The Influence of Amyloid Burden on Cognitive Decline over 2 years in Older Adults with Subjective Cognitive Decline: A Prospective Cohort Study

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Keywords

Subjective cognitive decline · Alzheimer's disease ·
Neuroimaging biomarker · Cognitive decline · Amyloidosis ·
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Abstract

Background: Subjective cognitive decline (SCD) is a self-perceived cognitive worsening without objective cognitive impairment. Due to its heterogeneity and potential risk of Alzheimer's disease (AD), baseline biomarkers to predict progression are clinically important. In the present study, cognitive trajectories during a 24-month period were compared between amyloid-positive SCD (A+SCD) and amyloid-negative SCD (A–SCD) subjects, and biomarkers associated with memory decline were investigated. **Methods:** Data from a prospective cohort study in Korea between 2016 and 2019 were analyzed. SCD subjects ≥ 50 years of age were eligible. All participants underwent neuropsychological tests, brain magnetic resonance imaging, and florbetaben positron emission tomography scans. Amyloid burden and regional volumes were measured. Cognitive changes corrected for age were compared between A+SCD and A–SCD groups. Biomarkers associated with memory decline were assessed. **Results:** Forty-seven SCD subjects (69.9 ± 6.7 years, mini-mental

state examination (MMSE) score 27.5) were enrolled, and 31 completed at least 1 annual follow-up (mean follow-up: 24.7 months). Baseline characteristics except age, hippocampal atrophy, and white matter hyperintensities were similar between A+SCDs ($n = 12$, 25.6%) and A–SCDs ($n = 35$). A+SCD subjects showed greater decline in the verbal memory function compared with the A–SCD subjects after adjustment for age. MMSE scores decreased more in the A+SCD (1.1 in the A+SCD; 0.55 in the A–SCD), although it was not statistically significant. Amyloid burden and baseline memory score were associated with memory decline. **Conclusions:** Within SCD, A+SCD subjects showed faster memory decline compared with the A–SCD subjects and amyloid burden might be associated with future memory decline in SCD.

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Introduction

Subjective cognitive decline (SCD) is characterized by self-perceived cognitive worsening in the absence of objective cognitive impairment. Cognitively normal individuals with SCD are thought to have higher risk of Alzheimer's disease (AD) dementia [1–5]. Because self-awareness and concerns regarding minor cognitive

decline could be an early sign of AD, subjects with SCD are the most appropriate target population for secondary preventions. However, due to the heterogeneity of both pathologies and cognitive trajectories, baseline clinical and biomarker findings to predict future cognitive decline are clinically important in this stage.

In recent studies, old age, apolipoprotein $\epsilon 4$ (APOE4) existence, and amyloid pathologies at baseline were reportedly relevant factors for cognitive decline in subjects with SCD [3, 6–8]. In SCD with amyloidosis, the risk of clinical progressions increases to 40–62% during approximately 3 years [5], which might be why SCD with amyloidosis is considered as the later stages of preclinical AD. In our previous cross-sectional data [9], amyloid-positive SCD (A+SCD) subjects differed from amyloid-negative SCD (A–SCD) in baseline small vessel disease markers, degree of hippocampal atrophy, and a few clinical features (existence of SCD-plus clinical features) regarding cognitive complaints [9, 10]. The results showed that A+SCD participants are different in baseline status and characteristics in regard to the complaints; however, it was not assessed whether the baseline amyloidosis is associated with future cognitive decline.

In this prospective observational cohort study, we included individuals diagnosed as SCD from a memory clinic cohort and underwent amyloid positron emission tomography (PET) scans and brain magnetic resonance imaging (MRI) to assess amyloid burden and neurodegenerations, with regular follow-up evaluations including MRI and cognitive tests during a 24-month period. In the present study, cognitive trajectories between A+SCD and A–SCD subjects were compared and relationships between baseline biomarkers and memory decline were measured to investigate whether amyloid burden is associated with future cognitive decline.

