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Clinical Significance of Physical Frailty in Subjects With Subjective Cognitive Decline: A Prospective Study With Amyloid PET Data

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Background and Purpose Physical frailty is known to be closely associated with cognitive impairment and to be an early sign of Alzheimer's disease. We aimed to understand the characteristics of physical frailty and define factors associated with physical frailty in subjects with subjective cognitive decline (SCD) by analyzing amyloid data.

Methods We prospectively enrolled subjects with SCD from a cohort study to identify predictors for the clinical progression to mild cognitive impairment or dementia from SCD (CoSCo). All of the subjects underwent brain magnetic resonance imaging, and brain amyloid positron-emission tomography (PET) to detect amyloid beta plaques. Self-reported exhaustion, handgrip strength, and gait speed were used to measure physical frailty.

Results Of 120 subjects with SCD, 26 (21.7%) were amyloid-positive in PET. Female (odds ratio [OR]=3.79, p=0.002) and amyloid-PET-positive (OR=3.80, p=0.008) subjects with SCD were at high risks of self-reported exhaustion. Amyloid PET positivity (OR=3.22, p=0.047) and high burden from periventricular white-matter hyperintensity (OR=3.34, 95% confidence interval=1.18−9.46, p=0.023) were significantly associated with a weaker handgrip. The subjects with SCD with self-reported exhaustion and weaker handgrip presented with lower cognitive performance in neuropsychological tests, especially for information processing speed and executive function. Subjects with a slower gait performed worse in visual memory function tests.

Conclusions Amyloid PET positivity was associated with a higher risk of self-reported exhaustion and weaker handgrip in subjects with SCD. The subjects with SCD and physical frailty also performed worse in neuropsychological tests.

Keywords physical frailty; subjective cognitive decline; Alzheimer's disease; amyloid positron emission tomography computed tomography.

INTRODUCTION

Frailty is a medical syndrome of decreased homeostatic reserve and diminished resistance to stressors due to age-related multisystem physiological changes.[1,2] Epidemiological data have revealed that frailty can increase the future risk of cognitive decline.[3,4] Cognitive impairment can also increase the risk of frailty.[5-7] Postmortem studies have found that brain pathologies such as Alzheimer's disease (AD) and cerebrovascular disease are independently associated with progressive physical frailty in old age.[8] These findings suggest that cognitive disorder and frailty interact in older age and share common biological pathways.[8] However, the mechanisms that underlie the relationship between frailty and cognitive impairment remain unclear.

Subjective cognitive decline (SCD) is defined by self-reported cognitive impairment that

cannot be detected by an objective neuropsychological evaluation.[9] SCD has recently been considered as the first stage of help-seeking and symptoms in geriatric cognitive disorder, based on accumulating evidence that older individuals with SCD have an increased risk of future pathological cognitive decline and dementia with an increased likelihood of biomarker abnormalities consistent with AD pathology.[10] Understanding the relationship between physical frailty and cognitive function in subjects with SCD, both as independent risk factors for dementia that appear early in the disease course, could contribute to the development of new interventions for the prevention and management of both conditions. However, few studies have explored the relationship between physical frailty and cognitive function in subjects with SCD.

In these contexts, we aimed to understand the characteristics of physical frailty and define the factors associated with it in subjects with SCD. Especially using amyloid positron-emission tomography (PET), we evaluated the association between amyloid pathology and physical frailty in subjects with SCD. We also investigated the association between cognitive function and physical frailty in these subjects.

METHODS

Participants

Individuals were drawn from a cohort study to identify predictors for the clinical progression to mild cognitive impairment or dementia from SCD (CoSCo).[11] The purpose of the CoSCo study was to identify early risk factors that could predict the progression to MCI or dementia by constructing a cohort of elderly people with amnestic SCD. A baseline survey was conducted from November 2018 to November 2019, which enrolled 120 subjects with SCD aged at least 60 years with a complaint of persistent cognitive decline from 6 different memory clinics. All participants underwent physical and neurological examinations and blood tests (i.e., tests of liver function, blood sugar level, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, protein, syphilis, thyroid function, vitamin B12, folate, and the apolipoprotein E [APOE] genotype). Assessments included the variables of age, sex, education duration, medical and family histories, current medications, comorbidities, and lifestyle factors (e.g., smoking, alcohol consumption, and exercise). Vital signs such as blood pressure and pulse rate and the height and weight were obtained to determine the Framingham cardiovascular risk profile. Those with brain lesions and blood-test abnormalities that might have affected their cognitive function were excluded from this study. Subjects with uncontrolled depression, schizophrenia, alcoholism, or drug dependence were also excluded.

