Sean X. Leng, MD, PhD, Yi Huang, PhD, Linda P. Fried, MD, MPH

Frailty and Molecular Inflammation in Older Adults

The evaluation and treatment of frail, older patients constitute a cornerstone of the care for older Americans, particularly in LTC settings. Recent work has led to the development and validation of an operational definition of frailty as a syndrome and a screening tool to identify those who are frail. Further progress has been made in better understanding the pathogenesis of this syndrome, particularly inflammation and its potential contributing role in the pathogenesis of frailty. Advancing the knowledge of frailty and its physiologic basis is critically important, because it not only improves the ability to identify this most vulnerable subset of older patients, but also provides a basis for potential development of interventional strategies that may prevent or delay its clinical consequences. This article provides an overview on the syndrome of frailty, including the role of molecular inflammation as an important pathophysiologic contributing factor.

Until recently, the term "frailty" had been used more frequently than it has been defined. Geriatricians have long been aware of a syndrome made up of multiple coexisting conditions, weakness, immobility, and poor tolerance to physiologic or psychological stress. Owing to a lack of diagnostic criteria, geriatricians say, "I know it when I see it, but what I see may not be the same as what everyone else sees." Given the ever-growing elderly population, particularly the rapid expansion of the segment aged 85 years and older (the "oldest old"), searching for a standardized definition of frailty and understanding its physiologic basis has become paramount.

Recent work by Fried and colleagues[1–4] suggests frailty is a syndrome in old age and a state of decreased physiologic reserve and high vulnerability for subsequent morbidity and mortality. Frailty has also been described as a syndrome with a loss of complexity in resting dynamics involving multiple organ systems, manifested by maladaptive responses to stressors, leading to a vicious cycle towards functional decline and other adverse clinical outcomes.[5,6] The phenotypic characteristic of frail older adults is now recognized to be a syndrome consisting of three or more of the following: weakness, low physical activity, slowed motor performance, exhaustion, and weight loss.[1,4] The presence of three or more of these characteristics is independently predictive of a host of adverse clinical outcomes, including acute illness, falls, hospitalization, dependency, and early mortality, adjusting for comorbidities.[1] The estimated prevalence of this syndrome is 7% to 10% among community-dwelling individuals aged 65 years and older and up to one-third of those aged 80 years and older.[1,6] The phenotypic characteristic described above was adopted at a recent American Geriatrics Society (New York City) and the National Institute on

Dr. Leng is Assistant Professor of Medicine, Division of Geriatric Medicine and Gerontology, Dr. Fried is Professor of Medicine, Epidemiology, Health Policy, and Nursing, Johns Hopkins University School of Medicine, Baltimore, and Dr. Huang is a faculty member at Erickson School of Aging Studies, University of Maryland, Baltimore.

This work was supported in part by the National Institutes of Health, National Institute on Aging, an R21 AG024235 (to Dr. Leng), the Paul Beeson Career Development Award K23 AG028963 (to Dr. Leng), and the Claude D. Pepper Older Americans' Independence Center Grant P30 AG021334 (to Dr. Field: Principle Investigator and to Dr. Leng: Research Career Development.)

Aging Research Conference on Frailty in Older Adults and is now widely used as the preliminary criteria for frailty.[3,4]

Based on the above validated and now widely used frailty criteria, the manifestations of frailty, as a clinical syndrome, encompass a constellation of symptoms including weakness, fatigue, inactivity, unintentional weight loss, and decreased food intake. Signs of frailty that are often cited include sarcopenia (loss of muscle mass), balance and gait abnormalities, deconditioning, and decreased bone mass (Figure). Weakness (as measured by muscle strength or power) and slowed motor performance (measured by walking speed) appear to be the central components of the frailty syndrome. Consistent with the definition of a syndrome, the symptoms and signs of frailty may vary across this constellation of possible manifestations with multiple components present, but they are not always the same ones from patient to patient.

