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Vulnerability: The Crossroads of Frailty and Delirium

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Abstract

Frailty and delirium, though seemingly distinct syndromes, both result in significant negative health outcomes in older patients. Frailty and delirium may be different clinical expressions of a shared vulnerability to stress in older patients and future research will determine whether this vulnerability is age-related, pathological, genetic, or environmental or, most likely, a combination of all of these factors. This paper explores the clinical overlap of frailty and delirium, describes possible pathophysiological mechanisms linking the two, and proposes research opportunities to further our knowledge of the interrelationships between these important geriatric syndromes.

Frailty, a diminished ability to compensate to stressors, is generally viewed as a chronic condition, while delirium is an acute change in attention and cognition. However, there is a developing literature on transitions in frailty status around acute events, as well as on delirium as a chronic, persistent condition. If frailty predisposes a patient to delirium and delirium delays recovery from a stressor, then both syndromes may contribute to a downward spiral of declining function, increasing risk, and negative outcomes. Additionally, frailty and delirium may have shared pathophysiology, such as inflammation, atherosclerosis, and chronic nutritional deficiencies, which will require further investigation.

The fields of frailty and delirium are rapidly evolving and future research may help to better define the interrelationship of these common and morbid geriatric syndromes. Because of the heterogeneous pathophysiology and presentation associated with frailty and delirium, typical of all geriatric syndromes, multicomponent prevention and treatment strategies are most likely to be effective, and should be developed and tested.

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INTRODUCTION

Frailty and delirium are key geriatric syndromes that can impact independent functioning. Geriatric syndromes are defined by a constellation of signs and symptoms to describe the heterogeneous response of the older patient to physiological and metabolic challenges, rather than the classic textbook presentation of a disease.[1, 2] This presentation results from the complex interaction of age, physiology, integrated control mechanisms, and pathology. Homeostasis is the regulation of an organ system to maintain a constant internal environment. The age-related decline in physiologic function in nearly every organ system results in a constricted range over which homeostasis can be maintained, which is termed presbyhomeostenosis.[3] Additionally, the reduction in responsiveness of integrated physiologic regulatory systems[4] limits the ability to recruit other organ systems to assist with the compensation to a stressor. Age-related pathology or systemic disease can further reduce homeostatic capacity and lead to symptomatic decompensation. This combination of decreased physiological reserve and system regulation reduces the capacity to adapt to stressors with age. Clinically, these stressors present heterogeneously (in the organ system made most vulnerable by homeostenotic processes) as geriatric syndromes such as falls, incontinence, delirium, or frailty.[5]

Frailty and delirium appear to be distinct clinical phenotypes. However, in practice, both syndromes can manifest in response to a stressor in vulnerable elders. Either frailty or delirium may predominate but the interactions between these syndromes and ensuing long-term consequences have not yet been identified. We propose that future research should focus on the time period before and after the stressor to elucidate mechanisms that precipitate functional decline in older patients.

This article proposes that frailty and delirium are different representations of decompensation to stress in vulnerable older patients that commonly co-present and potentiate risk with unmeasured consequences and thus, need further examination in longitudinal studies.

FRAILTY AND DELIRIUM DEFINED

Table 1 compares the definitions, timing, and criteria of frailty and delirium. Frailty is a state of increased vulnerability to stress related to diminished homeostatic capacity across multiple physiologic systems.[4] Frailty can be characterized by sarcopenia, reduced energy expenditure, and weight loss, and occurs commonly in the presence of chronic conditions.[6, 7] Of the several proposed working definitions of frailty, the most adopted criteria are those of Fried et al that are derived from the Cardiovascular Health Study and include: weight loss, poor grip strength, slow walking speed, exhaustion, and low physical activity.[7] The frail state was defined by presence of three or more of these criteria while one or two criteria characterize pre-frailty (an intermediate state between robustness and frailty).