The study protocol was reviewed and approved by the Institutional Review Boards of each institution: The Catholic University of Korea, Seoul St. Mary's Hospital (IRB No. KC18ONDI0394), Ewha Womans University Mokdong Hospital (IRB No. EUMC2018-08-022-005), Gachon University Gil Medical Center (IRB No. GAIRB2019-231), Seoul National University Bundang Hospital (IRB No. B-1808/486-004), and Inha University School of Medicine (IRB No. INHAUH2018-08-006-005). All participants provided informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

Neuropsychological evaluation

All participants underwent a comprehensive neuropsychological test battery, the Seoul Neuropsychological Screening Battery-2nd Edition (SNSB-II), to evaluate their cognitive function.[12] The SNSB-II consisted of a digit-span forward test, the Korean version of the Boston Naming Test (K-BNT), the Rey-Osterrieth Complex Figure Test (RCFT; comprising copying, and immediate and 20-minute-delayed recall), the Seoul Verbal Learning Test (a 20-minute-delayed recall trial of 12 items), the Digit Symbol Substitution Task, the phonemic Controlled Oral Word Association Test (COWAT), the Korean Trail-Making Test−Elderly: Part B (K-TMT-E:B), and the Korean Color Word Stroop Test (color reading of 112 items over a 2-minute period). Patients with SCD were defined as those whose score was -1.5 standard deviations (7th percentile) or higher in the neuropsychological test. General cognition was assessed using the Korean version of the Mini Mental State Examination (K-MMSE).

Acquisition of brain MR images and ^{18}F-florbetaben PET

Brain magnetic resonance imaging (MRI) included acquiring T1-weighted axial and T2-weighted images, fluid-attenuated inversion recovery (FLAIR) images, and three-dimensional T1-weighted thin-section images using a 3T MRI scanner. A trained neurology specialist visually rated white-matter hyperintensities (WMHs) on axial FLAIR images using the Fazekas scale.[13] Periventricular WMHs (pvWMHs) were graded as 0 (no lesions), 1 (caps or a thin line), 2 (smooth halo), or 3 (extension into the white matter). Deep WMHs were graded as 0 (no lesions), 1 (punctate foci), 2 (beginning confluence of foci), or 3 (large confluent areas). We defined a high burden of WMH as a Fazekas-scale score of >2. The presence and number of lacunar infarcts and cerebral microbleeds were also evaluated.

All participants underwent florbetaben PET at the base-

line. Existing PET data were used for the analysis when florbetaben PET had been performed within 1 year of the baseline. A trained nuclear medicine specialist from one of the participating hospitals determined amyloid PET positivity using a visual rating brain amyloid plaque load score.[14] MATLAB (release 2013) and SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) were used to obtain quantitative regional amyloid burden data. The standardized uptake value ratio (SUVR) was calculated using whole voxels in florbetaben PET images based on uptake in the cerebellar gray matter as a reference region. Global SUVR was calculated as the average of 90 regional uptake values.

Assessment of physical frailty

Frailty was defined as a clinical syndrome where three or more of the following criteria were present: unintentional weight loss, self-reported exhaustion, weak handgrip, slow walking speed, and low physical activity level.[15] Of these dimensions, handgrip strength, gait speed, and self-reported exhaustion were measured as indicators of physical frailty in this study. We measured body mass index (BMI) using a bioelectrical impedance analyzer (InBody H20, InBody Japan, Tokyo, Japan) prior to making these measurements. Handgrip strength in kilogram-force was assessed using a digital grip dynamometer (T.K.K.5401 Grip-D, Takei, Niigata, Japan). Patients were asked to stand or sit with their arm outstretched horizontally away from the body and to squeeze the dynamometer as hard as possible using their dominant hand. The mean handgrip strength was calculated from two attempts.