Materials and Methods

Participants

This study was performed at a university-affiliated dementia clinic from December 2016 to July 2019. Elderly subjects who visited the hospital due to cognitive worsening and were diagnosed with SCD after dementia work-up were consecutively recruited during the study period. The dementia work-up included detailed neuropsychological test battery, MRI, and routine blood sampling for syphilis, thyroid function, vitamin B deficiencies, and APOE genotyping. The study inclusion criteria were the following: (1) existence of persistent self-reported cognitive complaints; (2) older than 50 years of age; (3) normal performance (above -1.0 standard deviation of norms) on all subtests of neuropsychological test battery named Seoul Neuropsychological Screening Battery (SNSB) [11]; (4) clinical dementia rating (CDR) [12] score of 0; (5) literate; and (6) agreement to partici-

pate in the study and could visit the hospital for annual evaluations. The exclusion criteria were the following: (1) any unstable or severe medical condition (e.g., severe hepatic or renal disease, unstable cardiovascular disease, severe asthma, active gastric ulcer, cancer); (2) neurological disorders such as Parkinson's disease, Huntington's disease, or normal pressure hydrocephalus; (3) major psychiatric disorders such as uncontrolled depression, schizophrenia, alcoholism, or drug dependency; (4) mild cognitive impairment (MCI) or dementia; (5) abnormal blood laboratory findings such as abnormal thyroid function, low vitamin B12 or low folate, or positive syphilis serology; and (6) brain lesions known to cause cognitive impairment (tumor, stroke, or subdural hematoma). All study participants underwent baseline physical and neurological examinations and florbetaben PET scans for amyloidosis. No pharmacological treatments or non-pharmacological interventions were administered to the participants. All participants underwent annual follow-up evaluations to assess cognitive decline/clinical progression, and brain MRI scans were performed at the second follow-up visit (after 24 months from the baseline) to assess atrophic changes during the study period. This study was approved by the Institutional Review Board (DAUHIRB-16-232), and written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and principles of Good Clinical Practice.

Neuroimaging

Brain MRI was performed using a 3.0-Tesla scanner (GE Medical Systems, Milwaukee, WI, USA), including fluid attenuated inversion recovery (FLAIR), gradient echo, and 3-dimensional (3D) T1-weighted images. The white matter hyperintensities (WMHs) were rated using a visual rating scale of axial FLAIR images. In brief, periventricular WMHs and deep WMHs were evaluated separately and rated as minimal (grade 1), moderate (grade 2), or severe (grade 3) [13]. Lacunes were defined as small lesions (3–15 mm in diameter), hyperintense on T2-, and hypointense on T1-weighted images, with a perilesional halo on FLAIR [14]. Cerebral cortical microbleeds were defined as round and homogeneously low-signal lesions <10 mm in diameter in lobar areas on gradient echo images [14]. Hippocampal atrophy was rated on coronal T1-weighted images using Scheltens' visual rating scale [15]. The mean of the left and right hippocampal atrophy scores was used. The number of lacunes, number of microbleeds, degree of WMH, and degree of hippocampal atrophy were measured by a neurologist (YB Kim) blinded to the data.

Florbetaben (18F) PET scans were acquired following the standardized protocol [16]. Using PET scans, a whole brain visual interpretation was performed by a trained specialist in nuclear medicine who was blinded to the patient diagnosis. A visual rating scale of florbetaben PET scans, the brain amyloid plaque load score (1 = negative finding, 2 = moderate amyloid depositions, 3 = pronounced amyloid depositions) [17], was used to categorize amyloid-positive and amyloid-negative participants. Brain amyloid plaque load scores of 2 or 3 indicated a positive finding for amyloidosis (A β +).

In addition, quantitative neuroimaging analyses were performed using PET scans and MRI 3D T1 images. First, amyloid depositions were assessed using MATLAB version 2013a and SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8>). Individual 3D T1-weighted MRI scans were estimated and co-registered into corresponding PET images. A volume-based template, incorporating 90 regions of interest (ROI), named automatic anatomical labeling

Fig. 1. Flowchart of the participants. SCD, subjective cognitive decline; PET, positron emission tomography.

(AAL), was aligned to individual T1-weighted MRI images. The voxels of florbetaben PET images were scaled using the mean uptake value in the cerebellar cortex to calculate the standardized uptake value ratio (SUVR), and partial volume corrections were performed. For partial volume corrections, the voxels located in gray matter with a probability <20 percent were discarded in each PET images. We selected 28 AD-specific cortical ROIs from the AAL atlas according to the previous methods [18] and the mean SUVR values were calculated as a global SUVR. Second, the volumes of regional cortical areas including anterior frontal, dorsolateral frontal, orbitofrontal, lateral temporal, medial temporal, lateral parietal, medial parietal, and occipital lobes were measured from individual 3D T1 images using MATLAB 2013a, SPM8, and the newly developed in-house program named Quick Brain Volumetry (QBraVo). The methods of the automated volumetry program, QBraVo, are described in the online supplementary data (for all online suppl. material, see www.karger.com/doi/10.1159/000519766). To assess early neurodegenerative changes in AD, hippocampal and entorhinal volumes were separately measured using the QBraVo.

