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Understanding Frailty, Aging, and Inflammation in HIV Infection

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Abstract

Frailty is a clinical syndrome initially characterized in geriatric populations with a hallmark of age-related declines in physiologic reserve and function and increased vulnerability to adverse health outcomes. Recently, frailty has increasingly been recognized as a common and important HIV-associated non-AIDS (HANA) condition. This article provides an overview of our current understanding of frailty and its phenotypic characteristics, and evidence that they are related to aging and to chronic inflammation that is associated with aging and also with long-term treated HIV infection. The etiology of this chronic inflammation is unknown but we discuss evidence linking it to persistent infection with cytomegalovirus in both geriatric populations and people living with HIV infection.

Keywords

frailty; inflammation; HIV infection; IL-6; T-cell immunity; CMV infection

INTRODUCTION

The number of older persons living with HIV/AIDS has risen dramatically over the past decade. As a result, chronic conditions commonly encountered in geriatric populations have increasingly become major health concerns for this vulnerable aging population. One example is frailty, an important age-related clinical syndrome characterized by diminished physiologic reserve and increased vulnerability for subsequent morbidity and mortality. A large body of literature suggests that chronic inflammation, an age-related immune dysregulation, may play an important role in the development of frailty in older adults in the general population. More recently, frailty has been described in several cohort studies of HIV-infected persons (1–6). This article provides an overview about our current understanding of frailty, aging, and chronic inflammation in people living with HIV infection.

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FRAILITY IN GERIATRIC POPULATIONS

In the geriatrics literature, frailty is defined as a state of increased vulnerability in old age. Frailty is recognized as an important clinical syndrome in old age, which a) results from age-related declines in physiologic reserve and complexity in resting dynamics involving multiple physiologic systems, b) manifests by maladaptive responses to every day or acute stressors, and c) leads to a vicious cycle towards functional decline and other serious adverse health outcomes (7–15). In older adults, this chronic condition is commonly described by two conceptual models: the phenotype model (frailty syndrome(7)) and the cumulative deficit model (frailty index (16)). As the frailty index is defined by counting the number of accumulated deficits identified by a comprehensive geriatrics assessment, which has not been validated in HIV-infected populations (17) and does not easily allow further investigation of underlying mechanisms of frailty, this article will focus on the frailty phenotype model. According to the most widely used model of this type, that described by Fried et al (7), the frailty phenotype (FP) in older adults consists of three or more of the following: weakness (measured by grip strength), low physical activity, slowed motor performance (measured by walking speed), exhaustion, and unintentional weight loss (7). Using this definition, frailty is a distinct clinical entity, differing from disability as measured by impairment in activities of daily living (ADL) and from comorbidity as defined by the presence of 2 diseases, i.e., two other prevalent conditions in older adults (7;18). Based on this definition and its various modified versions, the estimated prevalence of frailty in the United States is 7–12% among community-dwelling men and women age 65 years and older, and over 25% among those older than 85 years (7;18), with significant geographic variation (19;20). The frailty phenotype independently predicts a number of serious adverse health outcomes in community-dwelling older adults, including acute illness, falls, cognitive decline, hospitalization, disability, dependency, and mortality, adjusting for comorbidities (7;8;21). In addition, substantial evidence suggest that assessment of frailty is useful for pre-operative evaluation for elderly patients who undergo surgery (22;23) as well as risk stratification in patients with cancer (24–26), cardiovascular diseases (27), and end-stage renal disease on chronic hemodialysis or after renal transplantation (28;29). Frailty may also be a clinical marker for overall immune functional decline in older adults, as it has been shown to identify those who fail to mount adequate immune responses to influenza and pneumococcal immunizations and are at high risk for these common infections and their complications (30;31).

AGING AND FRAILITY IN HIV-INFECTED POPULATIONS

Similarities between frailty, aging, and HIV infection were recognized early in the HIV pandemic. For example, weight loss was recognized as a cardinal feature of untreated HIV infection, along with immune activation and high levels of catabolic cytokines and other bioactive molecules (32;33). After the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s, life expectancy for HIV-infected persons increased dramatically (34); in effect, HIV became a treatable disease with long life possible, and the question shifted to the effect of chronic treated HIV infection on health and longevity. It is estimated that about half of the HIV-infected individuals in the United States will be > 50 years of age by 2015 [CDC. HIV/AIDS among persons aged 50 or over. <http://>

www.cdc.gov/hiv/surveillance/resources/reports/2005report/. 2014]. Aging of the HIV-infected population is also evident in Asia and even in sub-Saharan Africa (35;36). As HIV-infected persons live longer, age-related chronic conditions termed HIV-associated non-AIDS (HANA) conditions have increasingly become major health concerns despite suppression of HIV viral load to clinically undetectable levels (37–39). Among HANA conditions, frailty is increasingly being recognized as an important syndrome that identifies HIV-infected people who are at higher risk for adverse health outcomes.

