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Original Research Article

Subjective Cognitive Impairment Is a Predominantly Benign Condition in Memory Clinic Patients Followed for 6 Years: The Gothenburg-Oslo MCI Study

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Keywords

Subjective cognitive impairment · Subjective cognitive decline · Memory decline · $A\beta_{42}$ · Cerebrospinal fluid biomarkers · Preclinical Alzheimer disease · Preclinical dementia

Abstract

Background/Aims: In the quest for prevention or treatment, there is a need to find early markers for preclinical dementia. This study observed memory clinic patients with subjective cognitive impairment (SCI) and normal cognitive function at baseline. The primary aim was to address SCI as a potential risk factor for cognitive decline. The secondary aim was to address a potential relation between (1) baseline cerebrospinal fluid biomarkers and (2) a decline in memory performance over the first 2 years of follow-up, with a possible cognitive decline after 6 years. ***Methods:*** Eighty-one patients (mean age 61 years) were recruited from university memory clinics and followed up for 6 years. ***Results:*** Eighty-six percent of the cohort remained cognitively stable or improved, 9% developed mild cognitive impairment, and only 5% (n = 4) developed dementia. Regression analysis revealed that low levels of $A\beta_{42}$ at baseline and memory decline during the first 2 years predicted dementia. When combined, these variables were associated with a 50% risk of developing dementia. ***Conclusions:*** Cognitive stability for 86% of the cohort suggests that SCI is predominantly a benign condition with regard to neuropathology. The low number of individuals who developed dementia limits the generalizability of the results and discussion of progression factors.

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Introduction

Interventions to prevent or modify Alzheimer disease (AD), cerebrovascular disease processes, and other forms of cognitive disorders and dementia [1, 2] are thought to be most effective very early in the disease process. Consequently, there is a need to find early markers for preclinical dementia among otherwise cognitively normal persons. The model by Jack et al. [3] suggests that AD begins with amyloid β (Aβ) deposition in the cortex, leading to a synaptic dysfunction, neurodegeneration, and finally to detectable cognitive changes and functional decline in activities of daily life associated with early dementia. It is assumed that the process from a detectable Aβ pathology until the development of dementia may take 10–15 years [4]. In the context of searching for early markers for preclinical dementia, patients with subjective cognitive impairment (SCI) are of special interest as SCI may be an early trigger for cognitive decline help-seeking.

Some studies have identified cognitively well-functioning persons at risk of future decline. Villemagne et al. [5] found that cognitively normal persons with a high Aβ deposition in the brain were more likely to develop mild cognitive impairment (MCI) after 3 years compared to those with normal Aβ levels in the brain. The same research group also found that the interaction of Aβ and genetic factors had an influence on progression rates [6]. SCI had no association with amyloid-related objective cognitive decline [7].

Based on the Alzheimer's Disease Neuroimaging Initiative (ADNI) data, a study [8] analyzed which cognitively healthy older individuals remained cognitively stable and which individuals developed MCI after 4 years. Significantly, poorer baseline composite cognitive function (ADAS-cog) [9] and verbal memory (RAVLT) [10] were found in those who declined over 4 years compared to those who remained stable. Associations were also found between hippocampal and entorhinal volume as well as posterior cingulate metabolism and whether the cognitively healthy individual suffered cognitive decline within 48 months or remained stable. These findings suggest that those who suffer from cognitive decline may express subtle biological differences compared to stable individuals up to 4 years prior to the neuropsychological indication of decline. Other studies of cognitively normal elderly have shown that subjective cognitive decline (SCD) may be associated with subtle AD-like features on MRI [11], altered AD biomarkers in cerebrospinal fluid (CSF) [12], and increased risk of progression to MCI and AD [13].

Recently, we have addressed the potential relation between CSF biomarkers and reduced cognitive function over 2 years in memory clinic patients with only SCI at baseline [14]. None of the patients developed dementia in the study period. The main finding was that patients with objective memory decline during the study period had significantly higher levels of total tau (T-tau) at baseline than the group with improved memory. Other baseline CSF variables ($A\beta_{42}$, phosphorylated tau [P-tau], and T-tau/$A\beta_{42}$ ratio) showed a trend towards more pathological values in the patients with memory decline compared to those who improved or remained stable. Additionally, and in contrast to the ADNI study [8], the baseline memory score of those who declined was significantly better than the baseline score of those who improved over 2 years. Thus, a memory cutoff indicating low baseline memory would not have identified the declining group.