Baseline and Follow-Up Neuropsychological Tests

All participants were diagnosed with SCD using the formal neuropsychological test battery SNSB [11], including the Korean version of the mini-mental state examination (K-MMSE) [19], CDR, activities of daily living (ADL), attention (digit span test), language (Boston naming test, tests for comprehension/repetition/fluency), visuospatial function (Rey Complex Figure Test, RCFT), verbal and visual memory function [Seoul Verbal Learning Test (SVLT) and RCFT recall test], and frontal executive function (contrasting program, go-no-go, Controlled Oral Word Association Test, and Stroop test) [11]. Age-, sex-, and education-specific norms based on normal controls were used to interpret the SNSB results. Scores ≥ 16 th percentile, which were compared to -1 standard deviation (SD) of the norm, were defined as normal. The severity of the cognitive complaints was assessed using a self-rated scale named Cognitive Failures Questionnaire (CFQ) (total score 0–100, higher total score means more cognitive complaints) [20]. Using a self-report questionnaire, “informant also report a cognitive decline of the participant,” “subjective concern about the cog-

nitive decline,” and “symptom’s onset after 65 years of age” were assessed at baseline and annual follow-up evaluations because the questions are parts of “SCD-plus criteria” and were associated with Alzheimer’s pathologic changes in our previous study [9].

Annual follow-up evaluations (visit window up to 3 months was allowed) included cognitive tests (K-MMSE, CDR, and verbal learning immediate/delayed/recognition tests), Korean version of the instrumental ADL (K-IADL) scale [21], neurological and physical examinations, and physician’s history taking to assess clinical progression to MCI or dementia. The cognitive tests were administered by a trained neuropsychologist. Participants with CDR score ≥ 0.5 or K-IADL score ≥ 0.43 were considered to have progressed to MCI or dementia.

Statistical Analysis

Independent *t*-test or nonparametric Mann-Whitney *U* test (based on normal distribution patterns) was used for comparison of continuous variables such as baseline demographics and clinical characteristics between A+SCD and A–SCD subjects. χ^2 tests were used to compare categorical variables between the 2 groups. Analysis of covariance (ANCOVA) corrected for age and baseline scores was used to compare cognitive changes between the 2 groups. To assess relevant baseline factors associated with verbal memory decline, multivariable linear regression analysis was performed. All statistical analyses were performed using SPSS (version 18.0; SPSS Inc, Chicago, IL, USA). *p* values <0.05 were considered to indicate statistically significant differences.

Results

Baseline Demographics

Initially, 62 subjects who were diagnosed as SCD were screened; 15 refused to participate in the study. A total of 47 participants with SCD (mean age: 69.9 ± 6.7 years) was enrolled at baseline, and 31 subjects with SCD completed at least 1 annual follow-up evaluation (Fig. 1). Sixteen

Table 1. Baseline characteristics and clinical findings between groups (total enrolled subjects)

