

Diagnostic Assessment & Prognosis

Longitudinal evaluation of criteria for subjective cognitive decline and preclinical Alzheimer's disease in a memory clinic sample

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Abstract

Introduction: Subjective cognitive decline (SCD) and biomarker-based “at-risk” concepts such as “preclinical” Alzheimer's disease (AD) have been developed to predict AD dementia before objective cognitive impairment is detectable. We longitudinally evaluated cognitive outcome when using these classifications.

Methods: Memory clinic patients ($n = 235$) were classified as SCD ($n = 122$): subtle cognitive decline ($n = 36$) and mild cognitive impairment ($n = 77$) and subsequently subclassified into SCDplus and National Institute on Aging–Alzheimer's Association (NIA-AA) stages 0 to 3. Mean (standard deviation) follow-up time was 48 (35) months. Proportion declining cognitively and prognostic accuracy for cognitive decline was calculated for all classifications.

Results: Among SCDplus patients, 43% to 48% declined cognitively. Among NIA-AA stage 1 to 3 patients, 50% to 100% declined cognitively. The highest positive likelihood ratios (+LRs) for subsequent cognitive decline (+LR 6.3), dementia (+LR 3.4), and AD dementia (+LR 6.5) were found for NIA-AA stage 2.

Discussion: In a memory clinic setting, NIA-AA stage 2 seems to be the most successful classification in predicting objective cognitive decline, dementia, and AD dementia.

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Keywords:

Memory clinic; Alzheimer's disease; Prediction; Neuropsychology; Dementia; Mild cognitive impairment; Clinical progression; Diagnosis; Classification

1. Introduction

The pathophysiological processes underlying Alzheimer's disease (AD) are assumed to develop many years before clinical evidence of a manifest dementia state [1]. Current research focuses on identifying characteristics of the early stages of AD, and several concepts have been developed to that end. In 2011,

the US National Institute on Aging–Alzheimer's Association (NIA-AA) group presented recommendations to identify “the preclinical stage of AD,” referring to a stage characterized by the presence of biomarker signs of AD but absence of verified cognitive impairment [2,3]. The NIA-AA stages were subdivided into stages reflecting a suggested temporal sequence of the pathway to AD: stage 0 = both amyloid and neurodegeneration markers negative; stage 1 = evidence of amyloidosis (e.g., lowered cerebrospinal fluid (CSF) amyloid β ($A\beta$)42 concentrations, neurodegeneration markers negative); stage 2 = evidence of amyloidosis and neurodegeneration (e.g., increased CSF tau concentrations); and stage 3 = biomarker

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pattern as in stage 2 but also with “subtle cognitive decline.” This model is not uniformly accepted, in part, because of the findings that place neurodegeneration temporally before amyloidosis [4–6].

Subjective cognitive decline (SCD)—self-perceived decline despite objectively unimpaired cognitive function—represents a possible presymptomatic stage of mild cognitive impairment (MCI) and AD [7]. SCD may be present, but is not required, in the NIA-AA “preclinical AD” stages. However, the target populations of these concepts are indeed overlapping. SCD has been reported 15 years before MCI [8] and mounting evidence implicates SCD as a risk factor for dementia [9–12] and AD-biomarker abnormalities [13,14].

Studies of the predictive value of subjective cognitive and/or memory symptoms have been limited because of the lack of conceptual and methodological consensus. Recently, the SCD Initiative suggested a conceptual framework for investigating SCD, including research criteria and features, which should be reported in SCD studies [15] (see [Supplementary Material](#) for these features specified for the present study). Additional features were listed under the term “SCDplus,” to further increase the likelihood of identifying preclinical AD: (1) subjective decline in memory rather than other cognitive domains; (2) onset of SCD within the last 5 years; (3) age at onset of SCD ≥ 60 years; (4) concerns (worries) associated with SCD; (5) feeling of worse performance than others of the same age group; (6) confirmation of cognitive decline by an informant; and if available (7) the presence of the apolipoprotein E (*APOE* $\epsilon 4$) genotype; and (8) biomarker evidence for AD (defines preclinical AD). Both the SCD and SCDplus criteria are described as research criteria that “require continuous refinement and validation to eventually serve as a standardized indicator for biomarker-based preclinical AD detection” [15]. Molineuvo et al. [16] recently presented recommendations on how to apply the SCD criteria.

A recent review concluded, after having summarized the current knowledge of CSF AD biomarkers in SCD, that there is emerging evidence that biomarkers differentiate between declining and stable SCD patients [17], although studies in clinical settings are scarce as are studies combining biomarkers and subjective or subtle cognitive decline [3,18]. Both the NIA-AA stages and SCD/SCDplus are recent concepts that need concurrent evaluation in longitudinal clinical samples to assess the clinical utility in predicting cognitive decline and AD-type dementia (ADD).

In this study, we examined SCD, SCDplus, SCDplusbio (i.e., SCDplus + *APOE* $\epsilon 4$ and biomarkers), NIA-AA stages 0 to 3 of preclinical AD, and MCI in patients seeking care at a memory clinic, with respect to

- (3) the individual contribution of each feature included in the classifications to predict cognitive decline and dementia.

2. Methods

2.1. Participants

All patients ($n = 235$) in the present study were included in the ongoing clinical prospective single-center Gothenburg MCI study [19] between 1999 and 2013. In the present study, inclusion criteria were age 50 to 79 years; self-reported cognitive decline with a duration of ≥ 6 months, assessed by specialist clinicians through interviews; available data at baseline with respect to CSF biomarkers, SCDplus features, and neuropsychological tests used to discriminate between SCD and MCI. Systemic and other somatic diseases possibly causing cognitive impairment, for example, subdural hemorrhage, brain tumor, hypothyroid state, encephalitis, unstable heart disease, and psychiatric disorders such as major affective disorder (not minor depressive disorder), schizophrenia, substance abuse, and confusion, were cause for exclusion. Of the 250 patients meeting inclusion criteria, 235 (94%) were followed up and were thus included in the analyses. There were no significant differences in age, Mini-Mental State Examination (MMSE) [20], or years of education between patients who were excluded ($n = 152$) because of missing data (missing data at baseline, $n = 137$; missing data at follow-up, $n = 15$) and the included patients ($n = 235$) (excluded patients' mean [SD = standard deviation] age, 63 (9); mean (SD) years of education, 13 (4); and mean (SD) MMSE, 29 (1). Included patients' mean (SD) age, 64 (8); mean (SD) years of education, 12 (4); and mean (SD) MMSE, 29 (2)). Baseline characteristics are presented in [Table 1](#). The most common reason for missing data was missing informant report. Some patients lived alone or were reluctant to ask their spouses or children to fill out a symptom questionnaire. All patients lived in the extended Gothenburg region in Sweden and sought care at the Sahlgrenska memory clinic. Patients were referred via primary health care, and a minor part was self-referrals.

Healthy controls, $n = 101$; mean (SD) age, 65 (6); mean (SD) years of education, 12 (3); and mean (SD) MMSE, 29 (1), were recruited through information meetings (in, e.g., senior organizations), and some were relatives of patients. Inclusion and exclusion criteria were identical for control subjects and patients, except control subjects had neither subjectively reported nor objective cognitive impairment, assessed by a clinician. Healthy control subjects were only included in the present study to generate cutoff values for neuropsychological test scores.

2.2. Assessments

All participants were examined at baseline and completed at least one biannual follow-up. Baseline assessments were

- (1) the proportion of cognitively stable and declining patients over time (descriptive report),
- (2) the ability of the classifications to predict cognitive decline, dementia, and ADD specifically, and

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