with DSP, suggesting that mitochondrial dysfunction and energetic failure in the distal axon could be responsible for DSP (Lehmann et al. 2011). This mechanism is particularly attractive because it accounts for the length-dependent pattern observed in HIV-DSP. There is little evidence of direct infection of neurons by HIV, with a paucity of virus in the peripheral nerves of these patients (Brinley et al. 2001).

In vitro studies of ATN suggest a pathophysiological mechanism distinct from that due to gp120 (McArthur et al. 2005). Exposure to dideoxynucleosides has been associated with inhibition of gamma DNA polymerase leading to a reduction of the amount of mitochondrial DNA (Chen and Cheng 1989) and mitochondrial metabolic abnormalities (Brinkman et al. 1998).

The effect of aging on HIV neuropathies

Normal aging is associated with peripheral neuropathy. Studies of asymptomatic, healthy elderly people show a high prevalence of clinical signs of diminished peripheral nerve function (e.g., loss of ankle reflexes and diminished distal sensation) and a decline in neurophysiologic parameters including sensory nerve and compound muscle action potentials and conduction velocity on nerve conduction studies (Bouche et al. 1993; Jacobs and Love 1985; Vrancken et al. 2002). Corresponding pathologic changes in sural nerve specimens include decreased density of large and small myelinated fibers and increased nuclear density (Jacobs and Love 1985). Intraepidermal nerve fiber density in the distal part of the leg may be diminished (Umapathi et al. 2006; Goransson et al. 2004). This pattern of abnormalities is consistent with a length dependent, axonal process similar to that observed in HIV (Herrmann et al. 2006).

Age is recognized as a risk factor for HIV-DSP in multiple studies (Ellis et al. 2010; Lichtenstein et al. 2005; Morgello et al. 2004). A recent large cohort study of 2,141 patients examined the prevalence of and risk factors for peripheral neuropathy in HIV-infected individuals who initiated ARV therapy between 2000 and 2007 (Evans et al. 2011). After 3 years of therapy, 32% of subjects had evidence of peripheral neuropathy while 9% were symptomatic, despite immune reconstitution with CD4 >350 cell/mm^3 and HIV-1 RNA <400 copies/ml. Older age was associated with both peripheral neuropathy and symptomatic

neuropathy, after adjusting for covariates. In addition, increasing age was associated with increased odds of peripheral neuropathy and symptomatic neuropathy among those prescribed neurotoxic ARV, and lower odds of recovery despite the withdrawal of neurotoxic ARV.

There are several potential explanations for the association of age with HIV-DSP including increasing burden of comorbid disease, mitochondrial dysfunction, and immunosenescence (discussed below). As the HIV population ages, age-associated comorbidities, long-term toxicity from ARV, and the physiological changes of the senescence process will likely play increasingly important roles in their health outcomes. Older individuals with HIV infection have more coronary artery disease, hypertension, hypercholesterolemia, diabetes, and renal disease than younger individuals, and these burdens increase with every decade of life (Vance et al. 2011). Diabetes and chronic renal disease, both known to be associated with peripheral neuropathy may increase the risk of HIV-DSP. In addition the number of prescribed medications increases with age, thus increasing the potential for drug–drug interactions and adverse effects (Vance et al. 2011). Many commonly used medications have well-documented neurotoxic side effects, for example vincristine.

The aging process itself may also contribute to the development of HIV-DSP. Although the mechanisms underlying aging are incompletely understood, a role for free radicals is likely. According to the free radical theory of aging, senescence is the result of accumulation of damage from oxidative stress (Harman 2001). As oxidative phosphorylation in the mitochondria contributes to the bulk of reactive oxygen species in the cell, the free radical theory of aging can be perceived as a mitochondrial theory of aging (Hofhaus et al. 2003). Other theories of aging also involve the mitochondria. The mitochondrial–lysosomal axis theory of aging explains the accumulation of lipofuscin, undegradable oxidative products of oxidative stress that contribute to the aging of cells (Brunk and Terman 2002). In addition, the accumulation of damage to mitochondrial DNA with age may trigger cell death (Hofhaus et al. 2003). Thus mitochondrial abnormalities associated with aging may accelerate the mitochondrial abnormalities seen in the distal axon in HIV-DSP.