It is a considerable challenge to identify relatively young elderly persons at risk for dementia before they develop MCI. Bassett and Folstein [15] found that as many as 43% of those aged between 65 and 74 years report subjective memory problems, while the prevalence of dementia in this age range is low with less than 2.5% [16]. Furthermore, due to normal variation, the frequency of below-normal test scores is, by definition, high even in healthy persons [17]. In addition, it is well known that persons with brain disease may achieve normal neuropsychological results [18]. Thus, because SCI is an unspecific phenomenon that

may either be normal or related to a range of neurologic and psychiatric conditions, specific criteria have been proposed by the Subjective Cognitive Decline Initiative (SCD-I) to identify a subgroup with SCD at risk for dementia [13].

SCI is common in the general population [15] and more likely associated with stress/depressive symptoms than risk factors for AD [15, 19, 20]. However, some studies find that cognitively normal persons with SCI have an increased risk for developing dementia [21–24] compared to persons without SCI. Based on the theory that detectable amyloid changes may occur many years before the development of cognitive symptoms [3, 4], a natural assumption is that the CSF biomarker status may serve to identify cognitively normal individuals at risk of developing dementia. Our previous findings [14] also suggest that objective cognitive decline from baseline in persons with only SCI may be a predictor of further cognitive decline as well as possible MCI and dementia.

In the present study, we observed memory clinic patients with SCI and normal cognitive function at baseline and followed them up for 6 years. In addition to observing the cohort over 6 years, we aimed to address the potential relation between (1) baseline CSF biomarkers and (2) a decline in memory performance over the first 2 years of follow-up with further cognitive decline and development of dementia after 6 years.

We hypothesized the following:

1. The majority of the patients would remain cognitively stable.
2. Low $A\beta_{42}$ at baseline would be the most powerful predictor of dementia development. Furthermore, other baseline CFS biomarkers would also be more pathological in patients who developed dementia after 6 years.
3. Patients with memory decline during the first 2 years of observation would be at a higher risk of both further cognitive decline and development of dementia after 6 years.

Methods and Materials

The Norwegian part of the project was approved by the South-Eastern Norway committee for medical research ethics. The Swedish part of the study was approved by the local ethics committee. At both sites, the research was conducted according to the Helsinki declaration.

Participants in the present study were recruited from the Gothenburg-Oslo MCI Study (GO-MCI), which is a collaborative longitudinal study of persons seeking care for cognitive complaints [25]. Ninety percent of the participants were referred by their general practitioners or a medical specialist, while the rest were self-referrals. The diagnostic procedure in the GO-MCI study is based on standardized cognitive screening tests and a standardized interview with both the patient and an informant [26]. To summarize, MCI was diagnosed by means of medical history, checklists, and an interview for cognitive symptoms: Stepwise Comparative Status Analysis (STEP) [27] (including memory disturbance, disorientation, reduced abstract thinking, visuospatial disturbance, poverty of language, sensory aphasia, visual agnosia, and apraxia), I-Flex, which is an interview for executive symptoms (including cognitive screening tests: items number-letter task, word fluency, anomalous sentence repetition, interference task, Luria hand sequences, and counting task) [28], Mini-Mental State Examination (MMSE) [29], and Clinical Dementia Rating (CDR) [30]. The information for CDR was gathered from both the patient and an informant. For inclusion in the GO-MCI database, evidence for cognitive decline for more than 6 months, provided by the patient or an informant, was required. Based on this procedure, patients were classified by the Global Deterioration Scale (GDS) [31]. This is a scale from 1 to 7, indicating stages from normal cognitive function to late dementia. In the GO-MCI database, 3 of these scores were employed with the following definition: GDS 2 = SCI, GDS 3 = MCI, and GDS ≥4 = dementia. Independent of the basic diag-

nostic procedure in the GO-MCI study, all patients underwent neuropsychological testing. This has been described elsewhere [24, 26].