The first studies of frailty in HIV+ men were done in the Multicenter AIDS Cohort Study (MACS) by Desquilbet et al in the late 2000s. The goal of these studies was to take advantage of data already acquired over many years (since 1994) to approximate the prevalence and import of frailty in people with HIV infection, since at this time frailty had never been studied in HIV+ populations. Available data was insufficient to assess the full Fried FP exactly, so it was approximated using available data that incorporated four of the five criteria of the Fried FP: weight loss, exhaustion, slowness, and low physical activity. (The assessment of weakness (i.e., grip strength) was not incorporated into the MACS protocol until October 2005 and therefore could not be used in this study.) The result was a phenotype defined by expression of 3 of the 4 criteria that were addressed. Thus, this phenotype differed slightly from that described by Fried et al; accordingly it was termed the frailty-related phenotype, or FRP. The FRP had a prevalence of 4.4% among HIV-uninfected men aged 65 years and older, which was similar to the prevalence of frailty observed in the Cardiovascular Health Study for men of similar ages (7). Additional analyses showed that the prevalence of the FRP was lower in the HAART era than in the pre-HAART era, and was inversely related to the CD4 T cell count in a similar way in both the pre- and post-HAART eras (3). Finally, presence of the FRP at the time of HAART initiation was an independent predictor of AIDS-free and overall survival after adjusting for other known predictors such as HIV viral load and CD4 T cell count (40). This suggested that the FRP was a valid measure of frailty in HIV+ men, i.e., that it was a predictor of adverse health outcomes, just as the FP has been shown to be in the elderly general population.

The studies by Desquilbet et al were retrospective, meant to use available data to start to understand the occurrence and meaning of frailty in an HIV+ population. However, it was also important to assess the same FP that had been validated in the elderly general population, i.e., the Fried FP. Therefore, as mentioned above, around the same time as the studies by Desquilbet et al were begun, the MACS began measuring walking speed and grip strength. Data from 2007 through 2011 were analyzed by Althoff et al (41), who published prevalence, incidence, and reversion statistics for HIV+ men who had received HAART and for HIV– men (Fig. 1). These analyses took advantage of a notable strength of the MACS, namely the ability to compare the HIV+ population to a demographically similar HIV– population rather than to the general aging population. The prevalence of the FP increased with age in both HIV– and HIV+ men, as expected, but there was an excess in the HIV+ men between the ages of 50–69. This excess was at least partially explained by a higher prevalence of several HIV-independent risk factors for the FP in the HIV+ men than in the HIV– men: diabetes mellitus, smoking, kidney disease, and depressive symptoms

(i.e., a score of 16 or more on the CES-D questionnaire administered at each semiannual MACS study visit).

The FP has not yet been validated in this cohort, which is younger than the HIV– cohorts in which it was initially validated and also differs in the inclusion of HIV+ people. Analyses to validate it by linking it to clinically meaningful outcomes are underway in the MACS. However, data from other studies have supported the clinical validity of the FP in HIV+ populations. For example, the Fried FP was measured cross-sectionally in the AIDS Linked to the Intravenous Experience (ALIVE) cohort of people with a history of injection drug use (IDU) in Baltimore, MD (2). This study found that expression of the Fried FP did indeed predict mortality in this cohort of IDUs. Recently, another study from the ALIVE cohort found that poor physical function, as assessed by the short physical performance battery (SPPB) was also an independent predictor of mortality (42). In addition, data from the Veterans Aging Cohort Study (VACS) showed that an adapted frailty-related phenotype was predictive for hospitalization and mortality in aging HIV-infected veterans (6). Other studies of the clinical aspects of frailty in HIV+ populations, as well as the definitions of frailty that have been used in these studies, have recently been reviewed in detail (17).

In these studies, factors that have been associated with frailty in HIV+ populations include age, lower current or nadir CD4 T-cell counts and other HIV-infection related measures, inflammation, hepatitis C co-infection and other comorbidities, depressive symptoms, and certain social factors (e.g., lower education, unemployment) (1;2;4;38;39;41;43).

