

Progression to Dementia in Clinical Subtypes of Mild Cognitive Impairment

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Key Words

Mild cognitive impairment · Mild cognitive impairment, follow-up · Mild cognitive impairment, prognosis · Dementia, clinical subtypes of MCI

Abstract

Objective: To examine the outcome among patients diagnosed with different types of mild cognitive impairment (MCI). **Patients:** A follow-up examination (average follow-up period: 3.49 ± 2.2 years) was performed in 81 cognitively impaired, non-demented patients aged >55 years at baseline. **Results:** 8 of 32 patients with amnesic MCI (25%), 22 of 41 patients with multiple-domain MCI (54%), and 3 of 8 patients with single non-memory MCI (37.5%) progressed to dementia. The clinical type of MCI is significantly associated with the likelihood of conversion to dementia. **Discussion:** When the clinical syndrome of MCI evolves on a neurodegenerative basis, the multiple-domain type of MCI has a less favorable prognosis than the amnesic type and may represent a more advanced prodromal stage of dementia.

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Introduction

In recent years the concept of mild cognitive impairment (MCI) has become increasingly popular. It has been conceptualized as a transitional state between the cognition and functional ability of normal aging and that of

mild dementia [1]. It is a heterogeneous clinical entity [2]. As suggested by an international working group, MCI can be divided into three clinical types according to the profile of the cognitive deficits: amnesic, multiple-domain, and single non-memory types [2]. The amnesic type refers to individuals who present with subjective memory complaint, preferably corroborated by an informant, and have an objective memory impairment compared with age and education norms, but perform reasonably well on indexes of general cognitive function and have generally preserved activities of daily living. When this form of MCI is on a degenerative basis, the vast majority of cases will progress to dementia. The multiple-domain variant involves subjects who exhibit subtle impairment in more than one cognitive domain, which is not severe enough to justify a diagnosis of dementia. MCI can also present as impairment in a single cognitive domain other than memory. Single non-memory MCI is characterized by an isolated decline of executive function, visuospatial processing, or language.

In patients selected by clinical criteria alone, the clinical syndrome MCI may be caused by many underlying conditions such as Alzheimer's disease (AD), cerebrovascular diseases, frontotemporal dementia, Lewy body dementia, primary progressive aphasia or depression. Consequently, some individuals fulfilling MCI criteria do not progress to dementia and remain stable or even improve with time, so that the prognosis of individual MCI patients can be highly variable [2, 3]. ¹⁸F-FDG positron emission tomography (PET) assessment of cerebral glu-

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cose metabolism, as a measure of synaptic activity, can identify the presence and localization of neurodegenerative processes in the brain. It has been shown to be a valuable aid in the diagnosis and differential diagnosis of pre-clinical and clinical syndromes with cognitive deficits [4–9]. The consistent set of brain regions that are affected in prodromal AD are hippocampal complex, anterior and posterior cingulate and the inferior parietal cortex.

Several studies have been undertaken to follow-up the natural course of MCI and to determine the conversion to dementia among MCI subjects. For the progression from MCI to dementia, rates between 10–15% over 1 year [10, 11] and 19–66% over 3–5 years [12–15] have been reported, depending on diagnostic criteria and patient selection (e.g. clinic-, community- or population-based studies). The incidence of dementia in healthy elderly individuals is significantly lower (1–2% per year) [10]. Therefore, patients with MCI represent a risk group for dementia and at least a proportion of these subjects have an incipient dementing process [16].