In the GO-MCI study, patients with a GDS score ≥4 and/or a MMSE score <25 were excluded as they were considered to fulfill criteria for dementia. Exclusion criteria also included major depressive and other severe psychiatric disorders, neurological diseases, cardiovascular accidents, other severe somatic illnesses, or current substance abuse. In the present study, we identified patients (n = 81) from the GO-MCI database who did not qualify for MCI at baseline based on the neuropsychological criteria that we describe below. This group with only subjective cognitive impairment was diagnosed as SCI [32]. No patients in the present group developed dementia after 2 years of follow-up, classified by the GDS [31]. As complete neuropsychological data were not available at the 6-year follow-up, cognitive classification at this stage, in this study, was done according to the GDS [31].

Neuropsychological Baseline Definition of SCI and MCI in the Present Study

For the purpose of the present study, the baseline definition of SCI and MCI solely relied on neuropsychological test scores. We employed the 4 tests of executive function and memory that were most frequently used at both sites. These included 2 memory tests, the Rey Auditory Verbal Learning Test, delayed recall (RAVLT) [10, 33] and visual reproduction from the Rey Complex Figure Test, delayed reproduction (RCFT) [34], and 2 executive measures, the Trail Making Test – B (TMT-B) [35] and verbal fluency (Controlled Oral Word Association Test [COWAT]) [36]. The RAVLT was scored by the norms provided by Schmidt [33]. Reproduction of the RCFT was scored by the normative data from Meyers and Meyers [34]. The TMT-B and the COWAT were scored by the demographic norms by Heaton et al. [17]. The National Institute on Aging and the Alzheimer's Association recommend that the cognitive cutoff criterion for MCI is set to 1–1.5 SD below the normative mean on cognitive tests [37]. Major studies like the ADNI [1] employ 1.5 SD below the mean as the cutoff for MCI. The GO-MCI database [25], from which the present cohort was selected, employs 1.3 SD below the mean (T score 37) as the cognitive cutoff. Similar to several other studies of MCI [14, 38–41], we also employed this criterion in the present study. At baseline, the patients included in the study did not score below T score 37 in any of the tests and were not classified as MCI. The investigator responsible for the assessment and scoring of the tests was blinded to biomarker values.

Objective Change in Cognitive Function

Average T score and change in average T score for the memory tests (RAVLT and RCFT) and for the executive tests (COWAT and TMT-B) were computed (Average Memory Score and Average Executive Score) at baseline and at the 2-year follow-up. We categorized a decline in function as an average reduction of 0.5 SD or more and an improvement in function as an increased score of 0.5 SD or more. Those who improved or declined less than 0.5 SD were categorized as having stable cognitive function.

CSF Biomarkers

CSF samples were collected from all patients through lumbar puncture through the L3/L4 or L4/L5 intervertebral space. Lumbar puncture was performed consecutively after inclusion at a standardized time of day, between 8 and 12 a.m. CSF $A\beta_{42}$, T-tau, and P-tau were examined in all patients by commercially available enzyme-linked immunosorbent assays (INNOTEST® β-AMYLOID (1–42), INNOTEST® hTau Ag, and INNOTEST® PHOSPHO-TAU (181P, respectively; Fujirebio Diagnostics, Inc., Ghent, Belgium). $A\beta_{42}$ ≤500 ng/L and P-tau ≥80 ng/L were considered pathological. T-tau level was considered abnormal if T-tau >450 ng/L [42]. The cutoff for T-tau/$A\beta_{42}$ ratio was set to 0.52 as recommend by Duits et al. [43] as a robust CSF Alzheimer profile cutoff for patients with MCI.

Table 1. Baseline demographic and clinical variables for all patients included and for the subgroups that were observed for 2 and 6 years, respectively