Delirium is defined as an acute change in cognition and specifically, attention (DSM-IV-TR®).[8] Key features of delirium include acute onset over hours to days and fluctuation over the course of a day, which help to distinguish it from other cognitive deficits. In addition, thought disturbances, perceptual disturbances, and fluctuations in consciousness may occur. The Confusion Assessment Method is the most widely used diagnostic algorithm for

delirium and requires the presence of a) an acute onset and fluctuating course and b) inattention, as well as, either c) disorganized thinking or d) altered level of consciousness.[9] Analogous to pre-frailty, "subsyndromal delirium" refers to a state in which some features of delirium are present, but not enough to support the full syndrome.[10]

Time course: "Chronic" frailty vs. "acute" delirium

The course of frailty is generally considered to be chronic with progressive decline. On the other hand, delirium commonly occurs acutely in response to a stressor such as hospitalization and classically is said to resolve quickly.[11] Thus, the time course of frailty and delirium are seemingly mutually exclusive; however, there is ongoing work examining the dynamic nature of both frailty and delirium.[12-14] Considerable fluctuation has been described in the severity of frailty,[14] especially around acute health events. Recovery is typically slow and incomplete following such an event. Meanwhile, delirium can persist for months, often at a subsyndromal level.[13] A recent systematic review found that up to 20% of hospitalized patients had persistent delirium at 6 months.[15] Thus, despite the classic representation that frailty is chronic and delirium is an acute process, they may co-occur with increased potential for negative outcomes.

Is frailty exclusively a physical state and delirium a purely cognitive syndrome?

Frailty has been operationalized as a disorder of physical function,[7] but several groups have proposed including cognitive impairment as a frailty criterion.[16, 17] Delirium is an acute disorder of cognitive function and may be a cognitive manifestation of frailty, where the brain is unable to compensate in the setting of acute systemic stressors. However, delirium is often associated with a decline in physical as well as cognitive functioning. The current frailty criteria, focused on physical function, are necessary for definitional purposes and have made a strong case for using predominantly physical elements. However, the functional approach to the geriatric patient makes it difficult to isolate physical from cognitive performance. The contribution of cognitive function to frailty is not well understood, but could be important and warrants further investigation.[18]

RESEARCH DIRECTIONS

Because frailty and delirium may be linked in a downward spiral of increasing risk and negative outcomes, there is a need for further investigation of the common mechanisms of risk, pathophysiology, and recovery. Additionally, long-term studies are necessary to determine if the negative outcomes of frailty and delirium can be prevented or treated. Table 2 highlights questions for research to better elucidate the potential reciprocal relationship between frailty and delirium. Below, we summarize the evidence available in the major research areas to provide a framework for continued study of the interrelationships of frailty and delirium.

Risk Factors

Frailty as a risk factor for delirium—At present, limited direct evidence is available examining frailty as a risk factor for delirium. In a small study of older non-cardiac surgical patients, preoperative frailty score independently predicts postoperative delirium.[19] Because function and frailty are intuitively linked, additional indirect evidence also supports a possible frailty-delirium association. Robinson et al found that pre-existing functional impairment was independently associated with postoperative delirium.[20] In a study of non-cardiac surgery patients, the Specific Activity Scale, a marker of preoperative functional capacity, was identified as an independent risk factor for delirium.[21] Inclusion of baseline frailty assessment in studies of acute delirium would improve the understanding of frailty as a risk factor for delirium.

Delirium as a risk factor for frailty—Following an acute stressor, recovery is reliant on patient, disease, and environmental factors. Foremost among the patient factors is intact cognitive function to complete the disease treatments and recovery protocol. Delirium has been associated with incident long-term cognitive impairment[22] and may accelerate existing cognitive decline and thus impede the recovery process.[23] Patients with persistent delirium have been shown to be less likely to regain ADL function.[24] Thus, the persistent or residual effects of delirium may retard both physical and cognitive recovery, ultimately resulting in new or increasing frailty and/or long-term disability and institutionalization.

Pathophysiology

Geriatric syndromes are typified by nonlinear relationships between multiple complex contributors.[1] Therefore, addressing potential mechanisms for these syndromes is challenging. However, current evidence suggests common factors, described below, may link frailty and delirium mechanistically. This work needs further refinement.

