Neurological Sciences (2019) 40:41–49
https://doi.org/10.1007/s10072-018-3620-y

REVIEW ARTICLE

Subjective cognitive decline: preclinical manifestation of Alzheimer's disease

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Received: 13 May 2018 / Accepted: 24 October 2018 / Published online: 5 November 2018

Abstract

Subjective cognitive decline (SCD), characterized by a very early and subtle cognitive decline prior to the appearance of objective cognitive impairment, is considered to be the preclinical manifestation of Alzheimer's disease (AD). Given the lack of significant abnormalities in standardized neuropsychological assessments for individuals with SCD, biochemical and neuroimaging biomarkers may be important indicators of the preclinical stage of AD. The application of various biomarkers derived from the cerebrospinal fluid and neuroimaging thus has the potential to make AD-related pathology detectable in vivo. In this review, we discuss the conceptual evolution of SCD as an entity and further elucidate characteristic cerebrospinal fluid and neuroimaging biomarkers of SCD.

Keywords Subjective cognitive decline · Alzheimer's disease · Preclinical · Biomarkers · Neuroimaging

Introduction

Subjective cognitive decline (SCD), a state in which self-perception begins to decline prior to the appearance of objective cognitive impairment, is considered as being a very early clinical syndrome of Alzheimer's disease (AD) [1]. The concept of SCD was first proposed by Reisberg et al. in 1982 [2], who suggested that cognitive impairment can be subdivided into seven clinically identifiable and ratable stages. Of these stages, "stage 2" was defined as a very mild cognitive decline in which individuals complain of memory deficits without objective clinical evidence. This preclinical manifestation of AD has been studied for decades based on different inclusion criteria. In 2012, the Subjective Cognitive Decline Initiative (SCD-I) working group proposed a unified conceptual framework for SCD and officially named it by 2014 [1, 3]. SCD is defined as a patient's subjective feeling of sustained cognitive decline compared to the normal state, without abnormalities on objective neuropsychological assessments.

SCD has been prospectively linked to underlying AD pathology, and it is thought to be likely to accelerate memory decline [4, 5]. One recent study has shown that SCD is associated with a 4.5-fold increase in the risk of a subsequent MCI diagnosis and a 6.5-fold increase in the risk of an eventual AD diagnosis [6–8]. SCD has also been associated with depression and anxiety, the levels of which are also correlated with annual rates of cognitive decline [9–11]. Mendonca et al. [12] performed a systematic review of community-based studies, concluding that SCD associated with worried complaints has the highest risk of progression to dementia. Given that individuals with SCD are at high risk for MCI and AD, focusing on the state of SCD may provide a crucial opportunity for postponing and even preventing the progression of this disease. Therefore, we performed a comprehensive literature review of SCD using the PubMed database as a resource. Inclusion criteria were as follows: (1) the study must be a controlled trial, (2) study participants must be older than 50 years of age, (3) the study must be published in English in an academic book or peer-reviewed journal, and (4)

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subjects must have a primary diagnosis of SCD or a conceptually equivalent diagnosis. Exclusion criteria were as follows: (1) less than 10 SCD patients, (2) insufficient data, and (3) indirect assessment measures.

Conceptual evolution

AD, characterized by episodic memory loss, impaired orientation, behavioral abnormalities, loss of motivation, and depression, is the most common form of neurodegenerative disease leading to dementia among the elderly population. Early detection and intervention have become increasingly essential to alleviate the burdens of suffering imposed upon patients and society at large by this serious disease. In 1982, Reisberg et al. [2] proposed that cognitive impairment can be divided into seven clinical stages based on clinical characteristics and psychometric concomitants of patients with AD. From stage 1 to stage 7, symptoms increase gradually in severity. Among these stages, stage 2 refers to a very mild cognitive decline in which patients complain of memory deficits, forgetting the names of familiar objects or people they formerly knew well. However, these patients present without objective cognitive impairment, and this stage was thus initially described as SCD. The concept of SCD has been described using various terms, including subjective cognitive impairment (SCI), subjective memory impairment (SMI), subjective memory decline (SMD), and subjective memory complaints (SMC). In 2011, the National Institute on Aging-Alzheimer's Association (NIA-AA) group proposed a similar framework, suggesting that AD can be subdivided into three clinical stages, with the first stage presenting as preclinical AD in which patients have AD-related pathology but exhibit normal performance on standard cognitive tests [13, 14]. Despite these numerous classifications and subdivisions, a unified definition of SCD remains poorly defined. In 2012, SCD-I working group was organized, with the end goal of generating consistency in the SCD framework. It operated until 2014, when Jessen et al. [1] proposed the name of SCD for use in the assessment of preclinical AD. SCD refers to self-reported cognitive decline that is easily affected by emotional factors such as anxiety, depression, and other personality traits. In 2017, Eckerstrom et al. [15] reported that in a memory clinic setting, compared to SCD plus and NIA-AA stage 1 or 3, NIA-AA stage 2 may be the most successful category for predicting objective cognitive decline, dementia, and AD dementia. SCD research provides valuable information for the early prediction and diagnosis of AD, and this newly canonized common framework will serve to enhance research reproducibility and reliability.

