Original Research Article

Correlates of Subjective and Mild Cognitive Impairment: Depressive Symptoms and CSF Biomarkers

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Key Words

Mild cognitive impairment · Subjective cognitive impairment · Cognitive complaints · Depression · CSF biomarkers · Degenerative diseases

Abstract

Aims: To improve early diagnosis of dementia disease, this study investigates correlates of cognitive complaints and cognitive test performance in patients with subjective (SCI) and mild (MCI) cognitive impairment. ***Methods:*** Seventy patients from a memory clinic, aged 45–79, with a score of 2 (n = 23) or 3 (n = 47) on the Global Deterioration Scale, were included. CSF biomarkers [$A\beta_{42}$, total tau (T-tau) and phosphorylated tau (P-tau)], depressive symptoms, cognitive performance, and complaints were examined. ***Results:*** Correlation analysis showed that cognitive complaints increased with decreasing cognitive performance in SCI and decreased with decreasing performance in MCI. Linear regression models revealed that cognitive complaints were associated with depressive symptoms in both groups of patients, while cognitive performance was associated with CSF $A\beta_{42}$ and P-tau in SCI and with T-tau and P-tau in MCI. ***Conclusion:*** These results suggest that depressive symptoms are associated with cognitive complaints, while degenerative changes are associated with objective cognitive decline in high-risk predementia states.

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Introduction

To differentiate between the individual diagnoses of patients presenting at memory clinics with cognitive complaints and often depressive symptoms, more accurate diagnostic measures are needed. The term subjective cognitive impairment (SCI) describes patients with subjective cognitive complaints and occurs before mild cognitive impairment (MCI) [1, 2]. MCI patients have objective cognitive impairment in addition to subjective cognitive complaints [3, 4]. Both conditions may represent predementia stages. In order to determine which persons should be treated or investigated further, it is important to find reliable correlates of both subjective cognitive complaints and objective cognitive impairment.

Objective cognitive impairment has been found in 11% of nondemented elderly [5], while estimates of memory complaints in nondemented elderly range from 22 to 56% [6]. For early diagnosis of dementia and Alzheimer's disease (AD), it is important to know when cognitive complaints are accurate, i.e. reflect actual performance, but the existing findings regarding accuracy of complaints in MCI are divergent [7, 8]. Significant associations between cognitive complaints and performance have been found in a few community-based samples [7, 9], while other studies have not found such associations [10, 11]. One review study suggests that nondemented individuals are generally able to accurately identify their cognitive problems [12], while patients with AD dementia underestimate their cognitive problems [13, 14]. Early AD is typically characterized by neuronal loss in the medial temporal lobes [15] and memory impairment [16]. The degree of awareness of one's cognitive state may decrease as the disease progresses and frontal lobe functions decrease [17].

Combinations of AD-related CSF biomarkers (tau and Aβ proteins) predict the development of dementia in MCI [18–21]. The findings from one recent study [22] indicate that CSF levels of $A\beta_{42}$ are already fully decreased at least 5–10 years before conversion to AD dementia, whereas total tau (T-tau) and phosphorylated tau (P-tau) seem to be later markers [23]. Previously, we have found associations between memory and CSF tau levels in the SCI/MCI sample [24, 25], and associations between CSF biomarkers and cognition in MCI have been found by other researchers [26–29]. Still, many aspects regarding the relationship between biological changes related to degeneration in terms of CSF biomarkers and clinical symptoms in predementia stages remain unclear. The association between CSF biomarkers and both cognitive complaints and performance has not been studied in SCI.

Depressive symptoms occur commonly in SCI and MCI [30] and constitute another known risk factor for dementia [31–35]. People that are depressed complain [36, 37], and the criteria for depression include SCI and/or objective cognitive impairment [38]. Positive correlations have been found between depression and memory complaints in a few studies of normal and cognitively impaired samples [8, 39, 40].

Our first hypothesis is that individuals with SCI judge their performance more accurately than MCI patients. The second hypothesis is that cognitive complaints are associated with depressive symptoms and CSF biomarkers are associated with objective cognitive impairment.

Methods

Research Participants

The project was approved by the South-Eastern Norway committee for medical research ethics. The participants' consent was obtained according to the Declaration of Helsinki [41]. Seventy patients were included in the study. Patients with subjective cognitive complaints which had lasted 6 months or more and who had attended a university-based memory clinic between September 2005 and January 2010 were assessed for inclusion in the study.