Although elderly individuals with MCI generally have an increased risk of dementia compared to cognitively unimpaired individuals of a comparable age [17], the three major subtypes of MCI may be associated with different outcomes [18, 19]. The rates of progression to dementia mentioned above for patients with MCI may only be valid for amnesic MCI, since a memory predominant set of criteria was used in these studies [2]. A previous study on the prognosis of MCI found a higher progression rate to dementia at 2 years for multiple-domain MCI (30%) compared with amnesic MCI (24%) or single domain non-memory MCI (4%) [20]. The notion of a multiple cognitive systems breakdown is consistent with data that conversion rates to AD over 3 years are considerably greater for patients with deficits in episodic memory and some other cognitive domain (e.g. verbal ability, visuospatial skill) at baseline than for those who have isolated memory deficits [21]. The study of Bozoki et al. [22] also showed that in a sample of non-demented elderly patients, those presenting memory loss alone rarely progressed to dementia, while the risk of developing dementia in those presenting impairments in other cognitive areas beyond memory loss was multiplied by eight.

The objective of this follow-up study was to examine the outcome among patients diagnosed with amnesic MCI, multiple-domain MCI and single non-memory domain MCI, as diagnosed by history, neurological, psychopathological findings, neuropsychological, cognitive and neuroimaging findings.

Patients and Methods

Patients

The patient register of the outpatient unit for cognitive disorders of the Department of Psychiatry, Technische Universität München, was screened for subjects who had been diagnosed with MCI between 1994 and 2003 and fulfilled the following inclusionary criteria at baseline examination: age >55 years, cognitive impairment affecting at least one cognitive domain (memory, language, attention or visuospatial processing), preserved basic activities of daily living according to an informant report, structural brain imaging (CT or MRI) and cranial ¹⁸F-FDG PET imaging. Exclusionary criteria were: diagnosis of dementia at baseline according to ICD-10 criteria [23]; baseline MMSE score <22; presence at baseline of an identifiable cause of cognitive impairment, such as use of medication known to alter cognitive abilities or a significant medical, neurological or psychiatric illness (e.g. major depression, seizure disorder, head injury, Parkinson's disease). Patients who fulfilled these selection criteria were contacted first with an invitation letter and then were phoned and asked for participation in a follow-up examination. Of 172 MCI patients traced, 91 either had moved, or had died, or refused to participate. We did not check the death certificates and medical records of the subjects that had died, since dementia is consistently underreported in clinical records and death certificates [24]. 81 subjects agreed to participate. Of these, 76 were examined in person, and 5 were examined over the telephone. The average follow-up period was 3.49 ± 2.2 (mean \pm SD) years (range 0.7–10.42 years).

Baseline Examination

At baseline, patients had undergone a standardized diagnostic procedure which had included the following assessments: history taken from the patient and from an informant; medical, neurological and psychiatric examination; global neurocognitive evaluation using the Mini-Mental State Examination (MMSE) and in a number of patients using the neuropsychological battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-NP) [25–30], which includes the MMSE and the clock-drawing test [31]; rating of the overall severity of cognitive deficits using the Clinical Dementia Rating (CDR) [32, 33]; structural brain imaging (CT or MRI) and ¹⁸F-FDG PET, and routine laboratory screening. The laboratory screening had included a chemistry group, complete blood cell count, blood glucose, vitamin B₁₂ and folic acid levels, basic thyroid hormone level, syphilis serological testing and Lyme borreliosis serological testing.

MCI had been diagnosed at baseline examination if patients had had: (1) an impairment in at least one of the following cognitive domains: memory, language, attention or visuospatial processing; (2) preserved basic activities of daily living; (3) no dementia according to ICD-10 criteria, and (4) CDR of 0.5 (questionable dementia).

MCI patients were retrospectively divided into the three clinical types according to the profile of their cognitive deficits, as documented by the neurocognitive evaluation and by the clinical judgment of the clinician [34]. Patients were classified as amnesic MCI if they had memory impairment, but were performing well on other cognitive domains. Patients were categorized as multiple-domain MCI if they had impairments in two or more cognitive areas. Patients were classified as single non-memory MCI if they had an isolated impairment in a single domain other than memory and not significant decline of memory.