Neuropsychological assessments

In recent years, an increasing number of studies have suggested that psychological factors are correlated with SCD. For example, the intensity of depressive symptomatology, the number of complaints pertaining to the activities of daily living, and the neurotic personality trait were all consistently found to be associated with SCD [12, 16, 17]. Neuropsychological assessments including neuropsychological tests and questionnaires or self-reports are widely used for the clinical diagnosis of MCI and AD. Nevertheless, SCD is largely defined based on self-reports due to the lack of objective cognitive impairment, underscoring the fact that it is difficult to detect SCD using conventional standardized neuropsychological assessments. To solve this problem, more targeted diagnostic self-rated questionnaires and tests have been produced. Gifford et al. [18] adopted the Subjective Cognitive Decline Questionnaire (SCD-Q), which can distinguish SCD from normal cognition from both patients and informant perspectives, allowing for reliable differentiation between subjective and objective cognitive impairments. Similarly, the Memory Complaint Questionnaire (MAC-Q) and Perception Questionnaire—Revised (IPQ-R) are also important questionnaires for testing for SCD [19, 20]. Results from the MAC-Q indicate that the most common cognitive impairment is episodic memory, followed by executive function [21]. Although questionnaires can screen out SCD patients, highly reliable and internally valid scales are required. Hao et al. [22] studied the correlation between the SCD-Questionnaire 9 (SCD-Q9) and the Auditory Verbal Learning Test-Long Delay Free Recall (AVLT-LR) in 2689 elderly residents and found that AVLT-LR had better predictive validity and that scores from the SCD-Q9 were negatively correlated with those of the AVLT-LR. Everyday Cognition scales (ECog) are clinical tools for testing individuals with SCD, and the development and validation of the shortened ECog-12 are more strongly correlated with relevant metrics [23, 24]. Recently, Sanabria et al. [25] produced the Face-Name Associative Memory Exam (FNAME), a paired associative memory test created to detect memory deficits in individuals with SCD. Declining FNAME scores were associated with increased Aβ burden, and this test is thus a promising neuropsychological tool for detecting SCD in individuals with preclinical AD. At present, there is a dearth of standardized neuropsychological tests for Chinese individuals, and further research is needed to improve the reliable diagnosis of early AD in preclinical stages for individuals of all backgrounds.

Biochemical biomarkers

NINCDS-ADRDA [26] first proposed the criteria for AD, and the International Working Group (IWG) [27] initially introduced biomarkers into the framework of AD diagnosis,

transforming what was previously a clinical pathological diagnosis into a biological diagnosis. Distinctive and reliable AD biomarkers are divided into two types: fluid biomarkers (including cerebrospinal fluid (CSF) biomarkers and blood-based biomarkers) and neuroimaging biomarkers. Many CSF biomarkers, including amyloid-β42 (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau), have been confirmed as being accurate predictors of AD progression [28]. Medial temporal lobe atrophy, in particular hippocampal atrophy, is considered to be the most prominent MRI marker indicating the transition from MCI to AD. According to a study by Manning et al. [29], the level and speed of cortical atrophy is correlated with the severity of cognitive impairment in AD patients. It is increasingly acknowledged that these above-mentioned biomarkers are present in individuals with SCD and are similar to those confirmed in patients with MCI and AD.