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Inclusion criteria were no or very mild problems with activities of daily living and Global Deterioration Scale (GDS) [42, 43] score 2 (SCI, n = 23) or 3 (MCI, n = 47) as determined from a clinical interview and screening tests. Screening tests included parameters 13–20 (memory, disorientation, abstract thinking, visuospatial ability, language, sensory aphasia, visual agnosia, and apraxia) from the stepwise comparative status analysis (STEP) [44, 45], word fluency, interference, and numeral-letter items from the I-FLEX [46], and items from the Neurobehavioral Cognitive Status Examination (Cognistat) [47] as well as Mini-Mental State Examination (MMSE) [48]. To be classified as GDS 2, subjects had to score ≥28 on MMSE, 0 on STEP variables, a total sum <2 on the elements from I-FLEX, and there had to be a maximum of one domain where they scored 0.5 on the Clinical Dementia Rating (CDR) scale [49]. Subjects classified as GDS 3 scored ≥26 on MMSE, ≤1 on STEP variables, ≤2 on I-FLEX variables, and there were more than one CDR domain where they scored 0.5, albeit none where they scored 1. The following criteria for exclusion were established: psychiatric disorder (including major depressive episode), stroke, cancer, drug abuse, solvent exposure or anoxic brain damage.

Neuropsychological Assessment and Cognitive Variables

Neuropsychological examination was performed not later than 3 months after inclusion in the study. The complete neuropsychological test battery is described elsewhere [50]. The four neuropsychological variables, used in the analyses, were termed: 'word list memory' (30-min recall) of the Rey Auditory Verbal Learning Test (RAVLT) [51], 'visual memory' (30-min recall) of the Rey Complex Figure Test (RCFT) [52], 'working memory' of the Letter-Number Sequencing subtest, Wechsler Adult Intelligence Scale – Third Edition [53], and 'response inhibition' (naming colors of the ink of inconsistently colored names) of the Color-Word Interference Test [54].

Depressive Symptoms

Self-reported depressive symptoms were assessed by the Symptom Checklist-90-R (SCL-90-R) [55] on the same day as the neuropsychological examination was performed. The questionnaire consists of 90 items and is designed to evaluate a broad range of psychological problems and symptoms of psychopathology, including a 13-item subscale for depressive symptoms. The items are rated on a five-point scale of distress from 'not at all' to 'extremely'. In addition to SCL-90-R, depressive symptoms were assessed using a short version of the Geriatric Depression Scale [56], namely GDS-15 [57]. Its items require a yes/no response.

Subjective Cognitive Complaints

SCL-90-R was used for the assessment of subjective memory and concentration complaints. Two of the SCL-90-R items concern memory and concentration complaints, which are rated on a five-point scale of distress from 'not at all' (0) to 'extremely' (4).

Lumbar Puncture

CSF samples were collected by lumbar puncture through the L3/L4 or L4/L5 inter-space. The lumbar puncture was performed consecutively following the patients' inclusion in the study. CSF concentrations of $A\beta_{42}$, T-tau, and P-tau were routinely examined using commercially available enzyme-linked immunosorbent assay kits (Innogenetics, Belgium). Raw scores of the CSF variables were used in all analyses. Both raw scores and frequencies of pathological levels are shown in table 1. $A\beta_{42}$ was considered pathological if ≤550 ng/l. P-tau was considered pathological if ≥80 ng/l. T-tau level was considered abnormal if T-tau ≥300 ng/l for patients under 50 years, >450 ng/l for patients from 50 to 69 years, and ≥500 ng/l for patients from 70 years and above [58].

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Table 1. Characteristics of the patients