Individual PET data had been screened for findings suggestive of AD with using the automated image analysis procedure NeuroStat [8]. After stereotactical normalization of the PET images, this program performs an observer-independent statistical comparison to an age-matched reference database. The patients were divided according to localization and severity of cerebral glucose metabolic deficits at baseline into the following groups: without metabolic abnormalities; non-significant hypometabolism in AD-typical regions; hypometabolism in AD-typical regions; inhomogeneous cerebral metabolism with multifocal abnormalities suggestive of ischemic lesions and not sufficient for the diagnosis of a degenerative disease.

Follow-Up Examination

The major objective of the follow-up examination was to determine the diagnostic status of the study participants (cognitively unimpaired, MCI, or dementia). Personal examinations included a history from the patient and from an informant; assessment of activities using the informant-rated Bayer-Activities of Daily Living Scale (B-ADL) [35]; medical, neurological and psychiatric examination; cognitive evaluation using the CERAD-NP, and rating of the overall severity of cognitive deficits using the CDR. Five study participants were examined over the telephone using the Telephone Modified Mini-Mental State Exam T3MS [36], which our team had translated from the original English version. The test consists of 34 items. The maximum T3MS score is 100. The T3MS was validated against an expert diagnosis based on a comprehensive diagnostic workup and was compared with standard in-person cognitive examinations. Following the diagnostic criteria of the ICD-10 classification of mental and behavioral disorders for dementia, the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for the diagnosis of AD [37] and of Petersen et al. for the diagnosis of MCI [2], scores <85 characterize dementia and scores between 89 and 85 characterize MCI. In the distinction between MCI patients and cognitively unimpaired individuals, the T3MS achieved a sensitivity of 82% and specificity of 100%. In the separation between cognitively unimpaired participants and patients with mild dementia the T3MS achieved a sensitivity and specificity of 100% [38].

MCI was diagnosed at follow-up examination if patients had: (1) an impairment in at least one cognitive domain (memory, language, attention or visuospatial processing); (2) preserved basic activities of daily activities; (3) no dementia according to ICD-10 criteria, and (4) a CDR score of 0.5. The diagnosis of dementia at follow-up was based on ICD-10 criteria.

Statistical Analyses

Descriptive statistics were applied to demographic variables. Baseline differences with regard to demographic variables and baseline MMSE score between the patients who were followed up and those who were not were tested using χ^2 or t tests. The baseline differences with regard to the mentioned variables and to the length of follow-up period among the three MCI groups were tested using one-way ANOVA; single comparisons were performed using Scheffé's test. A multivariable logistic regression was performed to investigate the influence of age, gender, length of the follow-up period, MCI clinical type and baseline level of global impairment (MMSE score) on converting to dementia. Analyses were performed using the Statistical Package for Social Sciences Version 12 (SPSS-12) for Windows (SPSS Inc., Chicago, Ill., USA).

Table 1. Demographic variables, initial MMSE scores and length of follow-up interval by MCI group (mean \pm SD)

Variable	Amnesic MCI	Multiple-domain MCI	Single non-memory MCI
n	32	41	8
Age, years	65.4 \pm 8.6	67.3 \pm 9.8	61.9 \pm 11.8
Sex: female, %	37.5	36.6	37.5
MMSE score	27.6 \pm 1.6	26.6 \pm 2.0	28.3 \pm 0.7
Follow-up interval, years	4.1 \pm 2.5	3.2 \pm 2.0	2.8 \pm 1.4

Results

Of 172 potential study participants, 81 agreed to participate. There were no statistically significant differences on age and initial MMSE scores between patients that were followed up and those who were not. Demographic variables, initial MMSE scores and length of follow-up interval for the 3 MCI subgroups are shown in table 1. Patients with single non-memory MCI were 5 years younger than the remaining participants, but this difference did not attain statistical significance. The difference of MMSE scores at baseline between the group of patients with multiple-domain MCI and the patients with single non-memory MCI tended to be statistically significant ($p = 0.056$). The mean initial MMSE score of the multiple-domain MCI group and that of the amnesic MCI group did not differ significantly ($p = 0.066$). No differences were found among the MCI groups in any other variable ($p > 0.05$). The single comparison between the length of the follow-up intervals of the amnesic MCI and of the multiple-domain MCI group, performed using Scheffé's test, did not show any significant differences ($p = 0.28$). No differences in demographic variables, initial MMSE scores, and length of followed-up interval were found between subjects who underwent CERAD-NP neuropsychological evaluation at baseline and participants who were examined with the MMSE only ($p > 0.05$). Across the 3 MCI subgroups the mean follow-up interval was 3.49 (SD 2.2 years).

