Subjective Cognitive Decline and Alzheimer’s Disease Spectrum Disorder

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INTRODUCTION

Alzheimer’s disease (AD) is the most common cause of dementia and characterized by a slow progression over several years to decades.1,2 Based on the fact that the presymptomatic and prodromal stages of AD exist before the AD dementia stage, new concepts of research criteria for AD have been proposed recently: first, the International Working Group (IWG) proposed 3 stages of AD including the asymptomatic at-risk stage of AD, prodromal AD, and AD dementia.3 Second, The US National Institute on Aging-Alzheimer’s Association (NIA-AA) group also proposed 3 stages of AD including the preclinical AD, mild cognitive impairment (MCI) due to AD, and dementia due to AD stages.4 Both criteria include preclinical, asymptomatic stage of AD, in other words, normal cognition with AD-related pathologies, which would be important in terms of a potential target for dementia prevention trials.5 AD-related pathologies in the brain include two pathologic hallmarks, amyloid plaques and tau neurofibrillary tangles.6 They can be assessed using various biomarker tools; for amylodosis, increased amyloid uptake on amyloid positron emission tomography (PET) and decreased cerebrospinal fluid (CSF) Aβ42 levels can be used; for tau pathologies, tau-related neurodegenerations such as hypometabolism on fludeoxyglucose-PET, brain atrophy on MRI, and increased CSF tau levels are currently used.4 Recently, tau PET scan which can detect in vivo tau depositions is also available. Preclinical AD is a biomarker-based diagnosis which means the presence of positive AD-related pathologic biomarkers with the absence of cognitive impairment on standard neuropsychological tests.6

However, evaluation for AD pathologic biomarkers and selection of preclinical AD from the general populations are hard to achieve. Subjective cognitive decline (SCD) represents subjective complaints about cognitive decline in the absence of objective impairment in neuropsychological tests. Recently, growing evidence has suggested that SCD might be the first symptomatic stage of Alzheimer’s disease (AD) spectrum disorders. However, SCD is a heterogeneous condition mixed with AD and non-AD related conditions. Hence, refinement of evidence from previous reports and standardization of the concept about SCD are needed to define appropriate target population with AD pathology. In this article, we review previous studies involving subjects with SCD, the new proposed research criteria, and characteristics of SCD in the aspect of preclinical AD. Biomarker status of SCD is also addressed. Future researches on SCD require a longitudinal follow-up with sufficient biomarker studies and proper outcome measures.

Key Words subjective cognitive decline, Alzheimer’s disease, biomarker, preclinical stage.

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on standardized cognitive testing and does not reach the level of objective impairment. Recently, SCD might be considered as the first help-seeking and symptomatic stage of AD spectrum disorders based on the biomarker evidence of a temporal lag between the emergence of pathologic Aβ accumulation and the appearance of clinical symptoms. After a long and slow rate of presymptomatic change of AD, subtle cognitive decline might be detected only on the subjective level. Thus, capturing a valid subjective report about the cognitive decline as an indicator of AD pathology would be rewarding in this population. Additionally, biomarker findings indicative of preclinical AD to select high-risk subjects might be critical in studies of SCD.

Previous studies in SCD have many limitations because there were no consensus on the diagnostic criteria and tools to detect the subclinical cognitive changes effectively. Subjective decline in cognition is nonspecific findings and might be related with numerous non-AD related conditions such as normal aging, personality traits, psychiatric disorders, and other neurological or medical conditions. Therefore, it is warranted to refine the knowledge about SCD and clarify the risk factors for progression. In this article, we aimed to provide a review of previous study results in subjects with SCD, address the new proposed research criteria, and discuss future directions of studies in this field.

**PREVIOUS STUDIES ON SCD**

The concept of SCD was first described in 1982. Since then, individuals with subjective complaints have been denoted as multiple terms including subjective cognitive impairment, subjective memory impairment, subjective memory decline, and subjective memory failure.

However, there has been no neuropsychological test to detect the subtle cognitive decline in individuals with SCD. Only a few studies investigated whether neuropsychological tests could show the difference between the SCD subjects and normal controls. Tests for prospective memory function or semantic interference showed significant differences between normal elderly and SCD subjects.