Reduced handgrip strength was defined as a grip strength of the dominant hand of <26 kg in males and <18 kg in females according to the Asian Working Group for Sarcopenia (AWGS).[16] Gait speed was measured by walking 7-meter as fast as possible, with the first 1.5-meter section considered the acceleration section and the last 1.5-meter section considered the deceleration section; we therefore analyzed the speed in the middle 4-meter section. The distance was walked twice and the mean gait speed was calculated. A reduced gait speed was defined by the AWGS as a gait speed of <0.8 m/s.[16] Finally, self-reported exhaustion was assessed by a self-reported scoring item derived from a lifestyle questionnaire: "What do you think about your overall health compared to a year ago?" Subjects scored their responses as follows: 0, very bad; 1, bad; 2, normal; 3, good; and 4, very good. Subjects who answered 0 or 1 on either of these questions were designated as fatigued; otherwise there were classed as nonfatigued.

Statistical analysis

To compare the baseline demographic characteristics between patients with each factor of physical frailty, we divided each physical frailty factor into normal and abnormal according to the reference value (refer to the Methods section). We then compared the baseline characteristics using a *t*-test, Mann–Whitney U test, or chi-square test. We also compared the neuropsychological performance between the two groups (with and without physical frailty) using *t*-tests.

We used multiple logistic regression analysis to determine the risk factors that were associated with physical frailty status. Factors that differed significantly between patients with and without physical frailty or that were associated with physical frailty were clinically relevant and selected as candidate predictors (age, sex, APOE ε4 carrier status, BMI, high blood pressure, depression, amyloid PET positivity, and high pvWMH burden) in the multivariate logistic regression model. The backward stepwise logistic regression (p=0.1) assisted in model selection.

All statistical analyses were performed using SPSS software (version 18, SPSS, Chicago, IL, USA), with p<0.05 was considered significant.

RESULTS

The CoSCo study enrolled 120 patients with SCD. Table 1 lists the demographic and clinical characteristic of the subjects. Their age was 70.9±6.1 years (mean±standard deviation) and 68 (56.6%) were female. Overall, 26 (21.7%) subjects (16 [30.7%] males and 10 [14.7%] females) were amyloid-positive in PET. Subjects with self-reported exhaustion (n=54, 45.0) were female predominant (38 [70.4%] and showed higher amyloid positivity in PET scan (10 [15.2%] vs. 17 [31.5%], p=0.033) compared to subjects without exhaustion. Subjects with weaker handgrip strength (n=20, 16.6%) tended to have a high pvWMH burden (27 [27.0] vs. 10 [50.0], p=0.062), but the difference was not significant. Subjects with slower gait speed (n=78, 65%) were more prevalent in female (17 [40.5%] vs. 51 [65.4%], p=0.009) and had a shorter education duration (12.64±3.46 years vs. 10.40±4.16 years, p=0.009).

Table 2 lists the neuropsychological performance according to physical frailty status. The subjects with SCD and self-reported exhaustion had lower global cognition scores on the K-MMSE (26.83±1.89 vs. 27.58±1.97, p=0.04), K-BNT (0.13±0.89 vs. 0.61±1.09, p=0.01), and COWAT (-0.02±0.90 vs. 0.42±1.08, p=0.02). The subjects with weak handgrip also had worse performance in global cognition on the K-MMSE (26.30±2.11 vs. 27.43±1.89, p=0.02), COWAT (-0.20±0.67 vs. 0.30±1.06, p=0.04), and K-TMT-E:B (-0.10±0.64 vs. 0.42±0.58,