According to the ^{18}F -FDG PET assessment of cerebral glucose metabolism at baseline, 15 of 32 patients with amnesic MCI, 21 of 41 patients with multiple-domain MCI and 4 of 8 subjects with non-memory MCI had metabolic abnormalities in AD-typical regions. There were no sufficiently diagnosed metabolic abnormalities indicating a degenerative other than AD (table 2).

Table 2. Cerebral glucose metabolism in the subjects of the three MCI groups at baseline

Cerebral metabolism	Amnestic MCI	Multiple-domain MCI	Single non-memory MCI
Without metabolic abnormalities	11	11	2
Inhomogeneous cerebral metabolism	6	9	2
Non-significant hypometabolism in AD-typical regions	12	11	3
Hypometabolism in AD-typical regions	3	10	1

Table 3. Diagnostic status of the subjects of the MCI groups at the point of the follow-up examination

MCI groups	New diagnosis			total
	NCI	MCI	dementia	
Amnestic MCI	8	16	8	32
Multiple-domain MCI	7	12	22	41
Single non-memory MCI	0	5	3	8
All patients	15	33	33	81

Table 4. Results of the multivariable logistic regression analysis of factors associated with progression to dementia

Variable	Regressions' coefficient	d.f.	p value
Age	0.044	1	0.133
Gender	0.194	1	0.732
Interval	0.014	1	0.170
MCI type	1.132	1	0.045
MMSE score	-0.322	1	0.039
Constant	2.611	1	0.616

During the follow-up period, 8 of 32 patients with amnestic MCI (25%), 22 of 41 patients with multiple-domain MCI (54%), and 3 of 8 patients with single non-memory MCI (37.5%) progressed to dementia. No cognitive deficits were diagnosed at follow-up in 8 patients with amnestic MCI and 7 with multiple-domain MCI. Due to the limited number of subjects with single non-memory MCI at baseline, this group of patients was not included in the statistical analysis. The cognitive status of the participants at the point of the follow-up examination is shown in table 3 and in figure 1. The difference between the patients of the amnestic MCI group and the patients

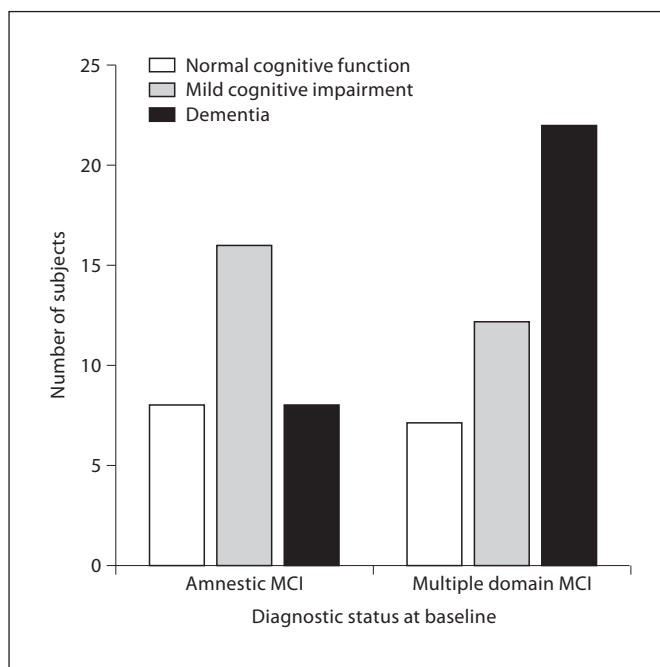


Fig. 1. Diagnostic status at the point of the follow-up examination of the subjects with amnestic and multiple-domain MCI at baseline.

with the multiple-domain MCI group who progressed to dementia is statistically significant ($\chi^2 = 6.098$, d.f. = 1, $p < 0.014$).