Previous longitudinal studies reported that individuals with subjective complaints showed an increased risk of future cognitive decline and future progression to MCI or AD dementia. Neuroimaging studies revealed cross-sectional evidence of neurodegenerative changes in subjects with SCD in terms of gray matter atrophic changes, white matter microstructural changes, and functional brain imaging abnormalities. In terms of the gray matter, SCD subjects showed intermediate medial temporal atrophy compared with those of healthy controls and MCI patients, thus mirror the temporal sequence of neurodegeneration in AD continuum disorders. A few studies reported that individuals with cognitive complaints showed similar patterns of decreased gray matter with MCI or AD relative to the healthy controls. Scheef and colleagues reported that subjects with SCD had reduced hippocampal volume compared with normal controls. As for white matter microstructural changes, some studies reported similar pattern or degree of microstructural degenerations in subjects with SCD compared with MCI patients. In the perspective of functional brain imaging, a study showed significant hypometabolism in precuneus and it was associated with longitudinal memory decline in the participants. Mosconi et al. divided SCD subjects into two groups according to the apolipoprotein E (APOE) ε4 existence and showed that ε4 carriers had decreased glucose metabolism in AD-related brain regions and CSF tau/βAmyloid 42 levels similar to AD compared with non-carriers. Altered default mode network connectivity in hippocampus of SCD subjects was reported to be in between normal controls and MCI patients. These data showed substantial evidence of early AD-related structural and/or functional changes in subjects with SCD and suggested that SCD might be a risk factor for AD dementia. However, they also showed conflicting results with regard to the rate of progression, risk of conversion to MCI or AD dementia, role of baseline biomarkers for detection of AD-related neurodegenerative changes, and pathologic changes. This might be due to the small sample size, lack of common terminology, research criteria, highly variable tools to assess the cognitive complaints, and different research environments.

**PROPOSED RESEARCH CRITERIA OF SCD**

SCD-initiative (SCD-I) was launched in 2012 to facilitate the development of a conceptualization for SCD. SCD-I suggested a common concept for terminology and conceptual framework to overcome the study limitations in this field. ‘SCD’ was suggested as a common concept representing normal performance with cognitive complaints. The meanings of the terminology of SCD are as follows: ‘subjective’ refers to the self-perception. ‘Cognitive’ refers to any cognitive domain, not only memory decline because the first symptom of AD may not be limited to memory problem. ‘Decline’ refers to a subjectively experienced worsening of cognition because the terminology reflects the progressive nature of cognitive deterioration in AD continuum disorders. In 2014, SCD-I suggested a new research criteria for SCD which must include following conditions, 1) self-experienced persistent decline in cognitive capacity in comparison with a previously normal
status and unrelated to an acute event; 2) normal age-, gender-, and education-adjusted performance on standardized cognitive tests which are used to classify MCI or prodromal AD. The exclusion criteria included 1) MCI, prodromal AD, or dementia and 2) can be explained by a psychiatric or neurologic disease (apart from AD), medical disorder, medication, or substance use.5 The diagnostic criteria was regarded as sensitive and potentially overinclusive because specific characteristics of SCD with preclinical AD are not yet established.5

**RISK FACTORS OF PROGRESSION IN SCD**

SCD-I suggested the characteristic features which increase the likelihood of preclinical AD in subjects with SCD based on the previous evidence in 2014.5 In the article, ‘SCD plus’ representing ‘preclinical AD’ should have following features: subjective decline in memory, rather than other domains of cognition, onset of SCD within the last 5 years, age at onset of SCD ≥60 years old, concerns (worries) associated with SCD, feeling of worse performance than others of the same age group, confirmation of cognitive decline by an informant, presence of the APOE ε4 genotype, and biomarker evidence for AD.5 We previously investigated the most relevant predictors of progression in SCD and combined the predictors with a new modeling scale in order to predict progression based on a nationwide longitudinal cohort data, named Clinical Research Centers for Dementia of South Korea (CREDOS).24 In the study, old age over 60 years, APOE4 carrier, lower Korean version of Mini-Mental State Examination (K-MMSE) recall score below 2, and lower verbal delayed memory score below 50th percentile compared to age-, sex-, and education-specific norms were the most relevant predictors of clinical progression of SCD.24 SCD with more predictors revealed more progression to MCI or AD dementia (HR=5.351, p=0.008).24

Recently, studies using AD-related pathologic biomarkers such as amyloid PET or CSF Aβ1-42/tau levels have been conducted to clarify the most relevant predictors and refine the relationship between subjective complaint and possibilities of preclinical AD.

**ASSESSMENT OF SUBJECTIVE COMPLAINTS**

Cognitive decline is a common manifestation in healthy older adults and has been reported to be approximately up to 50% of the community-dwelling elderly people.25,26 Considering the diversity of the complaints, various personality traits, and the statistical possibilities of type I error of false positivity, clarifying and quantifying the first-person experience might have some limitations in scientific studies. First, the internal experience of cognitive decline is characteristically complex in their phenomenology and difficult to assess quantitatively.27 Second, self-report measures are largely affected by the subject’s factors such as demographics, educational attainment, personality, and mood disorders. Third, too many questions to assess the cognitive complaints might result in type I error rather than true differences.