Frailty is recognized as a distinct clinical entity distinguished from comorbidity and disability, two other prevalent conditions in older adults, especially in LTC settings.[1,6] These three conditions, at various degrees, are all predictive of adverse clinical outcomes, and as a result, have significant overlap. However, the main features of frailty (including decreased functional reserve, impairment in multiple physiological systems, and reduced ability to regain physiological homeostasis after a stressful and destabilizing event) make the distinction of frailty from disability or comorbidity relatively easy. Disability suggests individuals have chronic limitations or dependency in mobility and/or activities of daily living (eating, bathing, dressing, toileting, and ambulating) or instrumental activities of daily living (shopping, housekeeping, cooking, driving, taking medications, and the handling of finances).

Although many (but not all) frail individuals are disabled, not all disabled persons are frail. For example, older patients who suffer severe disability secondary to a major cerebral vascular accident or stroke may maintain relatively intact function in other physiological systems and thus, are not frail. As time passes, these individuals may develop frailty if they do not recover from their disability. Therefore, disability is likely an outcome of frailty or a contributor to frailty.

Comorbidity indicates the presence of multiple chronic diseases. Not surprisingly, comorbidity is associated with increased risk of adverse outcomes, as evidenced by higher short-and long-term mortality, and significantly increases physical disability when compared with those who do not have diseases. However, the mere presence of two or more diseases in itself, even if in relatively severe forms, may not identify the vulnerable group of patients or those who are frail. If these comorbid conditions are inadequately treated and/or more diseases accumulate, these patients may develop frailty.

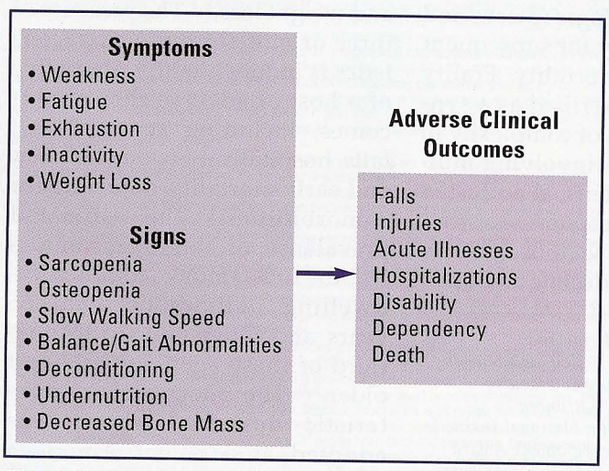

Figure. Clinical manifestations and consequences of the geriatric syndrome of frailty.

The etiology for the syndrome of frailty is currently unknown. Disability, comorbidity, and malnutrition are potential risk factors. Old age is clearly another risk factor, as the prevalence of frailty increases with age. Emerging evidence suggests that age-related molecular inflammation may significantly contribute to frailty in older adults.

MOLECULAR INFLAMMATION AND AGING

Inflammation has been defined as a local and acute process characterized by cardinal signs of heat, pain, swelling, redness, and loss of function. Contrary to this classic definition of local inflammatory response, molecular inflammation refers to a chronic inflammatory process, albeit operating at much lower than acute levels, as demonstrated by the enhanced expression of several mediators such as interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α).[7] The molecular inflammatory process, with or without apparent underlying etiology, usually presents itself in a graded and continuous, although not always linear, manner. Although the relationship between molecular inflammation and aging is yet to be fully understood, numerous studies have demonstrated an age-related increase in circulating levels and production of IL-6, TNF-α, and other molecules mediating molecular inflammation. In addition, C-reactive protein (CRP), generally considered as a biomarker and gross measurement of molecular inflammation, increases during aging. More importantly, molecular inflammatory processes have been implicated as predictors or initiators of, or even

contributors to, chronic diseases and conditions of aging.[7] For example, molecular inflammation has been linked with cardiovascular diseases, osteoarthritis, osteoporosis, Alzheimer's disease, sarcopenia, cancer, insulin resistance and diabetes, and rheumatoid arthritis —diseases or conditions primarily associated with aging.

