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EDITORIAL

Cognitive frailty: a potential target for secondary prevention of dementia

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1. Introduction

Dementia and its most common form, Alzheimer's disease (AD), are multifactorial incurable syndromes characterized by absence of information on the cause and a dramatic socio-economical burden. For AD, no disease-modifying treatment is available. In the final stages of dementia and AD, patients lose their ability to communicate, become bedridden, and require continuous care. The targets of disease-modifying treatment for AD need to be updated. The interest in treating early AD evolved from consideration that a risk state can be identified before the onset of the dementia syndrome. Deposition of β-amyloid (Aβ), one of the principal AD neuropathological hallmarks, precedes cognitive deficits or clinical manifestation by decades. Considering that the environmental factors influenced the epigenetic landscape of an organism and that can be more easily modified with lifestyle [1], earlier intervention should be probably attempted with secondary prevention trials in asymptomatic genetic forms of AD and in individuals with no cognitive dysfunction suspected to be at an asymptomatic stage of sporadic AD.

On the other hand, chronic diseases accelerate aging, thereby diminishing the body's adaptation via the relevant stress responses. Multiple subclinical and age-related comorbidities in older age may exacerbate the decline in the physiological reserves of several systems, which would then result in a homeostatic imbalance or frailty. Frailty is a critical intermediate status of the aging process that is at increased risk for negative health-related events, including falls, disability, hospitalizations, and mortality. This heterogeneous clinical syndrome includes physical, cognitive, and psychosocial domains or phenotypes [2]. A recent and growing body of epidemiological evidence suggested that frailty may increase the risk of future cognitive decline and that cognitive impairment may increase the risk of frailty suggesting that cognition and frailty may interact in advancing aging [2]. Several studies examined frailty and cognitive impairment as both antecedents and outcomes [3]. The mutual influences between frailty and impaired cognition have been discussed, including the proposed construct of 'cognitive frailty' [2,4]. This last is held to be a combination of mild cognitive impairment (MCI) and physical frailty, which is defined by five features, three of which (i.e. reduced activities, motor slowing, weight loss) are known to be risk factors for dementia [4]. From a pathophysiological point of view, the etiology of the cognitive-frailty link appeared to be multifactorial and hormonal and inflammatory processes, together with nutritional, vascular, neuropathological, and metabolic influences may be of major relevance [2,5]. Therefore, other questions may address the underlying mechanisms and determine which is the most relevant component among the suggested mediators between frailty and cognition.

2. The potential for reversibility of different cognitive frailty models

Among frailty phenotypes, cognitive frailty has been proposed as a clinical entity with cognitive impairment related to physical causes, with a potential reversibility, and as an important target of secondary intervention in early or asymptomatic stage of dementia [2,4,5]. In 2006, this clinical label was first used to indicate a particular state of cognitive vulnerability in MCI and other similar clinical entities exposed to vascular risk factors and with a subsequent increased progression to dementia, particularly vascular dementia (VaD) [6]. In 2013, a consensus on the definition of cognitive frailty was reached by an international consensus group from the International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics (IANA-IAGG) [4]. The proposed diagnostic criteria for this novel and heterogeneous clinical age-related condition included the simultaneous presence of physical frailty operationalized with the Cardiovascular Health Study phenotypic/biological model and cognitive impairment diagnosed with a Clinical Dementia Rating (CDR) scale of 0.5 (i.e. questionable dementia, a stage of the dementia continuum similar to MCI) without a concurrent diagnosis of AD or other dementias [4].

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In 2015, the first systematic review on this intriguing topic, suggested that frailty indexes based on a deficit accumulation model were associated in hospital- and population-based studies with late-life cognitive impairment and decline, incident dementia and AD [5]. Furthermore, also physical frailty models may be associated with late-life cognitive impairment and decline, incident AD and MCI, VaD, non-AD dementias, and AD pathology in older persons with and without dementia, so giving support to identify cognitive frailty as a new clinical condition [5]. Very recently, a meta-analysis suggested that the frailty was a significant predictor of AD, VaD, and all dementia among community-dwelling older people, with frail women at higher risk of incident AD than frail men [7].