Fluid biomarkers

Cerebrospinal fluid biomarkers

Numerous studies have detected decreased concentrations of Aβ42 and increased levels of total and phosphorylated tau in the CSF of patients with AD. As a means of predicting the transition from MCI to AD, t-tau and p-tau protein levels are the most accurate indicators, and the combination of these CSF biomarkers is the most reliable approach in AD patients, whereas in SCD patients the results of this approach are mixed. Some studies have concluded that there are no significant differences between individuals with SCD and healthy older adults [30–32]. Similarly, Antonell et al. [32] and Rami et al. [33] have suggested that the levels of t-tau or p-tau are comparable between these two groups. In contrast to these findings, however, some studies have indicated that there are detectable differences in CSF biomarkers between those with SCD, MCI, and AD [34, 35]. Rolstad et al. [36] suggested that Aβ42 was the best biomarker for predicting the clinical progression of AD, being more reliably predictive than the above-mentioned combination of biomarkers. Schoonenboom et al. [37] similarly reported that individuals with SCD have significantly higher levels of Aβ42 relative to those with AD. Fortea et al. [38] found that levels of Aβ42 were correlated with semantic memory test performance and were linked to early cognitive changes in SCD groups. In summary, although amyloid and tau markers have not yet been able to effectively distinguish between those with SCD and normally aging individuals, recent studies suggest that there are detectable differences in CSF biomarkers between these groups. Indeed, those with SCD exhibit a greater pathologic biomarker burden than do control subjects without SCD, and those who have SMIs are found to have lower average Aβ42 levels in the CSF at follow-up points years later. Aβ42 is the best means of determining where an individual lies on the spectrum from healthy aging to AD dementia, with t-tau and/or p-tau being the second best predictive marker. SCD patients with detectable biological markers are more likely to experience cognitive impairment during the course of disease progression.

Blood-based biomarkers

SCD, given that it is considered to be an early stage of AD, should present with the same or similar blood-based biomarkers as does AD. Recently, evidence has suggested that the apolipoprotein ε4 allele (ApoE ε4) genotype is a well-established genetic risk factor for AD and SCD [39, 40]. Carriers of the ApoE ε4 allele have worse episodic memory and smaller right hippocampal volumes than control subjects without this allele [41]. Amyloid imaging studies have found that ApoE ε4 carriers have a greater amyloid burden than do non-carriers [42], suggesting a potential correlation between ApoE and AD-related pathology. Rowe et al. [43] found that SMCs are related to elevated PiB binding in ApoE ε4 carriers. Similarly, Chetelat et al. [44] found that in individuals with SMCs, PiB retention significantly increased with ApoE ε4 allele copy number. The cognitive effects of ApoE ε4 differ between populations. A meta-analysis performed by Wang et al. [45] suggested that populations in Northern Europe, Australia, and the USA had higher ApoE ε4 carrier rates on average than those in Asia, Middle Europe, and Southern Europe. Notably, several studies have found that a range of other biomarkers may also relate to SCD. For example, Verdile et al. [46] found that luteinizing hormone was associated with plasma $A\beta_{1-40}$ and $A\beta_{1-42}$, and that follicle-stimulating hormone was correlated with $A\beta_{1-40}$. In previous studies, blood-based biomarkers associated with AD were also associated with SCD, although further validation of these associations is necessary. The identification of blood-based biomarkers of SCD will play an important role in the early detection and prevention of AD.

Neuroimaging biomarkers

Structural MRI

Structural MRIs reflect changes in brain morphology primarily by measuring cortical volume. According to a study by Meiberth et al. [47], cortical thickness reduction appears in the bilateral entorhinal cortex and the parahippocampal cortex of patients with SCD. In a cross-sectional and longitudinal study, Dore et al. [48] found that the degree of temporal and frontal lobe atrophy was related to patients' primary cognitive

complaints. Perrotin et al. [49] analyzed the gray matter volumes of 17 patients with AD, 21 patients with SCD, and 40 healthy controls, and they found that the cornu ammonis 1 (CA1) region exhibited atrophy in both SCD and AD patients. Moreover, Cherbuin et al. [50] found that SCD was associated with longitudinal hippocampal atrophy that tends to worsen over time upon follow-up. Taken together, these results coupled with the further development of relevant research, structural MRI is expected to be an effective tool for aiding in diagnosing SCD.

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is an MR-based technique for tracking changes in the white matter fiber, which indirectly reflect tissue microstructures. DTI has been suggested as a potential biomarker of disease progression in SCD. Selnes et al. [51] have shown that DTI is better as a predictor of cognitive decline and medial temporal lobe atrophy in those with SCD and MCI than are CSF biomarkers. Compared to control group, the radial diffusivity (DR) and mean diffusivity (MD) show extensive changes in SCD patients. Shu et al. [52] used DTI and graph theory approaches to investigate the topological alterations of the brain structural connectome in SCD and control groups, and they found that the SCD group exhibited disrupted topologic efficiency in the brain's structural connectome. Lamar et al. [53] found that a greater leukoaraiosis load may contribute to poorer learning in SCD patients. In addition, Ryu et al. [54] analyzed gray matter volume and measured DTI values such as DR, MD, and fractional anisotropy (FA) in the hippocampal and entorhinal regions in SCD and control groups, and they ultimately concluded that in SCD patients the entorhinal region exhibited both macrostructural and microstructural changes, while the hippocampus only exhibited microstructural changes. DTI changes are considered to be independent of regional brain atrophy.