The results of the multivariable logistic regression analysis revealed the MCI type to be a significant predictor of conversion to dementia (d.f. = 1, $p = 0.045$). The other significant predictor in the model was the MMSE score (d.f. = 1, $p = 0.039$) (table 4).

Discussion

The concept of prodromal dementia was rediscovered in recent years in studies investigating the border zone between normal aging and mild dementia. The MCI concept covers a heterogeneous group of patients and it is an unanswered question whether subgroups of MCI could be separated, and whether these subgroups differ with regard to future outcome. The major objective of the present study was to examine the outcome among patients diagnosed with amnesic MCI, multiple-domain MCI and single non-memory domain MCI.

While there is good agreement on the concept of MCI, there is considerable variability concerning the specific diagnostic criteria, and there is still no common consensus on them. We considered MCI in a broad clinical context, according to which MCI is a clinical entity between normal cognitive function and mild dementia. We implemented diagnostic criteria based on a more general approach to the diagnosis of MCI and not restricted to the amnesic clinical presentation of the syndrome. The criteria we used referred not only to memory deficits, but also to impairments in other cognitive domains. The definition used in the present study resembles in fact the new recommendations for the general criteria for MCI, which do not exaggerate the role of memory disturbances, as the old criteria proposed by Petersen et al. [2, 39] did.

Memory complaints were not included in the criteria for the diagnosis of MCI in this study, since the self-perception of memory troubles had been proved to be the most problematic criterion of the criteria of Petersen et al., because they are less obvious to define [3]. Furthermore, according to the data of a large population-based study with 1,435 participants, about half of the people who developed dementia had not reported memory complaints in the pre-clinical phase, due to the fact that many elderly people regard memory deficits as part of normal aging [24]. Another work suggested that self-reported memory impairments may be more closely related to the presence of depressive symptomatology than to objective cognitive deficits [40].

The diagnosis of MCI and dementia in this study was based on the physician's clinical judgement. Since excessive reliance on neuropsychological data in the absence of clinical judgement can lead to exaggerated inclusion of patients into the MCI cohort [41, 42], it is important to underline that the diagnoses were made both at baseline and follow-up on a clinical basis. While the neurocognitive examination and brain imaging were supportive of the clinicians' judgement, the final diagnosis was rendered by a clinician.

The neuropsychological test results at baseline showed that patients with multiple-domain MCI had a slightly greater cognitive impairment than patients with other MCI types as documented with MMSE [20]. The difference however did not attain statistic significance. The mean initial MMSE score of the multiple-domain MCI subjects was one point lower than the mean initial MMSE score of the amnesic MCI group. Despite this difference, the multivariable logistic regression revealed that MCI type is an independent significant predictor of progression to dementia. Nevertheless, verifying the outcome among MCI subgroups without differences in the initial MMSE performance should be a task for future studies.

In spite of the similarities on demographic data (age, gender) and on the length of the follow-up period, the proportion of patients diagnosed with multiple-domain MCI type who had already developed dementia at the time of the follow-up was higher than the proportions of the two other MCI types and significantly higher than that of amnesic MCI. A higher probability of conversion to dementia of the multiple-domain MCI type, which we found, has also been reported by others [20–22, 24]. Our findings are in accordance with previous studies which have shown that the cognitive profile of patients in the prodementia stage is characterized by impairments in multiple domains [43–45].