Variables	Amyloid PET+ (n = 12)	Amyloid PET– (n = 35)	p value
<i>Demographics</i>			
Age, years	74.17±4.47	67.09±6.71	0.001
Female, n (%)	7/12 (58.3)	23/35 (65.7)	0.733
Education, years	7.83±2.86	9.61±4.76	0.132
APOE4 allele, n (%)	5/12 (41.7)	5/35 (14.3)	0.096
Hypertension, n (%)	7/12 (58.3)	14/35 (40)	0.270
DM, n (%)	4/12 (33.3)	7/35 (20)	0.435
Hyperlipidemia, n (%)	3/12 (25)	11/35 (31.4)	0.734
<i>Neuroimaging findings</i>			
Global SUVR, ratio	1.53±0.25	1.17±0.06	0.001
Hippocampal atrophy, grade	1.17±0.94	0.36±0.59	0.015
Ant frontal vol., cm ³	50.66±7.10	56.39±8.31	0.045*
Dorsolateral frontal vol., cm ³	67.34±8.86	71.75±10.76	0.225
Orbitofrontal vol., cm ³	33.47±4.64	37.11±5.89	0.068
Ant temporal vol., cm ³	30.45±4.38	32.01±5.42	0.392
Med temporal vol., cm ³	31.14±3.00	32.47±3.58	0.272
Lat temporal vol., cm ³	133.29±16.39	137.95±18.66	0.462
Lat parietal vol., cm ³	121.92±12.49	127.31±16.98	0.337
Med parietal vol., cm ³	68.48±7.04	70.41±8.83	0.513
Occipital vol., cm ³	141.41±15.41	142.45±18.75	0.868
Entorhinal cortex vol., cm ³	2.01±0.23	2.16±0.30	0.134
Hippocampal vol., cm ³	3.13±0.32	3.37±0.32	0.039*
Lacune, n	2.25±4.16	1.91±4.69	0.827
Cortical microbleed, n	2.22±3.19	0.27±0.83	0.105
Periventricular WMH, G1/2/3	3/7/2	25/6/4	0.009
Deep WMH, G1/2/3	6/5/1	28/6/1	0.126
<i>Cognition and self-reported symptoms</i>			
Cognitive complaints (CFQ total score)	31.09±19.92	28.50±12.51	0.691
Existence of subjective concern about cognitive decline, n, %	8/11, 72.7	30/34, 88.2	0.337
Existence of informant's report a decline, n, %	8/11, 72.7	15/34, 44.1	0.099
Symptom's onset, years	70.27±7.51	64.29±7.32	0.024
K-MMSE, total score	27±2.05	27.69±1.81	0.279
Digit span_attention, %	55.16±28.54	67.54±30.64	0.226
Boston naming test, %	66.24±18.89	57.22±24.82	0.258
SVLT immediate recall, %	37.20±20.24	48.44±22.79	0.137
SVLT_delayed recall, %	47.82±20.71	41.57±23.24	0.414
SVLT_recognition, %	51.01±22.99	45.93±25.73	0.549
RCFT_copy, %	76.01±11.41	66.98±20.52	0.156
RCFT_immediate recall, %	66.28±29.81	53.77±21.31	0.123
RCFT_delayed recall, %	66.45±26.70	50.80±22.68	0.056
RCFT_recognition, %	46.85±25.62	48.67±27.92	0.844
COWAT_phonemic, %	47.83±27.09	46.29±23.94	0.853
Stroop_color reading, %	52.38±33.87	60.15±27.38	0.429

PET, positron emission tomography; APOE4, apolipoprotein ε4; DM, diabetes mellitus; SUVR, standardized uptake value ratio; vol, volume measured using QBraVo program; CFQ, cognitive failure questionnaire; WMH, white matter hyperintensities; K-MMSE, Korean version of the mini-mental state examination; SVLT, Seoul Verbal Learning Test; RCFT, Rey Complex Figure Test; COWAT, Controlled Oral Word Association Test. * The statistical significance disappeared after adjustment for age. %: percentile scores (0–100) after adjustment for age, gender, and education. Higher scores indicate better cognition.

Table 2. Baseline characteristics and clinical findings between groups (follow-up completers)