Variables	Baseline (n = 122) (1)	Dropped out after 2 years (n = 41) (2)	Followed up for 6 years (n = 81) (3)	ANOVA p value	Post hoc p values (Tukey)
Mean age, years	62.5 (7.9) [45–79]	65.3 (8.2) [48–79]	61.0 (7.5) [45–78]	0.02	1 vs. 2 = 0.11 ns 1 vs. 3 = 0.41 ns 2 vs. 3 = 0.01**
Education, years	12.5 (3.3) [6–20]	13.0 (3.7) [6–20]	12.3 (3.1) [6–18]	0.47	ns
GDS	2.5 (0.5) [1–3]	2.5 (0.5) [1–3]	2.5 (0.5) [1–3]	0.20	ns
MMSE	28.8 (1.1) [25–30]	29.1 (1.0) [27–30]	28.7 (1.2) [25–30]	0.97	ns
T-tau, ng/L	302.4 (173.3) [79–1,090]	325.1 (218.9) [90–1,090]	291.0 (145.5) [79–660]	0.77	ns
P-tau, ng/L	55.1 (23.6) [22–188]	52.9 (31.5) [22–188]	56.3 (18.6) [24–100]	0.60	ns
$A\beta_{42}$, ng/L	686.2 (242.4) [160–1,507]	650.2 (232.0) [220–1,140]	704.2 (246.9) [160–1,507]	0.52	ns
T-tau/$A\beta_{42}$ ratio	0.54 (0.52) [0.07–3.76]	0.63 (0.73) [0.16–3.78]	0.49 (0.37) [0.07–1.68]	0.36	ns
Females, n (%)	67 (54.9)	24 (58.5)	43 (53.1)	χ^2	ns

Values in parentheses are SD, and values in square brackets are ranges, unless otherwise indicated. ns, nonsignificant. ** $p \geq 0.01$.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS 22.0) was used for all statistical analyses. One-way ANOVA was performed to compare baseline demographic and clinical variables for the initial patient sample and for patients who remained in the study for 2 and 6 years, respectively. Then, descriptive statistics of the demographic, clinical, and cognitive characteristics of the present patient population were computed. A series of independent t tests were performed comparing mean differences between the baseline variables of interest (CSF values, cognitive function, and cognitive decline at 2 years of follow-up) for those who remained stable, had declined to MCI, or developed dementia at 6 years of follow-up. As there is no generally accepted approach to appropriately correcting for multiple comparisons in this type of study, no such corrections were made. Odds ratios for the development of dementia and MCI were estimated with logistic regression analysis. First, the variables of interest were tested in a logistic univariate model. Based on this analysis, independent variables were chosen to be tested in a multivariate logistic model.

Results

Demographic and Clinical Characteristics of Patients at Baseline and of Those Who Remained in the Study for 2 and 6 Years, Respectively

Baseline demographic and clinical variables of the total patient sample and of those who remained in the study for 2 and 6 years, respectively, are shown in Table 1. The subgroup that was only observed for 2 years was significantly older than the group that stayed in the study for 6 years (65.3 vs. 61.0 years, p = 0.01). The other demographic and clinical variables did not differ between the groups. Both groups achieved a mean score on the MMSE and had mean CSF values within the normal range [42, 43]. Additional analysis shows that the drop-out group (consisting of 34% of the original group) had a higher mean MMSE score and higher T scores on all tests employed at the 2-year follow-up than the 81 patients (Gothenburg: 57, Oslo: 24) who were followed for 6 years. All the mean T scores for both groups at 2 years of follow-up were above 50 and mean MMSE scores were above 29, suggesting normal neuropsychological function. Furthermore, there was no significant difference in cognitive change between the 2 groups during the first 2 years of follow-up. Baseline neuropsychological

Table 2. Baseline neuropsychological scores for patients who were followed up for 6 years

Tests	All patients (n = 81)
RAVLT, delayed recall	
T score	53.9 (9.0) [37–81]
Raw score	9.9 (2.4) [5–15]
RCFT, delayed reproduction	
T score	55.2 (10.4) [38–80]
Raw score	18.9 (4.9) [9–30]
COWAT	
T score	54.6 (9.4) [38–75]
Raw score	45.0 (12.7) [22–88]
TMT-B	
T score	51.6 (7.8) [37–72]
Raw score	81.7 (27.6) [41–195]
Average Memory *T* score	54.5 (7.4) [40–70]
Average Executive *T* score	53.1 (6.2) [40–71]

Values in parentheses are SD, and values in square brackets are ranges.

scores for patients who were followed for 6 years are shown in Table 2. Based on neuropsychological criteria, none of the patients were diagnosed with MCI at baseline. All the mean *T* scores at baseline were close to or slightly above the normative mean.