Functional neuroimaging

Functional MRI (fMRI) is an increasingly popular neuroimaging technique that provides a promising opportunity to non-invasively investigate intrinsic brain functional characteristics in those with SCD [55]. Numerous studies have demonstrated that there are several resting-state network systems in the brain, and patients with SCD have shown decreased activity in the default mode network as assessed by fMRI, especially in the right hippocampal area [56, 57]. This suggests that neurodegenerative alterations have already begun to occur by the SCD stage of disease, and that resting-state fMRI can identify these changes. Using resting-state fMRI and structural MRI, Sun et al. [58] investigated the amplitude of low-frequency fluctuations (ALFF) and regional gray matter volume in patients with SCD, finding that resting-state fMRI is a sensitive imaging technique for SCD diagnosis. Similarly, Contreras et al. [59] used resting-state fMRI to assess changes in brain functional connectivity (FC) and found that patterns of FC were differently associated with neurocognitive variables thought to change early in the course of AD. Hu et al. [60] recruited 20 participants with SCD and 24 control participants who took part in an fMRI task on intertemporal decisions, and they found that individuals with SCD exhibit myopic future-oriented decisions and an absence of modulation by episodic future imagination.

Fluoro-2-deoxyglucose (FDG)-position emission tomography (PET) is another sensitive method that can be used to detect SCD, and it further has great value as a means of predicting AD and MCI. Scheef et al. [31] found that compared with healthy controls, SCD patients exhibit hypometabolism in the right precuneus lobe and left parietal lobe, whereas they present with hypermetabolism in the right medial temporal lobe. Functional thus neuroimaging provides a readily available means of capturing brain alterations, and as such, this approach may complement and supplement the absence of other neuropsychological tests and CSF biomarkers available for SCD diagnosis.

Amyloid-PET

Amyloid PET is a potential imaging technique that has the potential to offer more meaningful insights into the abnormal neuropathological lesions associated with AD. Many studies have confirmed that the observed increase in Aβ deposition is related to the decline of subjective executive function in patients with SCD. Snitz et al. [61] used PiB-PET to detect Aβ deposition in 14 patients with SCD and 84 normal elderly controls, and they found that the amount of Aβ deposition in the brain of SCD patients was increased relative to that of the control participants. It has also been suggested that the progression of cognitive impairment may be related to the amount of Aβ deposition in the brain. Combining FTP-PET (the specific anatomy of tau deposition revealed with flortaucipir F 18 PET) and PiB-PET, Buckley et al. [62] found that SCD is indicative of the accumulation of early tauopathy in the medial temporal lobe, specifically in the entorhinal cortex.

A summary of current putative biomarkers for SCD is listed in Table 1.