The phenomenon of immunosenesce may also be relevant in the pathophysiology of HIV-DSP and other neuromuscular complications of HIV. Immunosenescence refers to changes in innate and adaptive immune function associated with age that may lead to increased susceptibility to infection, malignancy, and autoimmunity. These changes are myriad and incompletely understood but include decreased production of IL-2 and IL-2 receptor (Bestilny et al. 2000; Fagnoni et al. 2000), leading to T cell dysfunction with a shift from a naïve to a memory T-cell phenotype (Negoro et al. 1986), increased levels of some proinflammatory cytokines, and decreased CD4/CD8 ratio (Deeks 2011). In addition, age-related low-grade chronic inflammation includes a decline in adaptive immune response and concurrent upregulation of the innate response (Giunta et al. 2008). Some of these changes resemble those found in HIV-positive persons, which is not surprising since it has been hypothesized that immunosenesence is related to chronic antigenic stimulation, for example chronic cytomegalovirus infection. Thus age-related immunologic senescence may compound HIV-associated immune dysfunction. Older individuals who are chronically infected may have a depletion of CD4+ T cells and delayed immune reconstitution following the initiation of HAART. In individuals with untreated HIV, chronic immune activation results in accelerated aging of T cells and is associated with faster disease progression (Cao et al. 2009). Immunosenescence has been examined in other forms of neuropathy including vasculitic and paraproteinemic neuropathies (Pletz et al. 2003). Potential mechanisms by which immunosenescence might lead to neuropathy include less specific inflammatory reactions or increases in antibodies which target neural or vascular epitopes. The role of immunosenescence in HIV-DSP is speculative, but to the extent that immune-mediated mechanisms are involved in its development, immunosenescence might be an exacerbating factor.

HIV-infected individuals, particularly those with poorer immune function, are at risk for neuropathic complications of other infectious agents, particularly varicella zoster virus (VZV) and cytomegalovirus (CMV). Prior to the initiation of routine vaccination in 1995, VZV was typically acquired in childhood. Following the acute illness (chicken pox), VZV becomes dormant in dorsal root ganglia. Reactivation typically occurs in older adults due to waning cellular immunity, resulting in herpes zoster, a painful vesicular rash in a dermatomal distribution, also known as shingles (Oxman et al. 2005). Neuropathic pain commonly persists even after the lesions have healed, a condition known as postherpetic neuralgia. The CDC currently recommends vaccination against VZV for all adults over the age of 60 (Harpaz et al. 2008). Herpes zoster is also common in HIV-infected individuals, even those with relatively preserved immune function. However since the vaccination is a live attenuated virus, it is not routinely given to HIV-positive patients due to safety concerns. Thus these patients may be at particular risk for herpes zoster as they age. A clinical trial evaluating the safety and efficacy of the VZV vaccine in HIV-infected individuals was recently completed and results are expected soon (http://clinicaltrials.gov/ct2/show/NCT00001125).

According to the CDC, 50–80% of adults have serologic evidence of CMV infection. Chronic latent CMV infection has been implicated as a stimulus responsible for the low-grade inflammation seen with aging and associated with increased cardiovascular risk (Simanek et al. 2011). In HIV, CMV typically reactivates in the setting of profound immunocompromise, typically with CD4+ cell counts of

<50/mm^3. Upon reactivation, CMV can affect multiple organ systems causing, for example, retinitis and gastroenteritis. CMV can also infect peripheral nerve directly, leading to inflammation and necrosis (Said et al. 1991). Clinically CMV neuropathy typically presents with motor and sensory deficits in the distribution of the infected nerves or nerve roots. These syndromes are not seen in the healthy elderly, but may become an issue in the aging HIV population.