Baseline Characteristics and Cognitive Change over 2 Years from Baseline for Patients Who Remained Stable or Improved within GDS Range 2–3 (SCI/MCI), for Those Who Declined to Either GDS 3 or 4 (GDS 3 = MCI, GDS 4 = Dementia) after 6 Years, and for Those Who Developed Dementia after 6 Years

Analysis based on the basic GO-MCI diagnostic procedure at the 6-year follow-up showed that 70 (86%) patients in the cohort remained cognitively stable or improved within the SCI/MCI spectrum (GDS 2–3) from baseline to follow-up after 6 years, and that only 11 (14%) declined based on GDS scores. Seven (9%) declined from GDS 2 to 3, and 4 (5%) developed dementia (GDS 4). None of the patients qualified for MCI at baseline according to the employed neuropsychological criteria. According to the GO-MCI-based GDS scores, more patients had GDS 2 (SCI) and less had GDS 3 (MCI) after 6 years, suggesting a slight overall improvement in cognitive function.

Table 3 shows the baseline characteristics and cognitive change over 2 years from baseline for patients who remained stable or improved within GDS range 2–3 (SCI/MCI) and for those who declined to GDS 3 or 4 (dementia) after 6 years. The groups were similar at baseline. The only difference between the groups was that the declining group showed a significantly greater decline in memory performance in the first 2 years of follow-up than the stable group within the SCI/MCI spectrum that on average improved their cognitive function. The Average Memory score in the declining group was reduced with a *T* score of 4.6 (SD = 10.0) as opposed to the average improvement of *T* score 1.6 (SD = 7.7) in the stable group (p = 0.02).

Table 4 shows the baseline characteristics and cognitive change over 2 years from baseline for patients who developed dementia versus patients with only SCI or MCI after 6 years. Of the 4 patients who developed dementia, 2 were diagnosed with AD, 1 with vascular dementia, and 1 with unspecified dementia. Those who developed AD and vascular dementia were characterized by significantly lower levels of $A\beta_{42}$ at baseline. All the patients who

Table 3. Baseline characteristics and cognitive change over 2 years from baseline of the patients who remained stable or improved within the GDS range 2–3 (SCI/MCI) and of those who declined to GDS 3 or 4 (MCI/dementia) after 6 years

	Declined to GDS 3 or 4 (n = 11)	Stable within GDS 2–3 (n = 70)	p value
Baseline characteristics			
Age, years	61.0 (5.7)	61.0 (7.8)	0.96
Education, years	11.7 (3.3)	12.4 (3.1)	0.55
MMSE	28.5 (0.9)	28.7 (1.2)	0.51
P-tau, ng/L	62.9 (21.7)	55.4 (18.2)	0.35
T-tau, ng/L	264.8 (87.4)	295.2 (152.8)	0.52
$A\beta_{42}$, ng/L	625.6 (227.3)	716.8 (249.1)	0.26
T-tau/$A\beta_{42}$ ratio	0.48 (0.3)	0.49 (0.4)	0.93
Average Memory *T* score	52.3 (6.6)	54.9 (7.6)	0.28
Average Executive *T* score	52.2 (9.2)	53.2 (5.6)	0.61
Cognitive change over 2 years from baseline			
Average Memory *T*-score change	–4.6 (10.0)	+1.6 (7.7)	0.02*
Average Executive *T*-score change	–0.8 (4.6)	+1.3 (5.6)	0.23

Values in parentheses are SD. * $p \geq 0.05$.

Table 4. Baseline characteristics and cognitive change over 2 years from baseline of the patients who developed dementia versus patients with only SCI or MCI after 6 years

	Demented (n = 4)	SCI/MCI (n = 77)	p value
Baseline characteristics			
Age, years	62.0 (7.0)	61.0 (7.5)	0.79
Education, years	13.0 (4.7)	12.2 (3.0)	0.66
MMSE	27.8 (1.0)	28.7 (1.2)	0.11
P-tau, ng/L	58.3 (29.9)	56.2 (18.3)	0.85
T-tau, ng/L	223.3 (110.7)	294.6 (146.8)	0.34
$A\beta_{42}$, ng/L	408.0 (150.0)	719.8 (241.6)	0.01**
T-tau/$A\beta_{42}$ ratio	0.63 (0.4)	0.48 (0.4)	0.44
Average Memory *T* score	49.4 (4.0)	54.8 (7.5)	0.16
Average Executive *T* score	46.5 (7.8)	53.4 (5.9)	0.02*
Cognitive change over 2 years from baseline			
Average Memory *T*-score change	–8.4 (8.1)	+1.2 (8.1)	0.02*
Average Executive *T*-score change	–1.3 (4.9)	+1.2 (5.6)	0.40

Values in parentheses are SD. * $p \geq 0.05$; ** $p \geq 0.01$.

developed dementia had a significantly poorer Average Executive score (although well within the normal range) at baseline. Furthermore, the group that developed dementia showed a significant decline in the Average Memory score from baseline to the 2-year follow-up, compared to the group that remained cognitively stable at the 6-year follow-up.

