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COGNITIVE FRAILTY: WHAT IS STILL MISSING?

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Abstract: In recent years, the complex relationship between frailty and cognitive functioning has been increasingly investigated. Accordingly, the concept of "cognitive frailty" was recently proposed to describe a clinical condition characterized by the simultaneous occurrence of both physical frailty and cognitive impairment, in absence of overt dementia diagnosis or underlying neurological conditions. This novel construct has several elements of novelty and may delineate a promising target for preventive and therapeutic actions against age-related conditions. In the present paper we discuss the main issues that are still limiting the clinical and research implementation of the cognitive frailty construct. In particular, a) how to operationalize its definition; b) the supporting epidemiological data; and c) the underlying clinical and biological characteristics constitute points that need to be addressed and clarified.

Key words: Frailty, cognitive frailty, cognitive impairment, aging.

The possibility of promoting successful and active aging has increasingly been investigated in recent years. There is growing awareness that acting on the preliminary phase of the disabling cascade may differentiate the "successful" from the "pathological" aging of the individual (1). This has concurred at raising the interest around the so-called "frailty syndrome". Frailty is a multidimensional syndrome characterized by reduced homeostatic reserves and increased vulnerability to endogenous and exogenous stressors (2). It has been associated with increased risk of major adverse health-related events in older persons (including falls, disability, hospitalization, and mortality) (3). At the same time, it has been indicated as a promising pre-disability condition to be targeted by tailored interventions for preventing or delaying the onset of negative age-related outcomes (4).

To date, frailty has been differently operationalized. Most of available definitions seem to have privileged the physical dimension of the frailty syndrome (5, 6). Nevertheless, more recently, the contribution of cognition to the frailty status of the individual has been increasingly recognized (7). A relevant body of literature is thus focused on the relationship between frailty and cognitive functioning (8, 9). Cross-sectional studies have repeatedly reported higher rates of cognitive impairment and lower cognitive performance in frail compared to robust elders (8). Moreover, frailty has been shown to increase the risk of future cognitive decline and incident dementia in longitudinal studies (8). Accordingly, various measures of cognitive performance have been included in recently proposed operational definitions of frailty (10).

Such emerging evidence on the topic has prompted an international panel of experts at recently hypothesizing and proposing the concept of the so-called "cognitive frailty" (11). This novel construct was proposed to describe a clinical condition characterized by the simultaneous occurrence of both physical frailty and cognitive impairment, in absence of overt dementia diagnosis or underlying neurological conditions. In other words, it represents the negative manifestation that physical frailty produces on cognition in the entropic system of the organism. Such hypothesis does not exclude that cognitive frailty may simply constitute the early sign of an incipient neurodegeneration responsible for future dementia. The underlying rationale for such novel categorization is that the cognitive impairment due to a physical condition would benefit from completely different interventions from the one caused by a neurodegenerative disorder.

The concept of cognitive frailty has several elements of novelty. First, it fills a gap in the field by indicating (for the first time) a clinical entity combining both the physical and cognitive domains, thus more globally reflecting the health trajectories of the aging individual. Moreover, the detection of a cognitive impairment associated with a physical condition delineates a promising target for preventive and therapeutic actions. In particular, it may potentially mean improving the personalization of care and facilitating the design of more effective interventions against age-related conditions, including neurodegenerative disorders themselves. In fact, by better observing the potential causes of the cognitive impairment, it might be possible to improve the identification and targeting of patients with a "real" neurodegenerative pathogenesis and potentially increase the effect size of the available treatments. It is also noteworthy that reinforcing cognitive abilities may produce relevant benefits on the overall frailty status of the individual and reduce the risk of physical disability. Along the same lines, acting on physical frailty may positively affect cognitive functioning, thus potentially contrasting the evolution towards overt dementing conditions.

Since the first publication in September 2013, the concept of cognitive frailty has been presented at scientific meetings and discussed in literature (9 articles citing the original paper over the last 13 months). Such interactions have stemmed debates in the scientific community, and allowed to identify specific points to be addressed and clarified. In particular,

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potential issues negatively impacting a potential clinical and research implementation of the cognitive frailty construct have been found in a) how to operationalize its definition; b) the supporting epidemiological data; and c) the underlying clinical and biological characteristics. These aspects are briefly addressed in the present paper and could represent matters for future research.

Operational definition

Cognitive frailty was tentatively operationalized, in occasion of its original conception (11), as a clinical condition meeting the following criteria:

1) physical frailty;

2) mild cognitive impairment (MCI) according to the Clinical Dementia Rating (CDR; i.e., score equal to 0.5) (12); and

3) exclusion of concurrent Alzheimer's disease (AD) and other dementias.

Such operationalization might present some issues worth to be noted. While the concept of physical frailty is theoretically well accepted, its translation into practice is still controversial (3). Several instruments have been developed in order to properly capture this syndrome and render it objectively measurable (2). Unfortunately, the available definitions are substantially different and probably unable to exhaustively capture the wide and heterogeneous complexity of the condition of interest (13). The lack of a unique instrument for measuring physical frailty has affected its rapid implementation in everyday clinical life because limits the design, standardization, and development of dedicated healthcare services and interventions. Intuitively, all these considerations can be directly extended to the cognitive frailty entity.