Table 1. Baseline demographics according to physical frailty status

Characteristic	Total (*n*=120)	Self-reported exhaustion			Handgrip strength			Gait speed		
		Normal (*n*=66)	Abnormal (*n*=54)	*p*	Normal (*n*=100)	Abnormal (*n*=20)	*p*	Normal (*n*=42)	Abnormal (*n*=78)	*p*
Age, years	70.87±6.10	70.02±6.00	71.91±6.11	0.650	70.38±6.00	73.30±6.16	0.680	71.29±6.66	70.64±5.80	0.260
Education duration, years	11.18±4.05	11.38±4.27	10.94±3.81	0.630	11.29±4.01	10.65±4.38	0.300	12.64±3.46	10.40±4.16	0.047*
Sex, female	68 (56.7)	30 (45.5)	38 (70.4)	0.009*	55 (55.0)	13 (65.0)	0.466	17 (40.5)	51 (65.4)	0.009*
Depression	9 (7.5)	5 (7.6)	4 (7.4)	1.000	8 (8.0)	1 (5.0)	1.000	5 (11.9)	4 (5.1)	0.179
APOE ε4 carrier	24 (20.0)	13 (19.7)	11 (20.4)	1.000	20 (20.0)	4 (20.0)	1.000	9 (21.4)	15 (19.2)	0.774
BMI, kg/m^2	24.79±3.17	24.50±2.79	25.14±3.58	0.089	24.89±3.20	24.29±3.03	0.978	24.56±3.28	24.92±3.13	0.229
Vascular risk factors										
HBP	55 (45.8)	29 (43.9)	26 (48.1)	0.714	44 (44.0)	11 (55.0)	0.463	18 (42.9)	37 (47.4)	0.631
DM	33 (27.5)	19 (28.8)	14 (25.9)	0.838	24 (24.0)	9 (45.0)	0.097	10 (23.8)	23 (29.5)	0.506
Dyslipidemia	50 (41.7)	32 (48.5)	18 (33.3)	0.136	42 (42.0)	8 (40.0)	1.000	18 (42.9)	32 (41.0)	0.846
CAD	7 (5.8)	5 (7.6)	2 (3.7)	0.456	5 (5.0)	2 (5.9)	0.330	1 (2.4)	6 (7.7)	0.236
Stroke	2 (1.7)	2 (3.0)	0 (0)	0.501	2 (2.0)	0 (0)	1.000	0 (0)	2 (2.6)	0.361
Mean SUVR	1.27±0.24	1.26±0.24	1.29±0.24	0.700	1.27±0.24	1.26±0.24	0.670	1.29±0.25	1.20±0.16	0.406
Amyloid PET positivity	27 (22.5)	10 (15.2)	17 (31.5)	0.033*	20 (20.0)	7 (35.0)	0.143	24 (25.0)	3 (12.5)	0.276
High pvWMH burden	37 (30.8)	20 (30.3)	17 (31.5)	0.889	27 (27.0)	10 (50.0)	0.062	30 (31.3)	7 (29.2)	0.843
High dWMH burden	30 (25.0)	17 (25.8)	13 (24.1)	0.832	23 (23.0)	7 (35.0)	0.268	23 (24.0)	7 (29.2)	0.605
Lacune†	12 (10.0)	4 (6.1)	8 (14.8)	0.134	10 (10.0)	2 (10.0)	1.000	7 (16.7)	5 (6.4)	0.074
CMB‡	27 (22.5)	4 (6.1)	7 (13.0)	0.219	10 (10.0)	1 (5.0)	0.689	3 (7.1)	8 (10.3)	0.573

Data are mean±standard deviation or *n* (%) values.
*Significant difference (p<0.05); †At least one lacune; ‡At least one CMB.
APOE, apolipoprotein E; BMI, body mass index; CAD, coronary artery disease; CMB, cerebral microbleed; DM, diabetes mellitus; dWMH, deep white-matter hyperintensity; HBP, high blood pressure; PET, positron-emission tomography; pvWMH, periventricular white-matter hyperintensity; SUVR, standardized uptake value ratio.