Prediction of Dementia and Decline

Univariate logistic regression analysis revealed a significant association between low $A\beta_{42}$ at baseline and conversion to dementia as well as near-significant associations both

Table 5. Predictors of dementia (GDS ≥4) after 6 years in patients with only subjective cognitive complaints at baseline (n = 81)

Baseline variables	Univariate analysis		Multivariate analysis		
	OR	p value	OR	95% CI	p value
$A\beta_{42}$ ≤500 ng/L	14.54	0.025	22.56	1.69–298.29	0.018
Memory decline ≥0.5 SD/2 years	9.83	0.054	15.51	1.15–208.29	0.039
Executive T score ≤46.5	7.56	0.057			
T-tau/$A\beta_{42}$ ratio >0.52	3.75	0.203			
P-tau ≥80 ng/L	4.06	0.274			
T-tau ≥450 ng/L	0.00	0.999			

between memory decline in the first 2 years of follow-up as well as slightly below normal executive T score at baseline, and development of dementia (Table 5). Multivariate regression analysis showed that both $A\beta_{42}$ <500 ng/L (OR = 22.56, p = 0.018) and memory decline >0.5 SD in the first 2 years (OR = 15.51, p = 0.039) were significant and strong predictors of dementia at the 6-year follow-up. A similar univariate regression analysis showed that the only significant predictor of cognitive decline to either GDS 3 or 4 was memory decline >0.5 SD in the first 2 years (OR = 7.00, p = 0.005). Of the 16 patients with $A\beta_{42}$ <500 ng/L at baseline, 19% (n = 3) developed dementia, while 12% (n = 3) of the 25 patients with memory decline >0.5 SD in the first 2 years developed dementia. The risk for dementia increased to 50% for the 6 patients who satisfied both these criteria. Of the 10 patients with T-tau ≥450 ng/L at baseline, none developed dementia, while 1 of the 9 patients with P-tau ≥80 ng/L developed dementia (AD).

Discussion

A cohort of relatively young memory clinic patients with normal neuropsychological function at baseline was followed for 6 years. Apart from being slightly younger, the cohort was representative for a larger group that we previously followed for 2 years [14]. In accordance with our first hypothesis, 86% of the present cohort remained cognitively stable or improved. This main result clearly supports previous findings, suggesting that SCI is a predominantly benign condition with regard to neuropathology [15, 19, 20]. Among the 14% who declined, based on GDS scores, 9% declined from SCI to MCI, and only 5% developed dementia. The declining group showed a significantly greater drop in memory performance in the first 2 years of follow-up than the stable group. Other variables were not associated with cognitive decline within the SCI/MCI spectrum. The group that developed dementia had significantly lower levels of $A\beta_{42}$ at baseline, significantly larger memory decline from the baseline assessment to the 2-year follow-up, and a significantly poorer Average Executive score (although close to normal) at baseline than those who did not develop dementia. Regression analysis revealed that both low levels of $A\beta_{42}$ at baseline and memory decline in the first 2 years of follow-up were significant and strong predictors of dementia at the 6-year follow-up. When combined, these variables were associated with a 50% risk of developing dementia. The findings were largely in agreement with hypotheses 2 and 3, but not with the assumption that other baseline CFS biomarkers would be more pathological in patients who developed dementia.