	Total group	SCI (n = 23)	MCI (n = 47)	p
Age (range 45–79), years	61.7 (7.2)	58.8 (7.2)	63.1 (6.8)	0.03
Education (range 7–18), years	12.5 (2.9)	13.4 (2.8)	12.1 (2.9)	0.08
Gender, n male	35 (50%)	10 (44%)	25 (53%)	0.45
Handedness, n right	66 (94%)	23 (100%)	43 (92%)	0.15
APOE-ε4, n carriers	33 (47%)	13 (57%)	20 (43%)	0.32
MMSE[1]	28.1 (1.4)	29.0 (1.0)	27.6 (1.3)	<0.001
Word list memory (RAVLT)	7.8 (4.1)	10.0 (2.9)	6.7 (4.1)	<0.001
Visual memory (RCFT)	13.0 (6.8)	17.3 (6.7)	10.9 (5.8)	<0.001
Response inhibition (CWIT)	75.6 (47.1)	61.1 (11.5)	82.5 (55.4)	0.02
Working memory (Letter-Number Sequencing)	8.3 (2.2)	9.1 (2.2)	7.9 (2.2)	0.04
Memory complaints (range 0–4)	2.4 (1.1)	2.5 (1.1)	2.3 (1.1)	0.58
Concentration complaints (range 0–4)	1.9 (1.2)	2.1 (1.2)	1.8 (1.2)	0.27
SCL-90-R depressive symptoms	0.9 (0.7)	1.1 (0.8)	0.8 (0.6)	0.28
GDS-15 depressive symptoms	3.3	3.4	3.3	0.22
$A\beta_{42}$, ng/l	842.2 (291.1)	869.1 (264.0)	829.1 (305.4)	0.54
$A\beta_{42}$, n pathological	15 (21%)	3 (13%)	12 (26%)	0.35
T-tau, ng/l	344.8 (201.4)	263.0 (81.9)	384.9 (229.5)	0.01
T-tau, n pathological	16 (23%)	2 (9%)	14 (30%)	0.07
P-tau, ng/l	75.8 (30.1)	65.8 (12.2)	80.7 (34.9)	0.06
P-tau, n pathological	24 (34%)	3 (13%)	21 (45%)	0.02

Values are presented as means (±SD) unless indicated otherwise. Raw scores of all variables are presented. The comparison of gender, handedness, APOE-ε4, and pathological levels of CSF biomarkers between the SCI and MCI groups was made with a χ^2 test (Pearson χ^2 test p value is shown). The independent-samples t test was used to compare the groups for the remaining variables. [1] MMSE: maximum score: 30.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS 16.0) was used for all statistical analyses. To compare characteristics of the patient groups, the independent-samples t test and the χ^2 test were used. The Pearson correlation method was used to test for associations between cognitive complaints and test performance. Linear multiple regression analysis was performed to assess the impact of depressive symptoms and CSF biomarkers on subjective cognitive complaints and cognitive performance. The variable of depressive symptoms was entered together with one of three CSF variables at a time as the predictor variables. Only one CSF variable was included per model because of the colinearity among the predictor variables. As there was a significant group difference in age, age was used as a confounder in each model. The term 'significant', used in this article, refers to $p < 0.05$. The term 'significant at trend level' refers to $p < 0.10$.

Results

Characteristics of the Patients

Table 1 presents patient characteristics. Demographic data were similar in SCI and MCI except for age. As expected, cognitive performance (MMSE, word list/visual memory, response inhibition, and working memory) was significantly better in SCI compared to MCI, but both groups reported a similar degree of memory and concentration complaints. Depressive symptoms were not significantly different between the groups, although there was a high

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Table 2. Correlations between cognitive complaints and test performance

	Word list memory	Visual memory	Response inhibition	Working memory
Memory complaints				
SCI	−0.361	−0.401	−0.482*	−0.390
MCI	−0.039	0.285	−0.030	−0.052
Concentration complaints				
SCI	−0.076	−0.433*	−0.448*	−0.156
MCI	0.361*	0.466*	0.250	0.017

Pearson correlation coefficients are listed for the SCI (n = 23) and the MCI (n = 47) groups. Inhibition scores have been multiplied with –1, so that a higher score means a better result for each test. * $p < 0.05$.

variability in depression scores in both groups. CSF $A\beta_{42}$ levels were higher (but not significantly so) in SCI compared to MCI, while T-tau levels were significantly lower and P-tau levels were lower at trend level in SCI compared to MCI.

Correlations between Cognitive Complaints and Performance

Table 2 shows the correlations between test performance and cognitive complaints. There was a significant negative relationship between visual memory performance and concentration complaints as well as between response inhibition and both memory and concentration complaints in patients with SCI (the better the test performance, the less complaints). In the same group, there were also negative relationships between memory complaints and performance on tests of working memory, word list and visual memory, but they were only significant at trend level. In MCI, significant positive relationships were found between word list/visual memory performance and concentration complaints, i.e. a lower performance was associated with less complaints. No significant associations were found between test performance and memory complaints in MCI.