Inflammation—Inflammation is a systemic reaction to injury or infection, which acts as a defensive and restorative mechanism. Cytokines are proteins secreted by cells of the immune system, which mediate local and systemic inflammation thru intercellular communication. Cytokines can be grouped into pro-inflammatory (CRP, IL-6, IL-1, TNF-α, etc) or anti-inflammatory (IL-10, IL-4, etc) cytokines.[25] With age, there is an increased amount of circulating inflammatory cytokines and this is heightened in age-associated conditions such as atherosclerosis,[26] cognitive impairment,[27] and frailty.[28] When primed by increased baseline levels, the pro-inflammatory response to stressors is more pronounced.[25] Preliminary studies have found that both delirium and frailty are associated with increased levels of peripheral inflammatory cytokines. Serum levels of Il-6 and Il-8 are elevated in hip fracture patients who experience delirium.[29] Similarly, frailty has been associated with increased levels of inflammatory cytokines in steady state.[30, 31] Future work could examine baseline inflammation, the acute inflammatory response to a stressor and cytokine levels during the subacute recovery phase as a common pathophysiologic pathway of frailty and delirium.

Atherosclerosis—Atherosclerosis is the leading cause of death and the most common systemic pathology in older patients. While the clinical sequelae of large vessel atherosclerosis are well described, small vessel disease is associated with many geriatric syndromes, including falls, urinary incontinence and depression.[32] Since frailty and delirium are also geriatric syndromes, and there is strong evidence for common risk factors for geriatric syndromes, small vessel disease likely also contributes to frailty and delirium.[1] Consistent with this, frailty has been associated with overt cardiac disease and atherosclerosis burden, as well as subclinical markers of cardiovascular disease.[33, 34] Furthermore, arterial stiffness is a risk marker for thigh sarcopenia which may contribute to reduced activity and slow walking speed- key components of frailty.[35]

The incidence of delirium is nearly doubled in patients undergoing cardiac and vascular surgeries, relative to elective orthopedic or abdominal surgery.[36] Additionally, atherosclerosis risk factors and atherosclerosis burden are risk factors for delirium. [11, 33, 37] In the brain, increased small vessel disease (i.e. leukoaraiosis, which describes white matter changes on brain imaging) is related to declining performance on measures of attention and executive functions.[38] Because delirium is primarily a disorder of attention, chronic deficits in attention or executive function may predispose patients to develop delirium in the face of a stressor.[39] However, the effects of small vessel disease may generalize beyond cognitive function. The Leukoaraiosis and Disability in the Elderly Study (LADIS) demonstrated a two-fold higher risk of transitioning to disability or death after 3 years in the group with

severe white matter changes versus the mild group.[40] Atherosclerotic risk and, in particular, radiological evidence of cerebrovascular disease burden should be incorporated into future studies examining the relationship of delirium and frailty.

Genetic link—Inheritance of the Apolipoprotein E4 allele (ApoE4) confers a greater risk for cardiovascular disease[41], Alzheimer's disease,[42] and according to a recent meta analysis, delirium.[43] The link between APOe4 and frailty status is less well defined; while the presence of Apoe4 allele was associated with increased mortality in the Canadian Study of Health and Aging, but there was no significant association between apoE4 and frailty (or apoE4 and delirium).[44] The work with ApoE4 lays an important foundation for future research to include genotyping of participants and to consider Genome-wide Association Studies to determine candidate genetic risk factors underlying frailty and delirium.

Nutritional Deficiency—Malnutrition is prevalent in the older population, particularly in the setting of chronic disease and in institutionalized elders.[45] Reductions in caloric intake may lead to sarcopenia and thus, to frailty. As noted above, “shrinking” is a conspicuous feature of the frailty phenotype.[7] The stressors of acute-on-chronic disease, such as exacerbations of chronic obstructive pulmonary disease and congestive heart failure, increase susceptibility to accelerated weight loss by muscle protein catabolism, inactivity and counter-regulatory hormone surges.[46] This combination of multiple physiological insults can breach the threshold of frailty and result in physical and functional decline and ultimately loss of independence.[47]

Particular interest has been invested in micronutrient deficiency relative to risk of negative health outcomes in older patients. Low levels of micronutrients (folate, and vitamins C, D, and E) have shown a cross-sectional association with frailty status,[48] and low vitamin E level was significantly associated with subsequent decline in physical performance in an older cohort.[49] Vitamin D is widely known to contribute to bone health and deficiency in Vitamin D leads to myopathy and can contribute to increased falls.[50] Recent work analyzing data from NHANES III shows a 3.7- to 4-fold increase in the odds of frailty if hypovitaminosis D is present.[51] While there is no clear link between vitamin D deficiency and delirium, there is a body of evidence suggesting lifelong supplementation may be neuroprotective.[52]