There is evidence that in individuals with unimpaired neuropsychological function, SCI may represent the first symptomatic manifestation of a developing dementia disorder, and it

is assumed that very early interventions in the degenerative disease process will be more effective with regard to possible prevention or treatment. Thus, it is easy to argue for an inclusion of persons with SCI in the search for early markers of preclinical dementia. However, there are many pitfalls associated with the study of SCI. Recent studies have revealed that persons with SCI constitute a heterogeneous group [13], including variations of normality, different medical conditions, mild psychological problems, daily life stress factors, as well as persons at risk for development of dementia. Recently, Edmonds et al. [44] have shown that subjective cognitive complaints actually could contribute to high rates of misdiagnosis of MCI as cognitively intact persons tended to overestimate cognitive problems, while those with MCI and objective memory deficit underestimated their cognitive difficulties. In addition, those with MCI and positive CSF AD biomarkers underestimated their cognitive problems in contrast to those who had negative CSF AD biomarkers. Significant correlations were evident between self-reported cognitive problems and depressive symptoms. We found similar results in a study of SCI and objective MCI [19] as patients with objective MCI underestimated their cognitive difficulties in contrast to those who only had subjective cognitive complaints. Depressive symptoms were associated with cognitive complaints, while degenerative changes (relating to pathological levels of CSF biomarkers) were associated with objective cognitive deficits. A weakness of the present study is that SCI only was defined by subjective cognitive complaints and average function on a very brief neuropsychological test battery not representative for all the relevant cognitive functions that may be impaired in MCI [1]. Thus, some of the study patients may have been categorized differently if we had employed a wider and more representative test battery.

The fact that 86% of the patients remained cognitively stable or improved implies that the group mostly consists of cognitively healthy persons at little risk of developing dementia. The 6-year observation of the SCI cohort did not succeed in detection of early markers of dementia with sufficient statistical strength as only 4 patients developed dementia. To increase the likelihood of the presence of preclinical dementia and make the concept of SCI more meaningful, the SCD-I [13] has suggested a set of SCD features (including biomarkers), which, in accordance with current knowledge, increase the likelihood of the presence of preclinical dementia and AD. The results from this study, suggesting biological and cognitive risk factors for cognitive decline and dementia, provide support for the employment of additional pre-dementia-related SCD risk factors [13], as recommended by the SCD-I [13], in future studies of SCI/SCD cohorts. The prediction of cognitive decline and dementia would have been more precise if this study had excluded the participants with above-cutoff CSF values and stable cognitive function in the first 2 years from further follow-up after 2 years. The employment of more specific SCI/SCD criteria also has ethical implications as a large number of the participants would be relieved from the suspicion of a potential predementia state several years earlier.

Despite a small target sample, multivariate logistic regression was employed, and the results suggest that $A\beta_{42}$ ≤500 ng/L as well as memory decline ≥0.5 SD in the first 2 years of follow-up are important risk factors for developing dementia. That said, the low number of individuals who developed dementia limits the generalizability of the results and discussion of etiological mechanisms. Of the 4 participants who developed dementia, the 2 patients with AD and the patient with vascular dementia had the most pathological $A\beta_{42}$ CSF levels at baseline. The findings were not in accordance with the 2-year follow-up of a larger sample of the same cohort [14] that found a significant association between higher T-tau at baseline and objective memory decline during the study period. Together, these findings do not fit consistently with the model by Jack et al. [3], suggesting that AD begins with Aβ deposition in the cortex, leading to a synaptic dysfunction, neurodegeneration, and finally to detectable cognitive changes and subsequent dementia.

One explanation for the different findings may be that a higher level of T-tau is an unspecific indication of neurodegeneration, associated with a range of neurological conditions [45–48]. Thus, memory decline may have different biological causes within this spectrum of cognitive function. Another explanation for the different findings may be related to the smaller sample size, implying a larger possibility for incidental results and lower statistical power in the present group. That said, high CSF T-tau levels have indeed been found to discriminate MCI patients who developed AD at follow-up [49]. In addition, a recent, large postmortem study at the Mayo Clinic found that the severity of T-tau, but not amyloid, predicted age at onset of cognitive decline, AD disease duration, and mental deterioration [50]. Other recent studies support the findings in the present study. Villemagne et al. [5], employing imaging of beta-amyloid plaques (PiB-PET) [51], found that healthy persons with an increased $A\beta_{42}$ deposition in the brain were more likely to develop MCI after 3 years compared to those with a normal Aβ load in the brain. The $A\beta_{42}$ CSF levels have been shown to inversely correlate with plaque load, visualized by in vivo amyloid PET, implying a true biological relationship to pathology [52]. Van Harten et al. [53] followed patients with SCI and found that those who did progress to MCI or AD had baseline levels of $A\beta_{42}$ that were significantly lower and levels of T-tau and P-tau that were significantly higher, with low $A\beta_{42}$ being the best predictor of progression. The findings of Visser et al. [54] were similar. They found no significant cognitive decline at follow-up in SCI regardless of baseline CSF status, but they found significant improvement in memory at follow-up only in those SCI patients who did not have a CSF AD profile at baseline (based on a combination of Aβ and T-tau levels). The referenced studies employ different methods and reveal somewhat different findings. However, all of them suggest that CSF biomarkers in SCI are associated with cognitive decline or reduced cognitive improvement at follow-up.