Variables	Amyloid PET+ (n = 9)	Amyloid PET– (n = 22)	p value
<i>Demographics</i>			
Age, years	73.78±4.52	68.27±6.92	0.037
Symptom's duration, years	4.69±5.17	3.64±4.12	0.554
Female, n, %	5, 55.6	15, 68.2	0.548
Education, years	7.33±2.18	9.80±5.20	0.074
APOE4 allele, n, %	4, 44.4	4, 18.2	0.185
Hypertension, n, %	4, 44.4	10, 45.5	0.637
DM, n, %	3, 33.3	6, 27.3	0.528
Hyperlipidemia, n, %	3, 33.3	5, 22.7	0.424
<i>Neuroimaging</i>			
Global SUVR, ratio	1.53±0.14	1.17±0.05	<0.001
Hippocampal atrophy, grade	0.55±0.53	1.00±0.87	0.084
Ant frontal vol., cm ³	50.26±6.94	55.91±7.20	0.077
Dorsolateral frontal vol., cm ³	66.25±8.04	71.06±9.51	0.237
Orbitofrontal vol., cm ³	33.13±4.82	36.85±5.33	0.110
Ant temporal vol., cm ³	29.85±4.25	32.44±5.79	0.284
Med temporal vol., cm ³	30.91±3.48	32.50±3.46	0.297
Lat temporal vol., cm ³	132.50±14.76	137.64±17.68	0.492
Lat parietal vol., cm ³	118.79±11.00	126.21±14.87	0.234
Med parietal vol., cm ³	65.82±5.48	70.23±9.08	0.236
Occipital vol., cm ³	141.41±16.17	143.07±19.08	0.836
Entorhinal cortex vol., cm ³	1.95±0.24	2.20±0.29	0.050
Hippocampal vol., cm ³	3.16±0.40	3.34±0.25	0.155
Lacune, n	1.22±1.20	2.86±5.73	0.214
Cortical microbleed, n	1.71±2.63	0.16±0.69	0.170
Periventricular WMH, G1/2/3	3/4/2	14/5/3	0.326
Deep WMH, G1/2/3	5/4/0	17/4/1	0.325
<i>Cognition and self-reported symptoms</i>			
Cognitive complaints (CFQ total score)	28.00±18.46	28.95±13.12	0.876
Existence of subjective concern about cognitive decline, n (%)	5 (71.43)	20 (86.96)	0.699
Existence of informant's report a decline, n (%)	6 (85.71)	13 (56.52)	0.339
Symptom's onset, yr	70.14±7.47	64.57±7.58	0.099
K-MMSE, total score	27.22±1.79	27.50±1.90	0.710
Digit span_attention, %	55.64±30.41	68.10±31.36	0.320
Boston naming test, %	66.97±17.25	62.11±23.12	0.575
SVLT immediate recall, %	31.33±14.43	49.50±21.13	0.026
SVLT_delayed recall, %	49.37±22.38	43.19±23.07	0.501
SVLT_recognition, %	47.45±17.40	50.38±22.10	0.726
RCFT_copy, %	73.58±11.95	67.71±20.66	0.434
RCFT_immediate recall, %	61.83±32.54	55.55±23.68	0.556
RCFT_delayed recall, %	62.92±28.01	52.03±25.24	0.303
RCFT_recognition, %	48.78±29.18	54.49±26.65	0.605
COWAT_phonemic, %	44.35±21.62	46.65±24.17	0.806
Stroop_color reading, %	53.82±35.07	59.72±26.81	0.615

%: percentile scores (0–100) after adjustment for age, gender, and education. Higher scores indicate better cognition. PET, positron emission tomography; APOE4, apolipoprotein ε4; DM, diabetes mellitus; SUVR, standardized uptake value ratio; vol, volume measured using QBraVo program; CFQ, cognitive failure questionnaire; WMH, white matter hyperintensities; K-MMSE, Korean version of the mini-mental state examination; SVLT, Seoul Verbal Learning Test; RCFT, Rey Complex Figure Test; COWAT, Controlled Oral Word Association Test.

Table 3. Cognitive and neurodegenerative changes in each group (subjects who completed follow-up)

Variables	A+SCD (n = 9)	A-SCD (n = 22)	p value	Model 1 p value	Model 2 p value
K-MMSE score change	-1.13±2.85	-0.55±2.82	0.624	0.588	0.771
SVLT-delayed recall % change	-4.69±33.03	18.11±21.75	0.036	0.018	0.075
Entorhinal vol. change, cm ³	0.16±0.28	-0.06±0.20	0.036	0.031	0.117
Hippocampal vol. change, cm ³	0.07±0.08	0.06±0.14	0.787	0.390	0.402

Model 1: adjusted for age. Model 2: adjusted for age, educational level, and baseline scores (K-MMSE, and SVLT-delayed recall scores). A+SCD, amyloid-positive subjective cognitive decline; A-SCD, amyloid-negative subjective cognitive decline; PET, positron emission tomography; K-MMSE, Korean version of mini-mental state examination; SVLT, Seoul Verbal Learning Test.

participants did not undergo follow-up evaluations due to refusal ($n = 14$) or moving to other regions ($n = 2$). At baseline, 35 participants (74.4%) were negative and the other 12 (25.6%) were positive for amyloid deposition based on visual ratings of florbetaben PET scans. Baseline demographics and clinical characteristics ($n = 47$) are shown in Table 1. The A+SCD participants were older ($p = 0.001$), had more advanced hippocampal atrophy ($p = 0.015$), and showed more periventricular WMH ($p = 0.009$) compared with A-SCD participants (Table 1). Baseline regional volumes (adjusted for age), small vessel disease findings, and neuropsychological test results (adjusted for age, sex, and educational level) were similar between the 2 groups (Table 1).