Malnutrition may be a significant predisposing risk factor for development of delirium.[11, 53] Conversely, the occurrence of delirium in a vulnerable older patient can stress at-risk fat and protein stores and potentiate sarcopenia. Nutritional requirements in the delirious intensive care patient are routinely addressed thru tube or parenteral feeding regimes, though these regimens often fail to meet the patient's caloric needs. Delirious patients outside of the ICU setting are particularly vulnerable to underfeeding and weight loss, none more so than in the nursing home setting.[54] Loss of independence with self-feeding, poor quality food, and polypharmacy are documented risk factors for undernutrition in the institutionalized older adult. Therefore, it behooves geriatricians to comprehensively screen for and treat malnutrition across care settings to prevent delirium, new-onset or worsening frailty, and functional decline.

Further work will more clearly define the relationship of malnutrition (at macro- and micronutrient level) with both frailty and delirium.

Recovery from Stressors

By definition, frail patients have a baseline vulnerability to stressors. Thus, when a frail patient is exposed to a stressor, there is often decompensation in function. (Figure 1) Clinically, this is frequently seen when patients become acutely ill or undergo surgery and

are unable to return to function at baseline levels. Delirium may be a presentation of this decompensation to the inciting stressor.

Logically, the amount of decompensation should be related to the “sum” of the magnitude of the stressor (e.g. sepsis is a larger stressor than a viral upper respiratory tract infection) and the baseline level of vulnerability (i.e. more frail patients are more susceptible to decompensation). However, age-related loss of complexity in multiple integrated physiologic systems makes this process less predictable.[4] Provided that the stressor is amenable to treatment and the patient survives, a period of recovery follows where function improves. After resolution of the stressor, the patient's course of recovery may help to define their pre-stressor frailty state. Incomplete recovery suggests that indeed the patient was unable to compensate to stressors and was frail. Complete recovery would suggest that the patient was able to compensate to stressor and therefore, was more robust. As a result, studies examining the impact of a uniform stressor, such as elective surgery or an acute medical condition, on long term functional status, could provide insight into pre-stressor frailty status. This would allow further validation of the frailty phenotype as a predictor of post-acute recovery while providing an individualized marker of physiologic reserve. Standardized identification of prevalent frailty will be necessary for any future frailty or delirium interventional trials.

Long-term outcomes

Frailty and delirium, independently, predict mortality, functional decline, and disability in the older patient.[7, 55] In the Women's Health and Aging Study, baseline frailty was associated with increased mortality, severe disability, and nursing home placement.[56] Similarly the mortality of delirium is comparable to that of an acute MI or sepsis[11] and several studies link incident delirium with subsequent functional decline and institutionalization.[11, 55, 57] While most of these delirium studies have focused on short-term and intermediate term outcomes, the long-term outcomes have shown similar effect. [57] However, significant study attrition, often related to the high mortality and morbidity of delirium, reduces statistical power to examine long-term outcomes after delirium. Currently, no studies have directly examined the long-term outcomes of concomitant frailty and delirium. We acknowledge that common adverse outcomes do not necessitate a common pathway, so future work should concentrate on the potentially shared pathophysiological contributors explored above.

Prevention and Treatment

The multifactorial nature of frailty and delirium as geriatric syndromes suggest that a single strategy for treatment and prevention will not work in all patients; instead, multicomponent prevention and treatment strategies will need to be tested. Delirium has the strongest evidence for multicomponent prevention, with up to 40% of delirium episodes being preventable.[11] Complex multidimensional initiatives such as the Hospital Elder Life Program (HELP) program, which targeted interventions at sensory, mobility, sleep, fluid balance, nutritional and orientation levels, reduce incident delirium in a controlled setting.[58] At present, there is less evidence supporting the benefit of delirium treatment strategies compared to prevention; these studies are challenging in that they require effective identification and treatment of the many possible underlying causes of delirium. Nonetheless, there have been some successes, mainly outside the U.S.[59, 60] Given the broad spectrum of frailty criteria, a multifactorial prevention and treatment approach with targeted interventions in multiple domains (e.g. mobility and balance programs, falls prevention, nutritional assessment and supplementation, strength training, cognitive stimulus, exploring social reserves and amenities, treating occult depression) will likely be needed. Rigorous

research is necessary so that evidence-based frailty and delirium intervention programs become integral components of the care pathway for vulnerable older adults.