MOLECULAR INFLAMMATION AND FRAILTY

A major characteristic of the syndrome of frailty is the anatomical and/or functional impairment of multiple physiological systems. Increasing evidence has demonstrated significant associations of frailty with abnormalities or dysregulations in multiple physiologic systems, including cardiovascular, hematopoietic, nutritional, endocrine, immune, and inflammation systems.[3,4] For example, Newman and colleagues[8] showed significant association of subclinical cardiovascular disease with frailty. In addition, Chaves and colleagues[9] suggested a significant effect of anemia and cardiovascular disease on frailty in community-dwelling older women. Data from two separate large cohort studies have shown that low nutrient intake and decreased micronutrient concentrations are associated with frailty.[10,11] In addition, other studies have shown that decreased levels of insulin-like growth factor-1 (IGF-1) and dehydroepiandrosterone sulfate (DHEA-S), two major endocrine parameters, are associated with frailty and its central components (muscle strength and walking speed).[12,13]

Significant evidence supports an important role of molecular inflammation in the syndrome of frailty. Elevated IL-6 levels have been observed in frail older adults compared with those in nonfrail older persons.[14] Data from the Cardiovascular Health Study have shown significant association of frailty with CRP.[15] A subsequent age-, race-, and sex matched pair study has shown that frail older adults have significantly higher IL-6 production by the peripheral blood mono-nuclear cells and the isolated immune cells, upon stimulation with lipopolysaccharide, compared with nonfrail controls.[16] In addition, more recent data have suggested that frailty is associated with elevated counts of white blood cells (WBCs), the cellular marker of this molecular inflammation, and that both WBC and IL-6 have independent contributions to frailty.[17] Furthermore, molecular inflammation may contribute to the syndrome of frailty through other intermediary systems, such as hematopoietic and endocrine systems. This is supported, at least in part, by the observations of inverse associations between IL-6 and hemoglobin levels and between IL-6 and IGF-1 levels only in the frail group, but not in the nonfrail group, and synergy between high IL-6 and low IGF-1 in their associations with decreased muscle strength and walking speed.[12–14] Therefore, the results of these studies strongly support the notion that molecular inflammation significantly contributes, directly and through other intermediary systems, to the syndrome of frailty.

Since elderly patients with frailty are the most vulnerable subset of older adults, meticulous and interdisciplinary geriatric care is critical in this patient population.

THE TREATMENT OF FRAILTY

From a therapeutic point of view, frailty syndrome can be classified into primary and secondary frailty. Frailty secondary to congestive heart failure, thyroid diseases, cancer, tuberculosis and other infections, and those diseases that are responsive to therapy should be treated accordingly. If diseases or conditions are ruled out as the cause of frailty and frailty appears to be primary, clinicians should institute supportive interventions early. These include targeting the environmental provocations that can trigger or accelerate the manifestations of frailty, especially low activity, inadequate nutrition, and catabolic medications. Attention to maintaining strength and nutritional intake may include the prescription of regular exercise and nutritional supplementation, if indicated.

Although no evidence is currently available to support the use of anti-inflammatory therapy for frailty, cytokine-based therapeutic modalities targeted to molecular inflammation are being explored in several other inflammatory conditions. In addition, data suggest that regular exercise may have an anti-inflammatory effect in older adults.

Since elderly patients with frailty are the most vulnerable subset of older adults, meticulous and interdisciplinary geriatric care to proactively manage and prevent comorbid conditions, disability, and risk factors is critical in this patient population. A comprehensive geriatric care plan that is tailored to the needs of these vulnerable patients, and that keeps their personal values and goals in mind, will help them maintain function, dignity, and quality of life.