The potential for reversibility of frailty and its different phenotypes suggests that these clinical constructs may be important secondary targets for the prevention of dependency and other negative outcomes in older age [2]. More recently, in an attempt to refine the framework for the definition and potential mechanisms of cognitive frailty, two subtypes for this clinical construct were proposed: 'potentially reversible' cognitive frailty and 'reversible' cognitive frailty [8]. The physical factors should be physical prefrailty and frailty for both the subtypes. The cognitive impairment of potentially reversible cognitive frailty should be MCI (CDR = 0.5), while the cognitive impairment of reversible cognitive frailty should be pre-MCI Subjective Cognitive Decline (SCD), as recently formulated by the Subjective Cognitive Decline Initiative (SCD-I) Working Group that proposed a basic conceptual framework for the study of the common concepts of SCD, pre-MCI SCD, and SCD in preclinical AD [8].

Some longitudinal population-based studies have investigated cognitive frailty models associated with disability and all-cause mortality [9–11], health-related outcomes traditionally linked to different frailty models (Table 1). Very recently, data from the Italian Longitudinal Study of Aging (ILSA) did not support a predictive role of a potentially reversible cognitive frailty model (physical frailty plus MCI) for the development of incident dementia compared with physical frailty or MCI alone in a 3.5-year follow up [14]. However, in the same study, older individuals with potentially reversible cognitive frailty and high level of inflammation showed a significant additional predictive effect only on the risk of disability, but not of all-cause mortality [14]. In the Singapore Longitudinal Ageing Studies (SLAS), continuous physical frailty score and MMSE score showed significant individual and joint associations with incident mild and major neurocognitive disorder [13]. In this study, potentially reversible cognitive frailty conferred additionally greater risk of incident neurocognitive disorder (mild plus major neurocognitive disorder) [13]. However, cognitive frailty is not an uncontroversial term. In fact, very recent findings from the Gait and Brain Study suggested that another model of potentially reversible cognitive frailty (physical frailty plus CDR of 0.5) increased incident rate but not risk for progression to dementia, although, the combination of slow gait and objective cognitive impairment posed the highest risk for progression to dementia when compared with physical frailty and cognitive frailty models [12]. A motor signature that preceded cognitive decline and which has been labeled as the 'Motoric Cognitive Risk' syndrome, further casted doubt on the empirical basis of the cognitive frailty syndrome [15]. Possible discrepancies in predicting cognitive-related outcomes may arise from different models of cognitive frailty in which cognitive impairment may be operationalized in different ways. However, the operationalization of clinical constructs based on cognitive impairment related to physical causes (physical frailty, motor function decline, or other physical factors) appears to be interesting for dementia secondary prevention given the increased risk for progression to dementia of these clinical entities.

At present, to the best of our knowledge, there is only one population-based study in which reversible cognitive frailty has been investigated as possible determinant of dementia and its subtypes and all-cause mortality as well how mechanisms could be associated with reversibility. In fact, very recently, other findings coming from the ILSA suggested that a model of reversible cognitive frailty (physical frailty plus pre-MCI SCD) was a short- and long-term predictor of all-cause mortality and overall dementia, particularly VaD [8]. In observational studies like the ILSA, in extreme cases, could be of interest to verify that an interaction may reverse the relationship between the risk factor and the outcome. Therefore, it was hypothesized that the role of vascular factors and/or depressive symptoms as effect modifiers could change the risk of dementia and all-cause mortality linked to the presence of reversible cognitive frailty. In particular, trying to support the reversibility of this new clinical construct, it was focused on the group of people without these risk factors as a proxy of optimal management of these factors. In the ILSA, the absence of vascular risk factors and depressive symptoms did not modify the predictive role of reversible cognitive frailty on these outcomes [8]. Probably, the identification of reversibility due to several possible interventions could be more useful in designing randomized controlled trials (RCTs), i.e. the multidomain preventive trials of cognitive decline and dementia, such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) [16]. In this RCT, a multidomain intervention with diet, exercise, cognitive training, and vascular risk monitoring could improve or maintain cognitive functioning in at-risk older people from the general population [16]