GDS classification at baseline was found to overclassify MCI compared to the brief neuropsychological assessment. Several factors may explain this. First, the GDS diagnosis relies on subjective report of cognitive dysfunction by both the patient and an informant, in addition to brief cognitive screening tests. As subjective cognitive complaints in this age group are very common among healthy persons [15], too much reliance on subjective symptom reports may contribute to misdiagnosis of cognitive impairment. In addition, the GDS classification procedure employs cognitive screening tests with less advanced normative data than the neuropsychological tests commonly employ [17, 33, 34]. Another factor that may explain some of the discrepancy in MCI classification between the 2 procedures is that the short neuropsychological test battery may fail to detect the full range of cognitive impairment that patients with MCI may have [26]. Thus, both GDS classification and brief neuropsychological assessment as employed in this study may have their shortcomings. More comprehensive neuropsychological assessments have been shown to increase the validity and robustness of MCI diagnosis [55, 56] and are recommended in future studies. If GDS classification lacks precision in diagnosis of MCI, with a tendency to overdiagnose, a relevant question is whether GDS also overdiagnoses dementia. However, this seems much less likely, as any diagnosis of dementia requires valid confirmation of actual disability or handicap due to cognitive dysfunction in activities of daily life.

A probable explanation for the relatively large drop-out rate (34%) from the 2- to 6-year follow-up is that the participants were largely cognitively healthy and wanted no more follow-up after 2 assessments (baseline and 2-year follow-up) with normal results not suggesting cognitive decline. At the 2-year follow-up, the drop-out group had higher mean *T* scores than the 6-year follow-up group on all the neuropsychological tests. At follow-up, all the mean *T* scores for both groups were above 50 and the mean MMSE scores were above 29, suggesting above-average cognitive function. As none of the baseline clinical variables differed between the 2 groups, the 6-year follow-up group is regarded as representative for the original SCI cohort, consisting of 122 participants.

The major dementias are biological conditions [2–4] and biological changes may be assumed to occur before development of cognitive impairment. The specificity of cognitive cutoff values in studies of both SCI/SCD and MCI is problematic due to both the relatively high frequency of neurologically healthy persons with poor cognitive function, resembling MCI [57], and the phenomenon that persons with different brain diseases and brain impairments may have normal cognitive function [18]. Based on our previous findings [14] and the results from the present study, we propose that in persons with only SCI, objective cognitive decline from baseline may be a marker of cognitive decline and possible future dementia, which deserves attention in future longitudinal studies of SCI. The declining memory group had average neuropsychological scores at baseline and did not qualify for any kind of cognitive impairment. Still, 12% of those with memory decline >0.5 SD in the first 2 years developed dementia after 6 years, and when combined with the criterion of $A\beta_{42}$ <500 ng/L at baseline, the risk for dementia increased to 50% in the present group.

In conclusion, 86% of a cohort of memory clinic patients with SCI at baseline remained cognitively stable or improved at the 6-year follow-up, clearly suggesting that SCI is a predominantly benign condition with regard to neuropathology. Only 5% developed dementia, and regression analysis found that both low levels of $A\beta_{42}$ at baseline and memory decline in the first 2 years of follow-up were significant predictors of dementia. When combined, these variables were associated with a 50% risk of developing dementia. The low number of individuals who developed dementia limits the generalizability of the results and discussion of progression factors. Longitudinal observations of similar cohorts with larger numbers of individuals developing dementia are needed for a stronger analysis of etiological mechanisms. The finding that SCI is a predominantly benign condition clearly supports the recommendation of the Subjective Cognitive Decline Initiative [13] to include additional, pre-dementia-related SCD risk factors in future studies of SCD cohorts.

Disclosure Statement

The authors report no conflicts of interest.

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