Treatment

There is currently no neuroregenerative treatment available for HIV-DSP and so treatment is focused on alleviation of the associated neuropathic pain. The selection of appropriate neuropathic pain treatment in the older patient requires careful consideration. Older persons are particularly susceptible to medication side effects such as sedation, confusion, or urinary retention. They also may be taking more medications than younger patients, increasing the risk of harmful drug interactions. Among the agents commonly used to treat neuropathic pain, particular caution should be used with the tricyclic antidepressants in older patients. Gabapentin, with some evidence for efficacy in painful HIV DSP, has demonstrated reasonable safety and tolerability in the elderly (Rowan et al. 2005). A high concentration capsaicin patch showed significant pain reduction in a controlled trial of painful HIV DSP (Simpson et al. 2008). A single 30-min local application of this topical agent to the feet provides at least 3 months of pain relief without systemic side effects. This may be particularly helpful in older patients who may be more vulnerable to side effects of medication.

HIV-associated myopathy

HIV-associated myopathy (HAM) is clinically and pathologically similar to polymyositis. It is characterized by a slowly progressive weakness of proximal limb muscles (Simpson and Bender 1988). Daily activities that are particularly affected by proximal weakness include arising from a low seat, climbing stairs, or holding the arms aloft. Other symptoms of myopathy include fatigue, myalgia, muscle cramps, and dysphagia. Neurological examination reveals symmetric weakness of proximal muscles, including neck flexors, with preserved deep tendon reflexes and sensation unless there is coexistent DSP. Laboratory evaluation typically reveals increased creatine kinase levels and myopathic changes on EMG. The diagnosis may be confirmed by muscle biopsy revealing myofiber degeneration associated with inflammatory infiltrates of T cells and macrophages (Illa et al. 1991).

HAM is sufficiently rare that the epidemiology is uncertain. There is no clear association with age and in fact the disorder was more common prior to the advent of ARVs when most HIV-infected individuals were young. However polymyositis in the general population is associated with older age. One large epidemiologic study found that the mean age of adult patients with polymyositis to be 60 (Bernatsky et al. 2009). The phenomenon of immunosenescence, discussed above, may play a role in autoimmunity in aging. Explanatory mechanisms include loss of self-tolerance and alteration of apoptosis in T cells leading to autoimmune diseases by an accumulation of clonal cells (Prelog 2006). The effects of aging on an immune system already compromised by HIV and reconstituted with HAART might be expected to heighten the risk of autoimmune diseases such as polymyositis. However it is unclear that this is the case since HAM continues to be quite rare, despite the aging of the HIV population.

Due to the rarity of HAM, the prognosis and best course of treatment are not well established. One series of 13 US patients found that over half of those treated with corticosteroids attained complete remission and were able to discontinue therapy after a mean of 9 months (Johnson et al. 2003). In another study of 14 HIV-positive African women with biopsy documented myositis, 9 improved with steroids. The outcome was not available for the remaining five (Heckmann et al. 2010).

Metabolic disorders of muscle in HIV

Aging is associated with changes in body composition including decreased muscle mass and increased adiposity (Boirie 2009). Loss of muscle mass is considered an important cause of disability in the elderly and has been referred to as sarcopenia of aging when muscle loss occurs in isolation and sarcopenic obesity when it is accompanied by an increase in adipose tissue (Schrager et al. 2007). Similar changes in body composition have been recognized in HIV (Yarasheski et al. 2011). Muscle wasting was observed commonly in the early AIDS epidemic, usually in association with advanced disease and overall weight loss. Although muscle wasting still occurs in the HAART era, it is now more often accompanied by accumulation of adipose, particularly in the abdominal region, resulting in no net change in weight or weight gain. The fullest form of these body composition changes is the lipodystrophy syndrome which is characterized by redistribution of fat from the limbs to the trunk and viscera accompanied by hyperlipidemia and insulin resistance (Carr et al. 1998). The similarity of body composition changes in HIV to those observed in the elderly may be an example of accelerated aging in HIV. The etiology of muscle loss in HIV and aging and the reason for its association with changes in fat distribution are not fully understood. In some HIV-infected patients with wasting

syndrome, defined as a greater that 10% loss of body weight, muscle biopsy revealed features of HIV myopathy (Simpson et al. 1990). The complex metabolic interplay between muscle and visceral and peripheral adipose and the role of hormonal and autonomic regulation are under study.