3. Expert opinion

Physical frailty and cognitive frailty are two important targets of secondary intervention in aging research to narrow the gap between life and health span. The emerging biomarkers of sarcopenia, physical frailty, and cognitive impairment will provide the basis to establish more reliable clinical and research criteria for cognitive frailty. In the near future, we could use different operational definitions for frailty and cognitive impairment and useful clinical, biological, and imaging markers for this novel clinical construct [17]. At this stage, secondary prevention strategies for cognitive impairment and physical frailty may be suggested. For the older subjects with cognitive frailty, particularly reversible cognitive frailty, secondary prevention is required, with a comprehensive geriatric assessment determining the cause of cognitive frailty and an evidence-based and individualized multimodal interventions

Table 1. Principal longitudinal population-based studies on the association of different cognitive frailty models with late-life cognitive decline, dementia, Alzheimer's disease (AD), vascular dementia (VaD) and other cognitive outcomes.

Reference	Study design and sample	Definition of cognitive frailty and cognitive outcomes	Principal results
Cross-sectional studies			
Montero-Odasso et al., 2016 [12]	Longitudinal population-based study with 5 years of follow up; 255 older individuals from the Gait and Brain Study	Potentially reversible cognitive frailty was defined with the presence of physical frailty operalizionated with the CHS criteria and cognition assessed using the MoCA score below 26 and a CDR of 0.5, and absence of concurrent dementia. Gait was assessed using an electronic walkway Cognitive outcomes: Cognitive decline operationalized as a decrease of at least two points in MoCA scores between baseline and the last assessment, incidence of dementia according to DSM-IV criteria and when CDR progressed to one or higher	The combination of slow gait and objective cognitive impairment posed the highest risk for progression to dementia (HR: 35.9, 95% CI: 4.0–319.2) when compared with physical frailty and potentially cognitive frailty models
Feng et al., 2017 [13]	Longitudinal population-based study with 3 years of follow up; 1575 older individuals from the SLAS	Potentially reversible cognitive frailty was defined with the presence of physical frailty operalizionated with the CHS criteria and cognition assessed with MMSE, and absence of concurrent dementia Cognitive outcomes: Incidence of neurocognitive disorder according to DSM-5 criteria	Continuous physical frailty score and MMSE score showed significant individual and joint associations with incident mild and major neurocognitive disorder, and potentially reversible cognitive frailty conferred additionally greater risk of incident neurocognitive disorder (mild plus major neurocognitive disorder)
Solfrizzi et al., 2017 [8]	Longitudinal population-based study with 3.5 and 7 years of median follow up; 2150 older individuals from the ILSA	Reversible cognitive frailty was defined with the presence of physical frailty with a modified phenotype operalizionated with the CHS criteria, pre-MCI SCD, diagnosed with a self-report measure based on item 14 of the 30-item GDS, and absence of concurrent dementia Cognitive and health-related outcomes: Incidence of dementia diagnosed with the DSM-III-R, AD diagnosed with the NINCDS-ADRDA criteria, VaD diagnosed with the NINDS-AIREN criteria, and all-cause mortality	Over a 3.5-year follow-up, participants with reversible cognitive frailty showed an increased risk of overall dementia (HR: 2.30, 95% CI: 1.02–5.18], particularly VaD, and all-cause mortality (HR: 1.74, 95% CI: 1.07e2.83). Over a 7-year follow-up, participants with reversible cognitive frailty showed an increased risk of overall dementia (HR: 2.12, 95% CI: 1.12–4.03), particularly VaD, and all-cause mortality (HR: 1.39, 95% CI 1.03–2.00). Vascular risk factors and depressive symptoms did not have any effect modifier on the relationship between reversible cognitive frailty and incident dementia and all-cause mortality
Solfrizzi et al., 2017 [14]	Longitudinal population-based study with 3.5 years of median follow up; 1575 older individuals from the ILSA	Potentially reversible cognitive frailty was defined with the presence of physical frailty with a modified phenotype operalizionated with the CHS criteria, MCI diagnosed with modified Petersen criteria, and absence of concurrent dementia Cognitive and health related outcomes: Incidence of dementia diagnosed with the DSM-III-R, AD diagnosed with the NINCDS-ADRDA criteria, VaD diagnosed with the NINDS-AIREN criteria, disability, and all-cause mortality	In potentially reversible cognitively frail older individuals with a high inflammatory state has been found a significant additional predictive effect on the risk of disability than in frail/non-MCI individuals, while it has not been found for dementia and all-cause mortality. In the potentially reversible cognitive frailty and high inflammatory state group, the predicted number of older subjects disabled was about 461 per thousand persons over a 3.5-year follow-up period