CHRONIC INFLAMMATION AND FRAILITY

The aging immune system is characterized by a low level chronic systemic inflammatory state, termed “InflammAging” (44). This inflammatory phenotype is marked by elevated circulating levels of markers of inflammation (e.g., C-reactive protein (CRP) and the pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α)), and is associated with increased morbidity and mortality in older adults (44–46). Clinically, an increase in the white blood cell (WBC) count is recognized as an important cellular marker of systemic inflammation. Studies over the past decade, including some from our group, have provided a large body of evidence supporting the role of heightened chronic inflammation in contributing to frailty in the geriatric populations above and beyond the age-related inflammatory state. For example, several studies demonstrated significant associations between frailty and elevated serum levels of IL-6, CRP, and TNF- α in community-dwelling older adults (47–52). Studies also showed direct associations between frailty and increased total WBC count, albeit still under the upper limit of the normal range, and counts of specific subpopulations including neutrophils and monocytes (50;53). With respect to T lymphocyte subpopulations, frailty is associated with increased counts of CD8+CD28– T cells and CCR5+ T cells, the latter of which has a type-1 pro-inflammatory phenotype (54–56). *Ex vivo* studies showed not only a frailty-associated increase in LPS-stimulated IL-6 production by peripheral blood mononuclear cells (PBMCs), but also upregulation in expression of inflammatory pathway-specific genes by purified peripheral monocytes (57;58). Moreover, constitutive upregulation in monocytic expression of CXCL-10, a potent pro-inflammatory chemokine, was highly correlated with elevation in

serum IL-6 levels in frailty (59). Elevated serum levels of neopterin, a well-known molecular marker for immune activation mediated by monocytes and macrophages, were associated with frailty in community-dwelling older adults, independent of IL-6 levels (60).

Individual inflammatory molecules, such as IL-6, may directly contribute to the frailty syndrome or its cardinal components (such as decreased muscle strength/power and slowed motor performance) (47;49;50;61;62). As frailty involves dysregulation in multiple physiologic systems (15), chronic inflammation may contribute to frailty through its detrimental effects on diverse physiologic organ systems. For example, studies have shown that circulating IL-6 levels have inverse associations with hemoglobin concentration and serum insulin-like growth factor-1 (IGF-1) levels in frail older adults, but not in non-frail controls; low hemoglobin and IGF-1 levels were each independently associated with frailty, as well (47;63;64). In addition, WBC counts were inversely associated with IGF-levels (65). Taken together, it is suggested that chronic inflammation plays a key role in the pathogenesis of frailty, directly or through other intermediate pathophysiologic processes.

Although immunological changes associated with frailty have been investigated in many studies in the general elderly population, few studies have been done in the HIV+ population. These immunological changes are very pertinent to studies of aging and frailty in HIV+ people, because the huge immune activation that is characteristic of untreated HIV infection, though dramatically improved by HAART, is not completely resolved even with achievement of clinically undetectable HIV viral load and the most complete viral suppression possible (reviewed in (66)). In particular, many immune activation markers that were associated with aging remain elevated, including IL-6 and TNF- α (67). This residual immune activation, along with the occurrence of many age-related diseases at younger ages in people living with HIV than in the general population, led to the hypothesis that people living with HIV experienced premature or accelerated aging (39). This hypothesis has been controversial, partly because of fundamental gaps in our knowledge of the biological basis and metrics of aging (68) and partly because the HIV-infected population is younger than the general population, thus predisposing to a younger age distribution of any aging-related disease in the HIV+ population than in the general population (69).

With these considerations in mind, recent studies have begun to address this question in HIV + populations. Erlandson et al (70) analyzed a panel of cellular and serologic immune activation markers in HIV+ people with high (n=49) or low (n=31) physical functioning, matched by age, sex, and date of HIV diagnosis. Frailty was assessed (as defined by the Fried phenotype), but frailty per se was not an outcome in this analysis, but was one of the criteria for low functioning, along with performance on the Short Physical Performance Battery. They found that the low-functioning group had higher serum IL-6 and T-cell activation (expression of CD38 and HLA-DR); the latter was statistically significant for CD8 T-cells. Significance persisted after adjustment for most recent CD4 T-cell count, tobacco use, and hepatitis B or C. Markers were not analyzed explicitly in relation to frailty, and there was no HIV- comparison population. In the VACS, the VACS risk index, which includes age, clinical biomarkers including CD4 T-cell count and plasma HIV RNA and predicts hospitalization and mortality, was also found to be related to markers of inflammation (71) and with fragility fractures (72).