Future directions

This paper has outlined common links between delirium and frailty. While frailty is prototypically a chronic condition, delirium is an acute condition and both syndromes represent significant sources of morbidity and mortality for older patients with considerable societal cost. These syndromes are multifactorial with risk factors and potentially causative mechanisms (e.g. inflammation, atherosclerosis, and poor nutrition) that overlap. Unfortunately, there are limited data in many of these biological mechanisms. We hope that this manuscript serves as a springboard for increased discussion and investigation around these mechanisms. Longitudinally, frailty may be a risk factor for delirium and delirium may precipitate or hasten frailty. Specific attention should also focus on transitions in frailty states (e.g. robust to pre-frail to frail and vice-versa) in elders who develop delirium when exposed to acute stressors, and in the post-delirium recovery period to determine the potential for reversibility of frailty. Finally, such studies could better explore the joint contribution of these geriatric syndromes to poor outcomes and begin the process of developing mutual prevention and treatment strategies.

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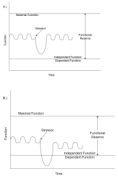

Figure 1. Functional decline after a stressor

In patient A, the stressor results in a decline in function which does not cross the threshold of independent function. The patient is likely non-frail, because the functional level returns to the baseline, indicating that the patient was able to fully compensate to the stressor. In patient B, a similar stressor causes a decline in function which transiently results in dependence. While the patient subsequently recovers independence, it is at a lower level of functioning than prior to the stressor. The patient is likely frail because she does not return to her baseline level of function, indicating that she was unable to fully compensate to the stressor. This patient has a constricted functional reserve compared with the patient above. Note: Day-to-day functional variation is depicted by a sine wave.

Table 1

Comparison of Frailty and Delirium: Definition, Time Course, and Features

	Frailty	**Delirium**
Definition	Vulnerability in multiple physiologic systems	Acute change in attention and cognition
Time Course	Chronic	Acute with fluctuation
	Acute change with stressors	Reversible in most cases
	Potentially reversible	Persistence in some cases
Features	Sarcopenia*	Inattention
	Reduced energy expenditure*	Thought disorders
	Nutritional Deficiency*	Altered consciousness
	Weight loss	
	Decreased physical activity	

*Note: these frailty features differ from the CHS phenotype criteria in the text- frailty may involve more features than defined in the CHS criteria.

Table 2

Future research directions to define the interrelationship of frailty and delirium

Research Area	Questions for Future Research
Risk Factors	Is frailty is an independent risk factor for delirium?
	Determine the role/impact/effect of cognitive functioning in frailty.
	How does comorbidity, both medical and neurological, interact with frailty and delirium?
Pathophysiology	What are the common pathophysiological mechanisms of frailty and delirium?
	Are there genetic predispositions?
	Do frailty and delirium share biomarkers (e.g. cytokines)?
Recovery from Stressor	Does delayed or incomplete recovery from a stressor signify pre-stressor frailty?
	Does delirium trigger a transition from a pre-frail state to frailty?
	Can delirium be used as a model for a stressor to examine the subsequent frailty course?
Long-term Outcomes	Is there anything unique about delirium as a “precipitant” of frailty that would modify the known relationship between frailty and adverse functional outcomes?
	Does delirium cause long-term cognitive and functional decline?
	Does recovery from frailty describe a resilience that protects against negative long-term outcomes?
Prevention	Does preventing delirium prevent subsequent frailty?
	Does prevention or treatment of frailty reduce delirium risk?
Treatments	Are there common prevention or treatment interventions that can be used for frailty and delirium?
	Will multidisciplinary programs impact on the course of frailty or delirium?
System	Are there systemic measures that can capture delirium and frailty in existing records to define the scope of the problem?
	Will incentives to prevent delirium have an impact on subsequent frailty?
	What are the cost implications of superimposed delirium and frailty to the patient, institution, physician, system, and society?