Baseline characteristics of the participants who completed follow-up evaluations ($n = 31$) are shown in Table 2. Among participants who completed the study, A+SCD participants ($n = 9$) were older and had lower verbal immediate recall scores (Table 2); 1 participant was excluded from quantitative PET imaging analysis due to poor imaging quality. Mean follow-up duration was 24.7 ± 7.5 months (range, 10–36 months). Participants who completed the study ($n = 31$) did not differ from subjects who dropped out ($n = 16$) in terms of baseline clinical characteristics such as age, sex, educational level, comorbidities, and cognitive scores (online suppl. Table 1).

Cognitive Decline and Medial Temporal Neurodegenerations

During the study period, no participant progressed to MCI or dementia. K-MMSE scores decreased by a mean of 1.13 points in the A+SCD group and 0.55 points in the A-SCD group, although the differences did not reach statistical significance ($p > 0.05$, Table 3). However, after adjustment for age, A+SCD participants showed greater de-

clines of verbal memory delayed recall function (SVLT-delayed recall score) than the A-SCD participants (Table 3). After adjustment for age, educational level, and baseline cognitive scores, SVLT-delayed recall scores showed a trend of more rapid decline in A+SCD participants compared with A-SCD participants (Table 3). Entorhinal cortical volume, a biomarker representing neurodegenerations, decreased more in A-SCD participants after adjustment for age although the volume changes were small (Table 3). Other variables including GDS, CDR, CDR sum of boxes score, and K-IADL scores did not show significant differences between the 2 groups during the study period (data not shown).

Correlations between Baseline Factors and Cognitive Decline

It was assessed whether baseline amyloid burden was the most relevant factor associated with future changes in SVLT-delayed recall score compared with other clinical factors and imaging biomarkers. In univariable regression analysis, baseline SVLT-delayed recall score, baseline number of microbleeds, and global SUVR values were the most relevant factors associated with changes in SVLT-delayed recall score (Table 4). Other baseline characteristics such as demographics, other cognitive scores, severity of the cognitive complaints, and neuroimaging biomarkers such as hippocampal volumes or small vessel disease markers were not related with SVLT-delayed recall score changes (Table 4). Because the baseline number of microbleeds was significantly associated with global SUVR values ($p = 0.004$, $r = 0.541$), the number of microbleeds was not included in the multivariable analysis. Global SUVR values and baseline SVLT-delayed recall scores were not correlated with each other ($p > 0.05$). In multivariable regression analysis, baseline SVLT score

Table 4. Correlations between baseline factors and verbal memory decline during 2 years

Variables	Univariable			Multivariable		
	β	95% CI	<i>p</i> value	β	95% CI	<i>p</i> value
Global SUVR (ratio)	−0.488	−125.121~−22.675	0.006	−0.354	−102.080~−5.352	0.031
Microbleed (<i>n</i>)	−0.429	−13.934~0.829	0.029			
Age (years)	0.056	−1.265~1.707	0.764			
Female gender	−0.189	−30.525~9.961	0.307			
Education (years)	0.134	−1.377~2.908	0.471			
Baseline SVLT delayed recall (%)	−0.543	−1.033~−0.259	0.002	−0.435	−0.8997~−0.137	0.009
Baseline CFQ score	−0.254	−1.134~0.207	0.168			
Concern about cognitive decline	0.009	−26.610~27.855	0.963			
Informant's report a decline	−0.280	−35.475~4.957	0.133			
APOE4	0.098	−16.614~28.256	0.600			
Lacune (<i>n</i>)	0.003	−2.030~2.065	0.986			
WMH, periventricular	−0.222	−20.552~5.159	0.231			
WMH, deep	0.032	−16.957~20.107	0.863			
EC vol. (cm ³)	0.037	−32.012~38.736	0.847			
Hippocampal vol. (cm ³)	0.058	−29.869~40.314	0.763			

%: percentile scores (0~100) after adjustment for age, gender, and education. Higher scores indicate better cognition. CFQ, cognitive failure questionnaire; APOE4, apolipoprotein ϵ 4; WMH, white matter hyperintensities; MMSE, mini-mental state examination; SUVR, standardized uptake value ratio; SVLT, Seoul verbal learning test; EC, entorhinal cortex; vol, volume measured using the QBraVo program.

and global SUVR value were the baseline factors associated with change in SVLT memory score (see Table 4). Baseline global SUVR value had an inverse relationship with verbal memory decline (Table 4).