CONCLUSION

Frailty is a common geriatric syndrome characterized by decreased physiologic reserve and increased vulnerability for subsequent adverse health outcomes. Recent development of the operationalized definition and diagnostic criteria has improved our ability for the evaluation of frailty in the elderly. It has also advanced the knowledge about the physiologic basis of this syndrome. Molecular inflammation, marked by elevated levels of inflammatory markers, appears to be an important contributing factor to frailty. Although no specific treatment is currently available for frailty, early recognition, treating underlying disease, and early institution of the supportive interventions with a comprehensive geriatrics care plan are critical to prevent frailty-associated adverse health outcomes, particularly in the LTC setting.

REFERENCES

1. Fried LP, Tangen CM, Walston J, et al: Frailty in older adults: Evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:146-156.
2. Fried LP, Walston JD: Frailty and failure to thrive, in Hazzard WR, Blass JP, Halter JB, et al (eds): *Principles of Geriatric Medicine and Gerontology.* New York City, McGraw Hill, 2003.
3. Walston J, Hadley E, Ferrucci L, et al: Research agenda for frailty in older adults: Toward a better understanding of physiology and etiology: Summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am Geriatr Soc* 2006;54: 991-1001.
4. Fried LP, Hadley EC, Walston JD, et al: From bedside to bench: Research agenda for frailty. *Sci Aging Knowledge Environ* 2005;31:pe24.
5. Lipsitz LA: Dynamics of stability: The physiologic basis of functional health and frailty. *J Gerontol A Biol Sci Med Sci* 2002; 57:115-125.
6. Fried LP, Ferrucci L, Darer D, et al: Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci.* 2004;59:255-263.
7. Tracy R, Ferrucci L, Harris T, et al: Workshop on Inflammation, Inflammatory Mediators, and Aging. Bethesda, MD, National Institute on Aging, 2004.
8. Newman AB, Gottdiener JS, McBurnie MA, et al: Associations of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci* 2001;56:158-166.
9. Chaves PH, Semba RD, Leng SX, et al: Impact of anemia and cardiovascular disease on frailty status of community-dwelling older women: The Women's Health and Aging Studies I and II. *J Gerontol A Biol Sci Med Sci* 2005;60:729-735.
10. Bartali B, Frongillo EA, Bandinelli S, et al: Low nutrient intake is an essential component of frailty in older persons. *J Gerontol A Biol Sci Med Sci* 2006;61:589-593.
11. Semba RD, Bartali B, Zhou J, et al: Low serum micronutrient concentrations predict frailty among older women living in the community. *J Gerontol A Biol Sci Med Sci* 2006;61:594-599.
12. Leng S, Cappola A, Andersen R, et al: Serum levels of IGF-1 and DHEA-S and their relationships with serum IL-6 in the geriatric syndrome of frailty. *Aging Clin Exp Res* 2004;16:153-157.
13. Cappola AR, Xue QL, Ferrucci L, et al: Insulin-like growth factor I and interleukin-6 contribute synergistically to disability and mortality in older women. *J Clin Endocrinol Metab* 2003;88:2019-2025.
14. Leng S, Chaves P, Koenig K, et al: Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: A pilot study. *J Am Geriatr Soc* 2002;50:1268-1271.
15. Walston J, McBurnie MA, Newman A, et al: Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: Results from the Cardiovascular Health Study. *Arch Intern Med* 2002;162:2333-2341.
16. Leng S, Yang H, Rose N, et al: Decreased cell proliferation and altered cytokine production in frail older adults. *Aging Clin Exp Res* 2004;16:249-252.
17. Leng S, Xue Q, Tian J, et al: Inflammation and frailty in older women. *J Am Geriatr Soc* 2007;55:864-871.

DISCLOSURE

The authors have indicated they have no relevant commercial or financial relationships to disclose.

Address for correspondence: Sean X. Leng, MD, PhD, Division of Geriatric Medicine and Gerontology, Johns Hopkins University School of Medicine, John R. Burton Pavilion, 5505 Hopkins Bayview Circle, Baltimore, Maryland 21224.