Assessment of subjective complaint might be divided into two aspects; categorization of the phenomenology and quantification of the complaint. The categorization is needed to define high-risk group with AD-related pathologies. Presenting symptoms, symptoms duration, concerns (worries) associated with cognitive decline, feeling of worse performance than others of the same age group, confirmation of cognitive decline by an informant can be assessed and used for the categorization. The latter, quantification of the complaint, represents the severity of cognitive complaint and can be used to measure the relationship between complaint and biomarker evidence such as neurodegenerative change and AD-related pathologic burden. Rabin and colleagues systemically overviewed the 34 self-report measures currently used in subjects with SCD and refined variability and consistency in the tools.28 Almost all self-report measures were administered in paper-and-pencil format and mainly targeted memory function, followed by executive function.28 Questions about memory function were mostly specific, rather than general, such as items related to memory for the names of people or remembering placement of common objects.28 They demonstrated wide variations in the format, range, time frame, and response options among the measures and the meaning of the complaints might vary according to demographic factors such as educational level and age.25 Thus, in regards of measuring cognitive complaints, careful approaches to the subjects with SCD using a homogeneous measurement tool with a larger sample size that allows a wider range of demographic factors would be needed for future studies.

**SCD IN THE ASPECT OF AMYLOID AND TAU BIOMARKERS**

Biomarker studies are promising methods for early identification of preclinical AD in SCD subjects, in particular, markers of amyloid and tau accumulation hold promise. However, in contrast to accruing evidence on AD-related biomarkers in subjects with MCI or AD dementia, biomarker use for SCD has not been sufficient yet.

We conducted a literature search using PubMed to over-
view previously reported biomarker studies using amyloid and tau PET scans or CSF amyloid beta/tau levels in subjects with SCD. We only retrieved English written articles before August 2016. The search terms included ‘biomarker’, ‘amyloid’, ‘amyloid-beta’, ‘tau’ combined with ‘SCD’, ‘subjective memory impairment’, ‘subjective cognitive impairment’, ‘subjective memory failure’, and ‘subjective memory complaint’. Studies that have not shown biomarker results such as amyloid/tau PET or CSF amyloid beta/tau levels were excluded from the review. In total, 28 studies were included in the main review. We divided the selected studies into three categories; 1) cross-sectional studies using amyloid or tau PET imaging (Table 1), 2) cross-sectional studies using CSF biomarkers (Table 2), and 3) longitudinal studies using PET or CSF biomarkers (Table 3). In summary of the included studies, AD-related biomarker positivity tended to be related with subjective cognitive complaints, however, there was little evidence that AD-related biomarker can differentiate SCD from healthy older adults. Among them, only a few longitudinal follow-up studies investigated the association among subjective complaints, AD-related biomarkers, and cognitive decline or clinical progression to AD dementia. Moreover, previous longitudinal studies using AD-related biomarkers have limitations in that the follow-up durations were relative-