Table 2. Neuropsychological test scores according to physical frailty status

Test	Self-reported exhaustion			Handgrip strength			Gait speed		
	Normal (*n*=66)	Abnormal (*n*=54)	*p*	Normal (*n*=100)	Abnormal (*n*=20)	*p*	Normal (*n*=42)	Abnormal (*n*=78)	*p*
K-MMSE	27.58±1.97	26.83±1.89	0.04*	27.43±1.89	26.30±2.11	0.02*	27.60±1.84	27.05±2.01	0.90
Digit-span forward test	0.55±1.06	0.67±1.16	0.55	0.63±1.13	0.43±1.00	0.46	0.51±1.0.	0.65±1.14	0.52
Boston Naming Test	0.61±1.09	0.13±0.89	0.01*	0.40±0.97	0.33±1.28	0.78	0.34±1.03	0.42±1.03	0.76
Rey-Osterrieth Complex Figure Test	0.16±0.69	0.34±0.51	0.12	0.21±0.60	0.38±0.71	0.26	0.07±0.64	0.33±0.59	0.40
Seoul Verbal Learning Test	-0.68±0.46	-0.64±0.48	0.62	-0.66±0.45	-0.67±0.57	0.93	-0.66±0.46	-0.66±0.48	0.87
Rey figure delayed-recall test	0.04±0.78	-0.11±0.78	0.29	0.03±0.81	-0.33±0.52	0.06	0.02±0.96	-0.05±0.66	0.01*
Digit Symbol Substitution Task	0.58±1.13	0.35±0.89	0.23	0.51±1.03	0.32±1.02	0.46	0.53±1.09	0.45±1.00	0.27
Controlled Oral Word Association Test	0.42±1.08	-0.02±0.90	0.02*	0.30±1.06	-0.20±0.67	0.04*	0.30±1.10	0.18±0.98	0.52
Trail-Making Test	0.31±0.67	0.36±0.57	0.67	0.42±0.58	-0.10±0.64	0.00*	0.44±0.62	0.28±0.62	0.67
Stroop Test	0.21±0.79	0.04±0.85	0.26	0.19±0.80	-0.19±0.87	0.06	0.16±0.85	0.11±0.80	0.40

Data are mean±standard deviation values.
*Significant difference (p<0.05).
K-MMSE, Korean version of the Mini Mental State Examination.

p<0.01). Subjects with slower gait (n=78, 65%) had worse performance in the RCFT (0.02±0.96 vs. -0.05±0.66, p=0.01).

The results from logistic regression analyses of the associations of frailty status with demographic characteristics and imaging factors are presented in Table 3. Female (odds ratio [OR]=3.79, 95% confidence interval [CI]=1.65–8.76, p=0.002) and amyloid-PET-positive (OR=3.80, 95% CI=1.425–10.155, p=0.008) subjects with SCD presented significantly higher risks of self-reported exhaustion. Amyloid PET positivity (OR=3.22, 95% CI=1.01–10.24, p=0.047) and high pvWMH burden (OR=3.34, 95% CI=1.18–9.46, p=0.023) were significantly associated with weaker handgrip. Females (OR=0.85,

Table 3. Associations of demographic and imaging factors with physical frailty status

Dependent variable	Independent variables	B	SE	Wald	Odds ratio	95% CI	*p*
Self-reported exhaustion	Female	1.335	0.426	9.795	3.799	1.647–8.764	0.002*
	Amyloid PET positivity	1.336	0.501	7.110	3.804	1.425–10.155	0.008*
Handgrip strength	Female	0.721	0.561	1.650	2.056	0.685–6.176	0.199
	Amyloid PET positivity	1.170	0.590	3.931	3.223	1.014–10.249	0.047*
	High pvWMH burden	1.205	0.532	5.141	3.338	1.178–9.462	0.023*
Gait speed	Female	1.047	0.400	6.842	2.849	1.300–6.242	0.009*
	High pvWMH burden	0.761	0.457	2.772	3.234	0.874–5.249	0.096

Multiple logistic regression analysis was performed using the backward stepwise method.
*Variables differ significantly ($p<0.05$).
CI, confidence interval; PET, positron-emission tomography; pvWMH, periventricular white-matter hyperintensity; SE, standard error.

95% CI=1.30–6.25, p=0.009) were significantly associated with a high risk of slower gait among subjects with SCD. Subjects with a high pvWMH burden (OR=3.32, 95% CI=0.87–5.25, p=0.096) also tended to have a high risk of slower gait, but the difference was not significant.