Linear Regression Analyses

In order to assess the impact of depressive symptoms and CSF biomarkers (explanatory variables) on the reported cognitive complaints and cognitive performance (the dependent variables), linear regression analyses were performed (tables 3, 4). SCL-90-R depressive symptoms, but not CSF biomarkers, predicted subjective memory and concentration complaints in both groups of patients. In contrast, CSF biomarkers ($A\beta_{42}$, T-tau, and P-tau) were significant predictors of cognitive test performance. In the SCI group (table 3), $A\beta_{42}$ was a significant predictor of word list/visual memory and P-tau was a significant predictor of response inhibition. In the MCI group (table 4), T-tau was a significant predictor of word list memory (significance at trend level was achieved for visual memory), and P-tau was a significant predictor of visual memory (significance at trend level was achieved for word list memory). We also explored the associations of depression with cognitive complaints and test performance, using GDS-15 as the depression measure. The results were largely similar in SCI, with the exception that the GDS-15 score was negatively associated with response inhibition. In MCI, the GDS-15 score did not correlate with cognitive complaints or test performance (data not shown).

Table 3. Multiple regression analyses with cognitive complaints and test results as the dependent variables and SCL-90-R depression scale and CSF variables as the predictor variables in SCI

Predictor variables	Dependent variables					
	subjective complaints		test results			
	memory complaints	concentration complaints	word list memory	visual memory	response inhibition	working memory
Model 1						
Depression	*−0.75 (0.001)*	*0.86 (<0.001)*	0.00 (0.999)	−0.26 (0.160)	−0.33 (0.118)	−0.26 (0.316)
Aβ$_{42}$	−0.13 (0.505)	−0.25 (0.130)	*0.42 (0.027)*	*0.44 (0.022)*	0.39 (0.074)	0.26 (0.316)
Model 2						
Depression	*0.78 (0.001)*	*0.91 (<0.001)*	−0.04 (0.835)	−0.30 (0.168)	−0.39 (0.087)	−0.29 (0.275)
T-tau	0.09 (0.593)	0.13 (0.402)	−0.02 (0.936)	0.04 (0.830)	−0.15 (0.473)	−0.05 (0.828)
Model 3						
Depression	*0.76 (0.001)*	*0.90 (<0.001)*	−0.04 (0.830)	−0.30 (0.157)	−0.39 (0.057)	−0.29 (0.279)
P-tau	0.04 (0.834)	0.26 (0.076)	−0.08 (0.649)	0.10 (0.593)	*−0.41 (0.026)*	−0.07 (0.780)

β (p) values are shown. Inhibition scores have been multiplied with −1, so that a higher score means a better result for each test (n = 23). Age was included in each model. The italicized numbers indicate a significance level of $p < 0.05$.

Table 4. Multiple regression analyses with cognitive complaints and test results as the dependent variables and SCL-90-R depression scale and CSF variables as the predictor variables in MCI

Predictor variables	Dependent variables					
	subjective complaints		objective test results			
	memory complaints	concentration complaints	word list memory	visual memory	response inhibition	working memory
Model 1						
Depression	*0.40 (0.005)*	*0.38 (0.002)*	0.18 (0.222)	0.20 (0.154)	−0.10 (0.491)	−0.02 (0.862)
Aβ$_{42}$	0.06 (0.685)	<0.001 (0.998)	0.15 (0.305)	0.23 (0.093)	0.20 (0.178)	−0.05 (0.730)
Model 2						
Depression	*0.41 (0.005)*	*0.36 (0.004)*	0.13 (0.369)	0.16 (0.263)	−0.13 (0.391)	−0.04 (0.815)
T-tau	0.03 (0.832)	−0.17 (0.165)	*−0.31 (0.039)*	−0.26 (0.076)	−0.18 (0.266)	−0.06 (0.727)
Model 3						
Depression	*0.40 (0.006)*	*0.37 (0.003)*	0.15 (0.304)	0.16 (0.238)	−0.12 (0.453)	−0.01 (0.945)
P-tau	−0.02 (0.885)	−0.14 (0.222)	−0.26 (0.072)	*−0.32 (0.019)*	−0.11 (0.492)	0.13 (0.917)

β (p) values are shown. Inhibition scores have been multiplied with −1, so that a higher score means a better result for each test (n = 47). Age was included in each model. The italicized numbers indicate a significance level of $p < 0.05$.

Discussion

This study has investigated correlates of cognitive complaints and cognitive test performance in patients with SCI and MCI. Depressive symptoms and CSF biomarkers were assessed as possible correlates because of their importance for the differential diagnosis of dementia. Subjects with SCI were included since they constitute a group of particular interest for the early detection of neurodegenerative disease. The study objectives were met and the hypotheses confirmed.