MCI patients in our study showed a heterogeneous pattern of mild disturbances in different cognitive areas and functional imaging results. This heterogeneity suggested that we were either dealing with several underlying conditions which are associated with different clinical phenotypes at the clinical stage of MCI, or with a single common disease entity which can have different clinical manifestations at this degree of severity, or a mixture of both. Taking into consideration the relative frequency of neurodegenerative diseases in the population at the age of our sample, as well as the localization and the degree of the cerebral glucose metabolic deficits, however, the assumption of a single common disease (AD) with large phenotypic variability is a probable, but not the only explanation. An MCI type with impairments in multiple domains which evolves on the degenerative basis of AD is probably an advanced clinical presentation of a process, progressing to dementia. This multiple-domain MCI of degenerative nature could be possibly conceptualized as an intermediate state between amnesic MCI and mild dementia.

Our results confirm that the clinical syndrome of MCI has a variable prognosis. 18.5% of the MCI subjects returned to normal. Under the hypothesis that MCI is in all

cases an intermediate stage before dementia or AD, this finding is unexpected and it does underline the heterogeneity of the concept of MCI. One possible explanation is that some of these subjects were depressed at baseline and both the depression and the depression-induced cognitive impairment resolved over the interval. This explanation seems unlikely because major depression was an exclusionary criterion. Another explanation is that a subset of MCI patients may have a fundamentally different response to the process that in others rapidly evolves to dementia, such as resistance to disease or a better ability to compensate for deficits. Further studies are needed to determine the underlying causes of the different responses or the different disease processes.

The design of this study has some shortcomings. Firstly, at the baseline examination a part of the participants was neuropsychologically examined only with MMSE. However, there were no statistically significant differences in demographic and clinical variables between the subjects who underwent at baseline a neuropsychological evaluation with CERAD-NP and the subjects that were neuropsychologically examined only with MMSE.

Secondly, our study was conducted on a sample of subjects recruited in a specialized outpatient unit. Our sample was highly selected and may not be representative of the general population of MCI patients. Therefore, an extrapolation of our findings to the general population of subjects with MCI is problematic.

Thirdly, the follow-up examination of 5 participants was performed over the telephone using the Telephone Modified Mini Mental State Exam, which our group translated in German and validated in a study with 48 participants.

Moreover, the small size of the single non-memory MCI group, which could have affected the power of the analysis, was excluded from the statistical analysis. Thus we were not in the position to compare the prognosis of this MCI group with the other MCI types.

Finally, the effect of psychosocial and pharmacological interventions was not addressed. The effect of the treatment of 21 participants with cholinesterase inhibitors and of 3 participants with medication controlling vascular risk factors was not taken into consideration. However, there is no convincing evidence to date that nutritional supplements or medications (e.g. non-steroidal anti-inflammatory drugs, cholinesterase inhibitors) or more recently identified risk factors (e.g. homocysteine plasma level) have any effect on the conversion rate to dementia in the MCI patients [46].

In conclusion, this study demonstrates that amnesic MCI has a more favorable prognosis than the multiple-domain type of MCI when the syndrome evolves on the degenerative basis of AD, and that MCI type may be useful for predicting the clinical outcome of MCI patients. According to our findings, patients with multiple-domain MCI have a higher risk of developing dementia than subjects with amnesic MCI. It remains important to examine the prognosis of the single non-memory MCI type and to compare it with the prognosis of the other MCI groups. The results of the current study are based on a relatively small population. However, the results are plausible and promising, and contribute both to the discussion of defining MCI types and to the discussion concerning the outcome of the different MCI types. Our findings inspire the need for further studies with longer follow-up periods and larger samples of patients with MCI, since cognitive impairments are in many cases not benign and should not be dismissed as a normal feature of aging. Nevertheless, MCI and MCI types remain a research construct and the outcome of MCI includes not only the possibility of progression to dementia, but also the possibility of clinical stability, or of reverting to normal. Under the light of the above-mentioned uncertainties, concerning the variability of outcome of MCI and of the still ongoing debate on defining MCI, separating MCI subjects into subgroups is based principally on the clinical phenotypes. The role of the contribution of the different underlying etiologies to the heterogeneous clinical phenotypes and to the prognosis of MCI subtypes does still remain an unanswered question.

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