DISCUSSION

In this study we found that the components of physical frailty were closely related to brain amyloid pathology and WMH in subjects with SCD, and those subjects presented worse cognitive performance in neuropsychological tests, especially in information processing speed and executive function.

First, the subjects with SCD who had self-reported exhaustion were likely to be amyloid-positive in PET, and performed worse in global cognitive function, confrontation naming ability, and verbal fluency. Previous studies found that fatigue was associated with brain atrophy and cognitive impairment in older adults[17] and longitudinally increased cognitive decline risk in older adults without dementia.[18] One cross-sectional study also found that subjects with fatigue had an increased amyloid-beta load specifically in the hippocampus, especially in the early stages of the disease.[19] Fatigue is known to be related to oxidative stress and proinflammatory mediators such as interleukin 6 and C-reactive protein.[20] Such changes in signaling could alter homeostasis, which would lead to subsequent increases in amyloid-beta deposition at the molecular level.[19,21]

Second, the subjects with SCD with weak handgrip were at higher risks of amyloid PET positivity and a high pvWMH burden. Several previous studies found that poor handgrip strength was associated with cognitive impairment and a higher risk of cognitive decline.[22,23] Other studies have also found an association between WMH and handgrip strength.[24-26] Handgrip strength is one of the main indicators of body muscle strength and can also be an overall indicator of the integrity of the central nervous system.[27] The relationship between decreased muscle strength and AD may be due to a shared pathology such as inflammation, oxidative stress, nutrition, immobility, or hormonal dysregulation.[28-30]

Third, our study found that gait speed was significantly associated with visual memory function. Gait not only relies on motor corticostriatal circuits, but also on cognitive functions such as attention, executive function, visuospatial processing, and memory.[31] From this perspective, gait and cognitive function might share similar pathological mechanisms. The prevalence of reduced gait speed was significantly higher in female subjects with SCD in our study. Gait speed could differ between the sexes, and the biological drivers of frailty may be sex-specific.[32]

Numerous previous studies found that the components of physical frailty were closely associated with cognitive impairment and could predict longitudinal cognitive decline.[27,33,34] However, evidence for the associations between physical frailty and cognitive function among subjects with SCD is rare. Our study demonstrated that subjects with SCD and physical frailty had poor cognitive performance compared with subjects without these conditions, especially in frontal executive functioning. AD is preceded by a 'silent' clinical period that can last longer than a decade.[35] Together that the present findings raise the possibility that the pathological features of AD contribute to both motor and cognitive decline in the early stage of the disease and that the components of frailty and SCD share common underlying pathologies.[36] Modifiable risk and protective factors that are shared by physical frailty and cognitive impairment could also be new therapeutic targets for preventing or delaying the progression of the two conditions, since both can be observed in the early stage of AD and may be reversible.

Our study had several limitations. First, we defined self-reported exhaustion by conducting our own questionnaires on lifestyle. Fried et al.[15] originally described exhaustion as being one of five components in the frailty phenotype, and it is measured by using two questions from the Center for Epidemiological Studies Depression Scale. However, a great variety of instruments has also been used to evaluate exhaus-

tion.[37] This heterogeneity in operationalization could obscure the pathophysiological mechanism underlying exhaustion. Establishing consensus criteria for exhaustion could help to understand the meaning of exhaustion in persons with frailty. Second, the sample was relatively small, especially for amyloid-positive subjects with SCD. Third, this study had a cross-sectional design and only analyzed baseline parameters, which means that the causal relationship was unclear. Future studies with large-scale longitudinal data are needed to clarify and strengthen these results.

Despite these limitations, our study had strengths in that it was the first to investigate physical frailty in patients with SCD and confirmed amyloid pathology. Few studies have examined the association between amyloid pathology and physical frailty using amyloid PET data. It is therefore meaningful that amyloid positivity in subjects with SCD was significantly associated with physical frailty, and the presences of physical frailty and cognitive performance are closely associated.

We plan to observe the effects of these physical factors on future cognitive decline by analyzing longitudinal data. If a decrease in physical performance has already been identified in patients with SCD and its effect on cognitive decline has been confirmed, this could provide an opportunity to reconfirm new prophylactic implications of improving these physical factors.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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