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In addition to neuropsychological data, we have studied both memory and concentration complaints, while most of the existing studies have aggregated the complaints into one complaint score instead of analyzing them by domain [59–61]. We have used the self-rating questionnaires SCL-90-R and GDS-15 for the assessment of cognitive complaints and depressive symptoms. Relatively high MMSE scores (SCI mean score 29 and MCI mean score 28) imply that most of patients are reliable sources of information. Still, a decrease in reliability is expected with disease progression (e.g., from SCI to MCI). The SCI and MCI groups studied reported a similar amount of memory and concentration complaints. Cognitive complaints increased with decreasing cognitive function in SCI and decreased with decreasing cognitive function in MCI. These results suggest that patients with incipient cognitive difficulties (SCI), not satisfying the clinical criteria for MCI, assess their cognitive abilities more correctly, while patients with MCI tend to underestimate their cognitive difficulties. Similarly, disagreement between patients and their informants was associated with MCI but not SCI in another recent study [62].

Depressive symptoms, but not CSF biomarkers, were significantly associated with cognitive complaints, which is in accord with the findings from earlier studies of normal and cognitively impaired samples [8, 34, 39, 40]. We have not found an association between depressive symptoms and cognitive impairment, except for the association between response inhibition and depressive symptoms as measured by GDS-15 in SCI. In comparison, depressive symptoms were negatively correlated with cognitive functioning in another recent study of healthy middle-aged and older adults [63]. Taking into account that depressive symptoms in midlife or in late life are associated with an increased risk of developing dementia [35], the association between depressive symptoms and response inhibition/cognitive complaints in our study may reflect an etiologic relationship between depression and very early cognitive changes due to dementia.

CSF biomarkers were related to objective cognitive impairment. We found negative associations between memory and CSF tau measurements in the MCI subsample and positive associations between $A\beta_{42}$ and memory in the cognitively healthier SCI subsample. We have previously found similar associations between tau and memory in the overlapping SCI/MCI sample, which was not divided into SCI and MCI [24, 25]. To our knowledge, this is the first study of patients with SCI and MCI, giving support to the amyloid cascade hypothesis [23] by using cognitive data. Here, we find the associations between memory and CSF $A\beta_{42}$ in SCI and the associations between memory and tau biomarkers in MCI, which agrees with recent findings of Buchhave et al. [22], suggesting that altered $A\beta$ metabolism precedes tau-related pathology and neuronal degeneration in AD.

The association between memory performance and cognitive complaints in SCI is not surprising. These patients have been referred to a memory clinic which focuses on diagnosing dementia. Incipient AD is the most prevalent underlying disease and is characterized by white matter diffusivity changes encompassing the memory network [24, 64]. In addition to memory performance, we have studied working memory and response inhibition. In SCI, response inhibition was significantly associated with memory/concentration complaints and CSF P-tau, while working memory was associated with memory complaints at trend level. These findings suggest that response inhibition is a sensitive measure of early cognitive decline in predementia phases. Previously, we have found that worse performance on response inhibition was associated with increased white matter diffusivity underlying the superior frontal cortex [65].

The study has some limitations. An important limitation has to do with the difficulties of detecting effect sizes in small group data sets, exposing the method to type II error. With few subjects in the SCI group, there was a high risk of neglecting consistent relationships among the studied variables. Another limitation concerns the heterogeneity inherent in the SCI and MCI concepts. Although an extensive screening procedure was used for the classification of

subjects, the groups may be overlapping and may contain, among other conditions, chronic ischemic disease, normal aging, early-stage AD, and non-AD predementia. Patients with major depressive episodes have been excluded. Still, a high variance in depression scores and high relationships between depressive symptoms and cognitive complaints suggest that some of the subjects could be included due to cognitive complaints related to their depressiveness. A cross-sectional study design may not be optimal since depressive disturbances can fluctuate and may not be present at every examination. The follow-up of the populations studied will help determine the long-term clinical significance of the results.

Conclusions

This study aims to improve early diagnosis of dementia by investigating correlates of cognitive complaints and cognitive test performance in SCI and MCI. Considering the question if cognitive complaints reflect actual performance, the results from this study demonstrate that patients with SCI, not satisfying clinical criteria for MCI, assess their cognitive abilities more correctly, while patients with MCI tend to underestimate their cognitive difficulties. Further, the findings shed light on the nature of cognitive complaints and cognitive impairment by demonstrating that depressive symptoms are associated with cognitive complaints, while degenerative changes (relating to pathological levels of CSF biomarkers) are associated with an objective cognitive decline in high-risk predementia states. The results of the present manuscript are preliminary and need further confirmation on larger, prospective samples.

Acknowledgements

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