Sarcopenia of aging is thought to be due to age-related changes in hormone levels and sensitivity to hormones as well as chronic low-grade inflammation associated with aging (Boirie 2009). Similar mechanisms have been cited in HIV-associated muscle loss. Hormonal factors include increased cortisol production, testosterone deficiency, and perturbation in the growth hormone/insulin-like growth factor-I axis (Coodley et al. 1994a). Results of clinical trials of tesamorelin, a growth hormone releasing hormone analog, have provided additional evidence of the importance of hormones in the regulation of body composition in HIV (Falutz et al. 2010). Patients with lipodystrophy who received tesamorelin experienced an increase in lean body mass, a decrease in visceral adipose tissue, a decrease in inflammatory markers, and no change in subcutaneous adipose. These changes were largely reversed after the drug was discontinued. Inflammatory mechanisms of sarcopenia of aging include myofibrillar protein degradation and decreased protein synthesis promoted by the proinflammatory cytokines TNF-α, IL-1, and IL-6 (Boirie 2009). Similar cytokine abnormalities have been proposed as a mechanism of muscle loss in HIV (Coodley et al. 1994b). Chronic viral infection in HIV-positive patients provides a clear source of inflammation. In aging, the accumulation of visceral adipose has been proposed as a source of chronic inflammation. Visceral adipose secretes a number of active mediators including TNF-α and IL-6 (Wajchenberg 2000). This may have direct relevance to lipodystrophy in which visceral adiposity is a prominent feature.

Inflammation, loss of muscle, and accumulation of visceral adipose can form a deleterious positive feedback loop in both sarcopenic obesity and the lipodystrophy syndrome. Visceral adipose appears to be relatively protected from insults that damage peripheral adipocytes, such as ARV or chronic inflammation. This resistance may be due to the trophic effect of local hormonal factors such as higher density of glucocorticoid receptors (Wajchenberg 2000) and increased ability to enzymatically convert cortisone to cortisol via 11β-hydroxy reductase (Bujalska et al. 1997). When peripheral adipocytes are damaged, they release lipid which may be taken up by myocytes or by visceral adipocytes. Both have metabolic consequences. Intramyocellular lipid is increased in HIV-positive patients with lipodystrophy (Luzi et al. 2003; Torriani et al. 2006) and may alter glucose entry and metabolism in the myocyte contributing to insulin resistance (Gan et al. 2002). More visceral adipose leads to increased production of proinflammatory cytokines, which is one mechanism by which visceral adipose increases cardiovascular risk (Van Gaal et al. 2006).

In addition to the potential role of inflammation, the metabolic effects of ARVs on muscle and adipose tissue have been extensively documented. The best example of ARV toxicity in muscle is the myopathy associated with high-dose AZT. Shortly after its introduction in 1987, several cases of a necrotizing myopathy were reported (Van Gaal et al. 2006). Theories as to the mechanism of the myopathy abounded and included: mtDNA depletion, AZT-induced oxidative stress, direct inhibition of mitochondrial bioenergetic machinery, depletion of L-carnitine, and myofiber apoptosis (Scruggs and Dirks Naylor 2008). Notably HIV-infected patients with myopathy who have not been exposed to AZT or d-drugs may show similar mitochondrial abnormalities on muscle biopsy (Morgello et al. 1995), suggesting that HIV itself is toxic to the mitochondria. Modern HAART regimens do not include AZT at doses sufficient to cause clinical myopathy; however, subtler metabolic changes likely persist. For example, ARVs have been reported to decrease the activity of glucose transporter 4 in the myocyte cell membrane, leading to decreased glucose uptake, insulin resistance, and hyperinsulinemia (Sathekge et al. 2010). ARVs also have multiple potentially deleterious effects in adipose tissue. ARVs may alter adipocyte gene expression leading to derangement in lipid metabolism within the adipocyte and secretion of proinflammatory cytokines (e.g., TNF-α and interleukin-6) (Pacenti et al. 2006; Lihn et al. 2003). ARVs may also lead to mitochondrial toxicity in adipose causing compromise of metabolic pathways and increased cellular apoptosis (Buffet et al. 2005).