Cognitive impairment was arbitrary operationalized by considering a CDR score equal to 0.5. This choice was motivated by the fact that this criterion has been frequently adopted to indicate a condition of MCI in the dementia continuum (14, 15). The CDR is not a mere measure of cognitive performance. In fact, it describes the impact of cognition over the physical function (12). It is true that the CDR scale is widely available and relatively easy to use. Nevertheless, it could be argued that other operational definitions (for example, considering measures obtained through extensive and more detailed neuropsychological evaluations) may provide a more accurate assessment of a cognitive impairment of mild entity.

Finally, the identification of a non-neurodegenerative cognitive impairment (i.e., cognitive frailty) inevitably implies the execution of diagnostic procedures (e.g., morphological neuroimaging) to rule out within an acceptable degree of approximation the existence of underlying neurological conditions. These instrumental assessments are expensive and time-consuming, thus potentially complicating the process required for the detection of cognitive frailty. Moreover, it is quite unlikely to find completely "normal" neuroimaging results with increasing age. In other words, at advanced age, it might be relatively easy to justify some cognitive issues with incidental neuroimaging abnormalities (e.g., leukoaraiosis or white matter hyperintensities), even if of modest amount or doubtful clinical relevance. The possible over-explanation of cognitive impairment in the absence of clear neuroimaging results may further represent an issue negatively affecting (i.e., underestimating) the relevance and prevalence of cognitive frailty in the population. Along the same line, the boundaries between pure neurodegenerative and non-neurodegenerative conditions become more vague with advancing age. In fact, in most of cases, neurodegenerative (e.g., brain atrophy) and non-neurodegenerative (e.g., vascular lesions) abnormalities are concomitantly detected, resulting in the so-called "mixed" diagnoses. This common overlap may limit the possibility of actually identifying cognitive frailty (i.e., a non-neurodegenerative cognitive impairment) in the elderly population.

In order to increase the possibility of detecting cognitive frailty and better capturing its complex nature, a temporal criterion might be considered in its operational definition. That is, the occurrence of physical frailty should temporally precede the onset of cognitive impairment. This additional criterion (i.e., the temporal sequence of onset of frailty and cognitive impairment) might potentially help in the differentiation between a physically driven cognitive decline versus a cognitive deterioration independent of physical conditions.

Epidemiological data

To date, no epidemiological data about cognitive frailty has yet been produced. In particular, the prevalence of cognitive frailty is still not estimated. The few available data have been derived by studies enrolling highly selected populations, thus not representative of the general population. To our knowledge, only one study has indirectly provided an estimate of the prevalence of cognitive frailty. Shimada and colleagues, despite not directly talking about a "cognitive frailty" condition, investigated the prevalence of physical frailty and MCI in a sample of 5,104 Japanese older adults living in the community (16). The combined prevalence of frailty (defined according to the frailty phenotype (5)) and MCI was 2.7%. The availability of more consistent and specific epidemiological data will inevitably represent a needed step for future research and a possible clinical implementation of the condition of interest.

Clinical and biological characteristics

The clinical manifestation of cognitive frailty should also be better described. Besides exploring the relationship between physical frailty and general cognitive functioning (mostly assessed by measures of global cognitive performance such as the Mini Mental State Examination (17)), a growing body of

literature has investigated the involvement of specific cognitive domains in the context of the frailty syndrome (8). To date, these studies have produced conflicting evidence showing that frailty is associated with the involvement of various cognitive functions such as memory, processing speed, orientation, and verbal fluency (8). Nevertheless, most of the available studies have observed a stronger and closer association with impaired attention and executive functioning (8, 18). Thus, it might be argued that a preeminent decline in executive functions might represent a useful element to tentatively operate a clinical distinction between the cognitive impairment due to physical versus neurological conditions. In fact, the most common neurodegenerative conditions (in particular, AD) are mostly characterized by preferential memory impairment.

These considerations may also be extended to the biological characteristics of cognitive frailty. Frailty and cognitive impairment may potentially be sustained by converging pathophysiological pathways (e.g., chronic inflammation, hormonal pathways, vascular disease, nutritional factors) (8). Nevertheless, there is still a lack of experimental evidence to support such observations. Moreover, the underlying mechanisms may not only be exclusively involved in the generation of the frailty condition, but 1) represent the main mechanisms regulating the organism's homeostasis and 2) being largely affected by aging. In other words, it is likely that the foundations of frailty (as well as of cognitive frailty) are to be drawn in the scenario of the system biology.

Conclusions and future directions

The concept of cognitive frailty has been proposed for framing the growing and consistent evidence linking physical and cognitive decline in older persons within recognizable and discriminative standards. The clarification and implementation of this novel entity may provide useful insights for improving the discrimination of different risk profiles and provide more personalized preventive and/or therapeutic options. However, some issues still limit the clinical and research adoption of this concept. In particular, formulating a robust operational definition, providing epidemiological data (preferentially coming from the "real world"), and characterizing its founding clinical and biological basis appear to be key steps for the future consideration of this newborn construct.

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