In the MACS, we have analyzed the relationships between a panel of 24 serologic immune activation markers, including pro-inflammatory cytokines, chemokines, and CRP (73), and frailty. For this study, we defined frailty (or non-frailty) as expression (or non-expression) of the Fried FP at two consecutive semiannual study visits. This definition was implemented because MACS studies indicated that nearly half of men who expressed the FP at one semiannual study visit did not express it at the next visit, and we wanted to minimize misclassification of frailty (41). The study was nested within a group of men in whom these markers had been measured over many years, which included a preponderance of HIV+ men. We found that many markers were significantly higher in the frail HIV+ men (n=109) than in the non-frail HIV+ (n=605) men, including IL-6, C-reactive protein (CRP), TNF- α , soluble CD14, and soluble TNF receptor II ((74) and manuscript submitted). The higher CRP remained significant after adjustment for demographics and comorbidities. It is noteworthy that most of these markers are similar to the markers that have been associated with frailty in the elderly HIV- population. These studies establish an association of immune activation, particularly of monocyte-macrophages (as evidenced by higher serum levels of IL-6, CRP, TNF- α , and related molecules), and frailty in HIV+ populations. Studies to assess whether this activation precedes or predicts the onset of frailty are now underway.

CHRONIC CMV INFECTION, FRAILTY, AND HIV INFECTION

Because of the profound medical, functional, and socioeconomic consequences of frailty for the vulnerable aging HIV-infected population, it is imperative to advance our understanding of the pathogenesis of this syndrome and use this information to develop interventional strategies. However, despite the apparent role of chronic inflammation in the pathogenesis of frailty, etiologies and mechanisms that underlie the immune and inflammatory pathway activation leading to chronic inflammation remain to be elucidated (see (66) for review). One important contributing factor may be chronic cytomegalovirus (CMV) infection. This virus, which is highly prevalent in both the geriatric population and HIV+ persons, may cause clonal T-cell expansion, leading to immune activation and chronic inflammation with their associated adverse health outcomes (75–79). The potential importance of CMV in the pathogenesis of systemic inflammation is supported by the fact that it is the target for a very large proportion of circulating T cells in both HIV- and HIV+ people, which is often greater than 10% and can be 30–40% (for example, (80)(81;82)). Some studies have found a direct association between positive CMV serology and frailty and functional decline in the elderly (49;83), but data are conflicting (84;85).

A possible explanation for this conflict is that anti-CMV IgG serology is a crude measure that merely indicates prior exposure to the virus, not necessarily a chronic (persistent) infection. We recently showed that defining chronic CMV infection by detection of CMV DNA in peripheral blood monocytes, rather than by positive CMV serology, led to a much stronger association of CMV infection with increased frequencies of CMV pp65 (NLV)-specific CD8+ T cells and immune activation (elevated serum neopterin levels) in an elderly population (86;87). In addition, we demonstrated higher serum IL-6 levels and increased CMV pp65 (NLV)-specific CD8+ T cells in older women with chronic CMV infection as assessed by CMV DNA in monocytes. (88). These findings support the hypothesis that

chronic CMV infection is correlated with immune activation. Although CMV infection is common in people infected with HIV, and a very large proportion of the T-cell repertoire is devoted to CMV in HIV-infected persons, even those on long term HAART, (39;81;82), it remains to be determined if CMV-induced immune responses are quantitatively related to systemic levels of inflammation or to frailty in either HIV+ or HIV- populations.

CONCLUDING REMARKS

Whether HIV infection is a good model for accelerated aging is debatable (89). It is clear that as HIV-infected individuals age, frailty, initially described as a geriatric syndrome, has increasingly been recognized as a common HANA condition in this population. Mounting evidence supports the role of chronic inflammation as a contributing factor to frailty in older adults, and this is likely to be true in people with chronic, well-treated HIV infection, who have higher levels of systemic inflammation than demographically similar HIV- people, some of which persist even after taking co-morbidities into account. The precise mechanisms of this residual immune activation are poorly understood, and it remains to be determined if the mechanisms of inflammation in normal aging and in treated HIV infection are similar or different. Chronic CMV infection, a common persistent viral co-infection in both older HIV- people and people living with HIV, appears likely to be an important etiology and underlying mechanism for activation of immune and inflammatory pathways that contribute to the development of frailty and other HANA conditions in this population (39;90). Trials of anti-CMV pharmacotherapy could help address this question (91). An attractive long-term perspective is the potential development of effective vaccine-based preventative strategy for CMV infection, based on promising results from recent studies on CMV immunization in other patient populations (92–95). However, much remains to be learned about this complex viral infection, particularly its diagnostic evaluation as well as its impact on T-cell immunity, and a more exciting era of this active research is coming.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.