In summary, HIV-positive patients may show body composition changes typically seen in older adults, including muscle loss and increased adiposity especially visceral adipose. These changes may be initiated by the inflammatory effects of HIV, by hormonal changes or by toxic effects of ARV. Once initiated the process of muscle loss and shift of adipose centrally may be self-perpetuating. It is likely that as HIV-positive patients age, this process will become more pronounced and could lead to significant disability.

The role of the autonomic nervous system

Changes in autonomic nervous system function are observed with advancing age. Cardiovagal modulation of heart rate is diminished, as is sudomotor function (Low et al. 1997). Counterintuitively, sympathetic activity is increased as demonstrated by studies of muscle sympathetic nerve activity (Ng et al. 1993). This increase in sympathetic activity is associated with both cardiovascular disease and body composition changes although authors have differed as to causality. For example, Christou and colleagues have focused on obesity as a cause of cardiovagal dysfunction and proposed that decline in cardiovagal function observed

in aging might be explained by increased adiposity in the elderly (Christou et al. 2004). Others have pointed to the autonomic nervous system as a mechanism by which obesity and age might lead to cardiovascular disease (Skrapari et al. 2007). Finally, autonomic neuropathy has long been recognized in diabetes, a metabolic consequence of obesity (Low et al. 2004).

If HIV indeed contributes to accelerated aging, and is associated with metabolic abnormalities, one might expect significant autonomic dysfunction in HIV-positive populations, especially considering the high prevalence of peripheral neuropathy in HIV and the frequent comorbidity between peripheral and autonomic neuropathy in other diseases. Early literature reported that autonomic neuropathy was common in HIV-positive patients (Cohen and Laudenslager 1989; Freeman et al. 1990). While these results have not been consistently reproduced in the HAART era (Sakhuja et al. 2007; Compostella et al. 2008), there are several studies from the cardiac literature that demonstrate cardiovagal autonomic dysfunction in HIV as reflected by decreased heart rate variability (Lebech et al. 2007; Mittal et al. 2004).

There are several reports examining the role of the autonomic nervous system in the lipodystrophy syndrome. The autonomic nervous system is an important determinant of body composition. Adipose tissue is innervated by both sympathetic and parasympathetic fibers and in turn produces endocrine and metabolic factors that may feed back to the hypothalamus (Fliers et al. 2003a). In general, sympathetic innervation promotes lipolysis and parasympathetic activity promotes fat accumulation. However these effects differ in visceral versus subcutaneous adipose, for example, visceral adipocytes are more sensitive to catecholamine-induced lipolysis (Wajchenberg 2000). Fliers and colleagues examined the somatotopic arrangement of autonomic neurons in the brainstem and found that neurons bound for visceral adipose were anatomically distinct from those bound for subcutaneous adipose. They hypothesized that the lipodystrophy syndrome might be a selective autonomic neuropathy (Fliers et al. 2003b). Later work has found some alteration in cardiovagal modulation in the lipodystrophy syndrome (Chow et al. 2006).

Conclusion

In many ways, the complications of chronic HIV infection in nerve and muscle resemble those of aging. These likenesses are apparent clinically and include a length-dependent axonal peripheral neuropathy and loss of muscle mass associated with accumulation of central adiposity. There are similarities in underlying mechanisms as well, including mitochondrial dysfunction, immunosenesence, and changes in hormonal and autonomic function. These similarities raise the concern that aging in the HIV-infected population may be a harmful synergy that leads to a greater prevalence of neuromuscular diseases. However there is also the potential that recognition of discoveries in the field of aging will lead to further understanding of the neurological complications of HIV.

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