CHS = Cardiovascular Health Study; MoCA: Montreal Cognitive Assessment;CDR: Clinical Dementia Rating scale; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-IV; HR: hazard ratio; CI: confidence interval; SLAS: Singapore Longitudinal Ageing Studies; MMSE: Mini-Mental State Examination; DSM-5: Diagnostic and Statistical Manual of Mental Disorders-5; ILSA: Italian Longitudinal Study on Aging; pre-MCI SCD: pre-mild cognitive impairment subjective cognitive decline; GDS: Geriatric Depression Scale; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; NINDS-AIREN: National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders-III revised

similar to that of the FINGER [16]. Other measures, such as drug treatment for chronic diseases, fall prevention, and exercise and nutrition support, which target physical, nutritional, cognitive, and psychological domains, may delay the progression and secondary occurrence of cognitive frailty-related adverse outcomes, such as progression to overt dementia. Although evidence on interventions in cognitive frailty subjects is limited, a small number of studies point to the cognitive benefits of physical activity and nutrition. In fact, physical activity protected against both sarcopenia and cognitive decline in experimental training trials and in observational studies [18]. Furthermore, findings from very recent preventive trials suggested that physical exercise training in combination with protein supplementation or alone [19] improved also cognitive outcomes in frail and pre-frail states, opening new viable routes for the prevention of cognitive and functional decline in these patients. In particular, for preclinical AD treatment, passive immunotherapy with anti-Aβ monoclonal antibodies has been involved in a preventive way in an attempt of modifying the AD course prior to widespread brain damage and clinical symptoms. A number of RCTs testing anti-Aβ monoclonal antibodies in both genetic at-risk [Alzheimer's Prevention Initiative (API) autosomal-dominant AD (ADAD) Trial, ClinicalTrials.gov Identifier: NCT01998841 and Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU) Biomarker Trial, ClinicalTrials.gov Identifier: NCT01760005) and biomarker-positive older individuals [Anti-Amyloid Treatment in Asymptomatic AD (A4) Study, ClinicalTrials.gov Identifier: NCT02008357] are underway [20]. These trials can be considered secondary prevention initiatives with the objectives of preventing cognitive decline in individuals showing signs that the disease process has begun in the brain, so investigating when exactly AD therapy has to be started to be really effective. Subjects with reversible cognitive frailty and no biomarker evidence of AD pathology could be individuals with normal cognitive aging or undetectable preclinical AD [17]. Reversible cognitive frailty subjects with cerebral amyloidosis (Aβ accumulation on positron emission tomography amyloid imaging) could be individuals with preclinical AD, early stage of dementia with Lewy bodies, or VaD [17]. Reversible cognitive frailty subjects with evidence of neurodegeneration or neuronal injury plus amyloidosis could be individuals with preclinical AD, while without amyloidosis could be individuals with normal cognitive aging or suspected non-AD dementias [17]. Therefore, reversible cognitive and functional damages as defined in these models of cognitive frailty could be an optimal target for a secondary prevention of cognitive and functional impairment also for AD, hopefully including in future preventive trials biomarker-positive reversible cognitive frailty individuals.

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