Table 1. A summary of cross sectional studies using amyloid/tau PET scans

| Author (year)          | Sample size | Mean age | Biomarkers          | Results                                                                 |
|-----------------------|-------------|----------|---------------------|-------------------------------------------------------------------------|
| Rodda et al. (2010)   | SCD: 5      | SCD: 64.2| 11C-PIB PET         | There were no significant differences between the SCD and controls in terms of PIB uptake ratio in any regions or on whole brain analysis. |
|                       | NC: 14      | NC: 63.93|                     |                                                                         |
| Amariglio et al. (2012) | CN: 131    | 73.5±6.6 | 11C-PIB PET         | Relationship between PIB retention and memory-related subjective complaint was found to be significant in older CN adults.          |
|                       |             |          |                     |                                                                         |
| Perrotin et al. (2012) | CN: 48     | 73.5±5.9 | 11C-PIB PET         | Significant positive correlations were noted between the PIB uptake of right medial anterior and posterior cortex and subjective cognition. |
|                       |             |          |                     |                                                                         |
| Amariglio et al. (2015) | CN: 257   | 73.7     | 11C-PIB PET         | CN subjects with positive on amyloid PET or neurodegenerations had more subjective complaints compared to biomarker-negative subjects. |
|                       |             |          |                     |                                                                         |
| Ivanoiu et al. (2015) | SCD: 21    | NC: 70.0 | 18F-flutemetamol PET | The SCD group was not different from controls but significantly different from the MCI patients in the point of amyloid biomarkers. |
|                       | NC: 31      | SCD+MCI: 70.8 |                     |                                                                         |
|                       | MCI: 39     |          |                     |                                                                         |
| Risacher et al. (2015) | SMC: 104   | SMC e4+: 72.5 | 18F-florbetapir PET | SMC APOE e4+ showed greater amyloid deposition than SMC APOE e4-, but no hypometabolism or medial temporal atrophy. SMC e4+ showed lower Aβ42 and higher tau/p-tau than SMC e4+, which was most abnormal in e4+ and cerebral amyloid positive SMC. |
|                       |             | SMC e4+: 70.3 |                     |                                                                         |
| Smitz et al. (2015)   | SCD: 14     | SCD: 68.1| 11C-PIB PET         | SCD participants presenting to a memory clinic had significantly higher PIB retention than CN in three of six regions of interest. |
|                       | CN: 84      | CN: 73.6 |                     |                                                                         |
| Smitz et al. (2015)   | CN: 92      | 81.2±8.4 | 11C-PIB PET         | Significant association between subjective cognition and brain amyloid-β deposition in healthy older adults was shown but measure-specific. |
|                       |             |          |                     |                                                                         |
| Zwan et al. (2016)    | CN: 307     | 72.7±6.8 | 11C-PIB PET         | Risk of high Aβ were greater when SMC were present (odds ratio=1.90) and the odds of SMC for high Aβ burden were increased in APOE4 carriers. |
|                       |             |          |                     |                                                                         |
| Merrill et al. (2016) | SMI: 24     | 62.6±10.7| FDDNP-PET           | Lower FDDNP-PET binding (amyloid plaque/tangle) was present in SMI adhering “often” to a healthy diet when compared with those “rarely” adhering to a healthy diet, while FDDNP-PET bindings were not different according to physical activities or BMI values in SMI. |
|                       | MCI: 20     |          |                     |                                                                         |

APOE: apolipoprotein E, BMI: body mass index, CN: cognitively normal, FDDNP: 2-(1-[6-(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malononitrile, MCI: mild cognitive impairment, NC: normal controls without cognitive complaint, PET: positron emission tomography, PIB: Pittsburgh compound B, SCD: subjective cognitive decline, SMC: subjective memory complaints, SMI: subjective memory impairment.
ly short ( ranged from 18 to 54 months) considering that preclinical AD progresses very slowly and two of them included all predementia subjects as well as MCI patients. Overall, longitudinal biomarker studies suggested that low Aβ42/ high tau levels might be the strongest predictor of clinical progression or cognitive decline. SCD subjects with preclinical AD pathologies either by amyloid PET or by CSF revealed clinical progression or cognitive decline, although one study did not show any significant cognitive decline in follow-up evaluations. Which is a more relevant predictor between amyloid or tau pathology has yet to be determined. Some stated that elevated tau levels in CSF would be more important to predict cognitive decline, because CSF Aβ42 is a very early marker, whereas tau elevation appears to be a marker closer to the actual functional impairment. On the other hand, others concluded that CSF amyloid level is the most relevant predictor in the elderly with normal cognition. This should be clarified in the future studies because there has been no prospective long-term follow-up study determining whether baseline amyloid or tau pathology in SCD can predict progression to AD dementia. Our summary of the previous studies regarding biomarker results in SCD is partially consistent with previous reviews. The conflicting results might be explained in several ways. First, SCD represents a heterogeneous group. While some may be in the early stage of AD and their cognitive complaints are attributable to un-