Discussion

This prospective observational cohort study was conducted in participants with SCD during a 24-month period and tested whether cognitive trajectories in A+SCD participants were different from those in A−SCD participants. In addition, the baseline factors associated with memory decline were assessed. Major findings of the current study showed that A+SCD participants experienced more rapid decline in verbal memory function compared with A−SCD participants. Furthermore, baseline amyloid burden was associated with verbal memory decline during the relatively short study period.

Participants in the 2 groups did not progress to MCI or dementia during the study period. Consistent with the clinical outcomes, ADL and CDR scores did not change at the study endpoint, as was expected, considering that the study participants were cognitively normal at baseline, and that clinical progression rates from SCD to MCI/

dementia are only 5–10% annually [4, 11, 22]. However, general cognitive scores based on K-MMSE differed between A+SCD and A−SCD participants. Notably, verbal memory scores based on SVLT-delayed recall tests showed significantly different changes between the 2 groups; greater verbal memory decline was observed in SCD participants with Alzheimer's pathologic changes despite the relatively short follow-up duration and agreement in baseline cognitive scores. Verbal memory delayed recall function might be associated with medial temporal function and decrease early and prominently in typical AD. Consistent with greater memory score changes in A+SCD participants, amyloid deposition, rather than other baseline factors, was a relevant risk factor associated with verbal memory decline. Furthermore, amyloid burden was associated more highly with memory changes than were other baseline factors such as entorhinal/hippocampal atrophy, small vessel disease markers (lacunes/WMHs/microbleeds), or age, all of which are known to be associated with verbal memory function. Based on previous evidence, neurodegenerations are known to be closely linked to cognitive decline while amyloid burden is not strongly related with short-term cognitive decline [23]. During the study period, entorhinal volume showed more decrease in A−SCD participants

compared with that in A+SCD participants, although the volume differences were numerically small and the entorhinal/hippocampal volume changes during the study period were not definite. The conflicting result can be explained that neurodegenerative changes are not definite yet in this early stage and neurodegeneration alone without considering amyloidosis may not cause aggressive progressions; neurodegenerations only combined with amyloid pathologies would likely show cognitive progression in elderly participants with SCD [24]. Hence, amyloid burden, rather than neurodegenerative changes, could be the more important factor affecting future memory decline in this very early stage of AD. In summary, assessment for existence of cognitive complaints and brain amyloidosis may enable predicting faster memory decline even in a short-term period.

The present study had a few limitations. First, follow-up duration was relatively short considering that annual progression rate of SCD is below 10% based on previous large cohort studies. Second, other risk factors such as tau-related biomarkers, lifestyle factors associated with clinical progression, and combined non-AD related pathologies such as Parkinson's disease were not studied. Because SCD is a heterogeneous condition with multiple pathologies, mood disorders, and personality factors, future studies should adopt detailed pathologic biomarkers and longer follow-up duration. The last, sampling bias might exist because this study was conducted in a single center, hence, generalization of the results need cautious interpretations.

Despite the few study limitations, the results have strength because participants were consecutively recruited using comprehensive neuropsychological test battery and underwent multiple biomarker evaluations. All participants underwent amyloid PET scans and regular brain MRI follow-ups and quantitative measures for amyloid burden and neurodegenerative changes. In addition, we assessed the intensity of subjective cognitive complaints and characteristics of the cognitive complaints using SCD-plus criteria although they did not show significant effects on cognitive declines. There have been few studies that investigated longitudinal cognitive trajectories of SCD based on baseline amyloid burden, neurodegenerations, and detailed clinical evaluations. The present results imply that faster verbal memory decline can be predicted in cognitively unimpaired elderly with both brain amyloidosis and SCD, which should be confirmed in future studies with long-term follow-ups.

Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki and the guidelines on good clinical practice. All eligible patients who had signed the consent form were included in the study. The study protocol was validated by the Dong-A University Hospital's Ethics Committee (DAUHIRB-16-232), Busan, South Korea.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

Y.J.H. and K.W.P. contributed to the study concept and design. Y.J.H. analyzed and interpreted the results. Y.J.H. drafted the manuscript. J.W.P., S.B.L., S.-H.K., Y.K., D.-W.R., K.W.P., and D.W.Y. were involved in data collection, recruitment, and evaluation of the patients. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material file. Further inquiries can be directed to the corresponding author on reasonable request.

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