Table 1 Summary of biomarkers for SCD

Biomarkers	Authors	Year	Subjects	Parameters/measures	Features
Cerebrospinal fluid					
	Visser et al. [30]	2009	79 controls 60 SCD 71 MCI	Ratio of Aβ(42): tau	The CSF AD profile was predictive of AD-type dementia.
	Antonell et al. [32]	2010	19 SCD 24 controls	Aβ(42), total-tau, and phosphorylated tau (181)	There are different CSF profiles in AD: normal, only pathologic Aβ(42), pathologic Aβ(42) plus pathologic total-tau, and/or phosphorylated--tau(181), and only pathologic total-tau and phosphorylated-tau (181).
	Rami et al. [33]	2011	19 controls 17 SCD 47 MCI 18 AD	Aβ42/t-tau/p-tau,	Memory performance is first related with Aβ42 levels and then with t-tau or p-tau.
	Rolstad et al. [36]	2011	105 SCD 60 controls	Aβ42/t-tau	Aβ42 is associated with cognitive functions from a potentially early to a later disease phase, and t-tau is more indicative of performance in a later disease phase.
	Wolfsgruber et al. [35]	2015	245 participants	Aβ42/t-tau/p-tau	Abnormal CSF β-amyloid 1–42 (Aβ42) and more depressive symptoms were associated with higher Subjective Memory Decline Scale (SMDS) and with the report of memory concerns.
Blood-based markers					
	Verdile et al. [46]	2014	151 controls 150 SCD 50 MCI 76 AD	APOE-e4 allele	In SCD, frequency of the APOE-e4 allele increased.
Structural MRI					
	Scheef et al. [31]	2012	31 SCD 56 controls	Gray matter volume	Gray matter volume was reduced in the right hippocampus.
	Meiberth et al. [47]	2015	41 SCD 69 controls	Structural 3D-T1 MR imaging	Cortical thickness reduction was observed in the subjective memory impairment (SMI) group compared to controls in the left entorhinal cortex.
	Perrotin et al. [49]	2015	40 controls 17 SCD 21 AD	Standard T1-weighted MRI and a dedicated high-resolution MRI proton-density hippocampal sequence.	Atrophy maps on hippocampal surface showed major involvement of the lateral part (CA1) in both SCD and AD.
	Cherbuin et al. [50]	2015	2551 SCD	Magnetic resonance imaging(MRI)	SCD at follow-up was associated with greater hippocampal atrophy. Associations were reduced but remained significant after controlling for anxiety and depression symptomatology.
DTI					
	Selnes et al. [51]	2013	15 SCD 51 MCI 28 controls	Diffusion-tensor magnetic resonance imaging	DTI and CSF biomarkers significantly predicted cognitive decline and atrophy in the medial temporal lobe.
	Shu et al. [52]	2018	51 controls 36 SCD	Diffusion-tensor magnetic resonance imaging and graph theory approaches	SCD had less global efficiency and local efficiency compared with the healthy control participants.
	Ryu et al. [54]	2017	18 SCD 27 controls	Gray matter (GM) volume / diffusion tensor imaging (DTI)	SCD had lower entorhinal cortical volumes than control participants, but no differences in hippocampal volume.

Table 1 (continued)

Biomarkers	Authors	Year	Subjects	Parameters/measures	Features
					SCD exhibited DTI changes in the hippocampal body and entorhinal white matter compared with controls.
Functional MRI					
	Rodda et al. [56]	2009	10 SCD 10 controls	Functional magnetic resonance imaging (fMRI).	SCD group demonstrated activation in left medial temporal, occipitoparietal and medial frontal cortex.
	Rodda et al. [57]	2011	11 SCD 10 controls	Functional magnetic resonance imaging (fMRI).	SCD group demonstrated increased activation in left medial temporal lobe, bilateral thalamus, posterior cingulate, and caudate
	Sun et al. [58]	2016	25 SCD 61 controls	Resting-state functional magnetic resonance imaging	SCD exhibited higher amplitude of low-frequency fluctuations (ALFF) values in the bilateral inferior parietal lobule.
	Contreras et al. [59]	2017	13 controls 16 SCD 21 MCI 8 AD	Resting-state functional magnetic resonance imaging (rsfMRI)	Specific patterns of functional connectivity (FC) were differently associated with neurocognitive variables thought to change early in the course of AD.
	Hu et al. [60]	2017	20 SCD 24 controls	Functional magnetic resonance imaging	SCD participants showed reduced future-oriented choices.
Amyloid PET					
	Snitz t et al. [61]	2015	14 SCD 84 controls	Pittsburgh compound B (PiB)-PET	SCD participants had significantly higher PiB retention (SUVR) than control groups in frontal cortex, lateral temporal cortex, and parietal cortex.
	Buckley et al. [62]	2017	133 clinically healthy participants	Amyloid PET and tau-PET	SCD is indicative of accumulation of early tauopathy in the medial temporal lobe, specifically in the entorhinal cortex, and to a lesser extent, elevated global levels of Aβ.

Conclusion and future directions

Over recent decades, many conceptual advances have been made regarding SCD, and current research is largely centered on the application of biomarkers to the diagnosis of asymptomatic AD. Although SCD extends the clinical spectrum of AD, there are still no approved treatments for early memory loss [63]. A wide range of underlying risk factors including age, low education, less social support, and daily drinking can hasten the progression of patients from a normal cognitive state to SCD, to MCI, and ultimately to AD [22]. The application of diagnostic biomarkers in SCD patients may reveal the pathological mechanisms underlying AD. Of the numerous available biomarkers that have been studied to date, neuroimaging techniques are the most promising, given their noninvasiveness, accessibility, and relatively low cost [10, 64]. Given that SCD research is still in its early stages, future larger scale multicenter and longitudinal studies are required to validate and broaden current findings and to develop patient treatment options.

Funding information This work was supported by grants from the National Science Foundation for Young Scientists of China (No. 81100972) and Science and Technology Planning Project of Shandong Province (No. 2012GSF12120).

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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