| Author (year) | Sample size | Mean age | Biomarkers | Results |
|---------------|-------------|----------|------------|---------|
| Mosconi et al. (2008) | SMC: 13, NC: 15 | 45–70 | T-tau, t-tau, Aβ42, Aβ40, F2-isoprostane using sandwich ELISA | Cognitively normal APOE ε4 carriers with SMC show altered AD-related CSF biomarkers (isoprostane, tau, and p-tau/Aβ42 ratio) and FDG-PET measures. |
| Grampaite et al. (2010) | SCD: 9, MCI: 36 | 61.1±7.9 | T-tau using ELISA | The SCD/MCI with increased t-tau showed more hippocampal atrophy and memory impairment than the normal t-tau group. |
| Antennell et al. (2011) | SMC: 19, NC: 24 | SMC: 68.3±8.4, NC: 61.2±14.1 | Aβ42, t-tau, p-tau using ELISA | There were no significant differences in the three CSF biomarkers between NC and SMC. SMC with pathologic CSF progressed to AD in the 1 year follow-up. |
| Rolstad et al. (2011) | SCD: 105, NC: 60 | SCD: 61.4, NC: 65.9 | T-tau and Aβ42 using sandwich ELISA | In NC and SCD, CSF Aβ42 predicted a significant proportion of semantic and working memory performance. |
| Stenset et al. (2011) | SCD: 8, MCI: 39, NC: 26 | SCD: 61.4±7.9 | T-tau using ELISA | SCD/MCI with pathologic t-tau levels had significantly lower FA and higher DR values using MRI diffusion tensor imaging analysis. |
| Grampaite et al. (2013) | SCD: 23, MCI: 47 | SCD: 58.8, MCI: 63.1 | Aβ42, t-tau, p-tau using ELISA | Cognitive performance was associated with CSF Aβ42 and p-tau in SCD subjects. |
| Risacher et al. (2015) | SMC: 104, Old adults (ε4-: 72.5, ε4+ 70.3) | CSF Aβ1-42, t-tau, p-tau using Luminex platform | SMC APOE ε4+ showed greater amyloid deposition than SMC APOE ε4-, but no hypometabolism or medial temporal atrophy. |
| Toledo et al. (2015) | SMC: 106, NC: 307 | SMC: 71.6±5.2, NC: 73.9±5.5 | CSF Aβ1-42, t-tau, p-tau using Luminex platform | SMC group showed lower CSF Aβ1-42 and higher p-tau181 levels than NC group. |
| Valech et al. (2015) | NC: 78 | Control: 64.8, Preclinical AD: 69 | Aβ1-42, t-tau, p-tau using ELISA | Subjective cognitive complaints were higher in the preclinical AD group than control group. |
| Mandecka et al. (2016) | SCD: 85, MCI: 87, AD: 80 | SCD: Old adults (<50), MCI: mean: 61.28, AD: | CSF Aβ1-42, t-tau, p-tau using ELISA | Verbal memory scores were associated with the levels of AD biomarkers in the whole sample. MCI group showed lower levels of Aβ and higher levels of tau than SCD group. |

AD: Alzheimer’s disease, APOE: apolipoprotein E, CSF: cerebrospinal fluid, DR: radial diffusivity, ELISA: enzyme-linked immunosorbent assay, FA: fractional anisotropy, FDG-PET: fludeoxyglucose positron emission tomography, MCI: mild cognitive impairment, NC: normal controls without cognitive complaint, SCD: subjective cognitive decline, SMC: subjective memory complaint.
derlying AD-related changes, others may not be non-AD conditions. Second, categorizing high versus low amyloid uptake is not always the same. Third, there are scanty of tau PET imaging studies, thus the status of tau deposition in SCD could not be clarified yet. Lastly, CSF biomarker results can be affected by analytical and preanalytical factors among the laboratories, resulting in different biomarker values due to inter-assay and inter-laboratory variation.

**FUTURE DIRECTIONS OF STUDIES ON SCD**

In spite of the conflicting results of previous studies, individuals of preclinical stage with AD-related pathologies would go through an initial full compensation stage followed by very first decline, thus SCD might serve as the first symptomatic indicator of preclinical AD. However, SCD is not identical with preclinical AD. Preclinical AD is a diagnosis based on the biomarker evaluations and does not require the existence of subjective complaints by definition. Given that SCD is a heterogeneous condition mixed with preclinical AD and non-AD related conditions, determination of SCD individuals with a high risk of progression, so called preclinical AD, would be important. In light of normal cognitive performance and the worried well of SCD population, subjective complaints in elderly SCD may potentially provide valuable information.
for early diagnosis of AD spectrum disorders and proper management plan of the disease. To enhance knowledge about specific features of SCD related with preclinical AD, the establishment of universal criteria, assessment tools, and diagnostic guidelines, combined with a biomarker use and longitudinal study design would be warranted. Appropriate selection of SCD with preclinical AD would be useful and practical in preventive clinical trials by enriching the target populations. For the adequate identification, detailed history taking, measuring the severity of cognitive complaints, and characterization of the complaints should be put into practice before going into further biomarker evaluations in the clinical setting.

CONCLUSION

We have reviewed the previous studies, the new proposed research criteria, and the characteristics of SCD in the aspect of preclinical AD. Recent study results using AD-related biomarkers have also been covered. Future researches on SCD require a prospective long-term follow-up with adequate biomarker studies and proper outcome measures to predict and determine the risk of progression in this help-seeking but underestimated group.

Conflicts of Interest

The authors have no financial conflicts of interest.

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