Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2006;22:27–34
DOI: 10.1159/000093101

Accepted: January 16, 2006
Published online: May 4, 2006

Progression to Dementia in Clinical Subtypes of Mild Cognitive Impairment

P. Alexopoulos[a, b] T. Grimmer[a] R. Perneczky[a] G. Domes[b] A. Kurz[a]

[a]Department of Psychiatry and Psychotherapy, Technische Universität, München, and [b]Department of Psychiatry and Psychotherapy, Universität Rostock, Rostock, Germany

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 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. 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 amnestic type and may represent a more advanced prodromal stage of dementia.

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: amnestic, multiple-domain, and single non-memory types [2]. The amnestic 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]. ^{18}F-FDG positron emission tomography (PET) assessment of cerebral glu-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1420–8008/06/0221–0027$23.50/0

Accessible online at:
www.karger.com/dem

Dr. med. Panos Alexopoulos
Klinik und Poliklinik für Psychiatrie und Psychotherapie, Universität Rostock
Gehlsheimer Strasse 20
DE–18147 Rostock (Germany)
Tel. +49 381 494 9501, Fax +49 381 494 9502, E-Mail palexopoulos@freemail.gr

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 preclinical 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 amnestic 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 amnestic 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 amnestic 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 ^{18}F-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 ± 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 ^{18}F-FDG PET, and routine laboratory screening. The laboratory screening had included a chemistry group, complete blood cell count, blood glucose, vitamin B_{12} 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 amnestic 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 that 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 ± SD)

Variable	Amnestic MCI	Multiple-domain MCI	Single non-memory MCI
n	32	41	8
Age, years	65.4±8.6	67.3±9.8	61.9±11.8
Sex: female, %	37.5	36.6	37.5
MMSE score	27.6±1.6	26.6±2.0	28.3±0.7
Follow-up interval, years	4.1±2.5	3.2±2.0	2.8±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 amnestic 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 amnestic 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 amnestic 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			
	NCI	MCI	dementia	total
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' coefficiency	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

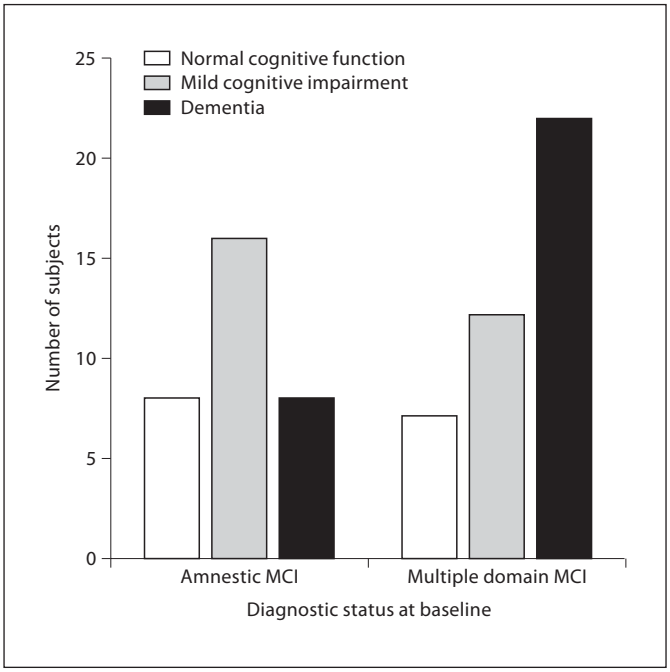

Fig. 1. Diagnostic status at the point of the follow-up examination of the subjects with amnestic and multiple-domain MCI at baseline.

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 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 amnestic 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 amnestic 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 preclinical 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 amnestic 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 amnestic 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 predementia 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 amnestic 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 amnestic 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 amnestic 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.

Acknowledgement

We would like to thank J. Nantke, Department of Psychiatry and Psychotherapy, Universität Rostock, Germany, for her advice and support in the statistical analysis.

References

1 American Psychiatric Association: Diagnostic and Statistical Manual of Mental disorders, ed 4. Washington, APA, 1994.

2 Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B: Current concepts in mild cognitive impairment. Arch Neurol 2001;58: 1985–1992.

3 Larrieu S, Letenneur L, Orgogozo JM, Fabrigoule C, Amieva H, Le Carret N, Barberger-Gateau P, Dartigues JF: Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. Neurology 2002;59:1594–1599.

4 Drzezga A, Lautenschlager N, Siebner H, Riemenschneider M, Willoch F, Minoshima S, Schwaiger M, Kurz A: Cerebral metabolic changes accompanying converse of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. Eur J Nucl Med Mol Imaging 2003;30:1104–1113.

5 Guze BH, Baxter LR Jr, Schwartz JM, Szuba MP, Mazziotta JC, Phelps ME: Changes in glucose metabolism in dementia of the Alzheimer type compared with depression: a preliminary report. Psychiatry Res 1991;40:195–202.

6 Ibach B, Poljansky S, Marienhagen J, Sommer M, Manner P, Hajak G: Contrasting metabolic impairment in frontotemporal degeneration and Alzheimer's disease. Neuroimage 2004; 23:739–743.

7 Arnaiz E, Jelic V, Almkvist O, Wahlund LO, Winblad B, Valind S, Nordberg A: Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in mild cognitive impairment. Neuroreport 2001;12:851–855.

8 Minoshima S, Frey KA, Koeppe RA, Foster NL, Kuhl DE: A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluoride-18-FDG PET. J Nucl Med 1995;36:1238–1248.

9 Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE: Metabolic reductions in the posterior cingulate cortex in very early Alzheimer's disease. Ann Neurol 1997;42:85–94.

10 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E: Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308.

11 Daly E, Zaitchik D, Copeland M, Schmahmann J, Gunther J, Albert M: Predicting conversion of Alzheimer's disease using standard clinical information. Arch Neurol 2000;57: 675–680.

12 Flicker C, Ferris S, Reisberg B: Mild cognitive impairment in the elderly: predictors of dementia. Neurology 1991;41:1006–1009.

13 Rockwood K, Wentzel C, Hachinski V, Hogan DB, MacKnight C, McDowell I: Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. Neurology 2000;54:447–451.

14 Kluger A, Ferris SH, Golomb J, Mittelman MS, Reisberg B: Neuropsychological prediction of decline to dementia in nondemented elderly. J Geriatr Psychiatry Neurol 1999;12:168–179.

15 Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, Berg L: Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 2001;58:397–405.

16 Tuokko H, Frerichs R, Graham J, Rockwood K, Kristjansson B, Fisk J, Bergman H, Kozma A, McDowell I: Five-year follow-up of cognitive impairment with no dementia. Arch Neurol 2003;60:577–582.

17 Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST: Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1133–1142.

18 Petersen RC: Mild cognitive impairment: Transition between aging and Alzheimer's disease. Neurologia 2000;15:93–101.

19 Celsis P: Age-related cognitive decline, mild cognitive impairment or preclinical Alzheimer's disease? Ann Med 2000;32:6–14.

20 Rasquin SM, Lodder J, Visser PJ, Lousberg R, Verhey FR: Predictive accuracy of MCI subtypes for Alzheimer's disease and vascular dementia in subjects with mild cognitive impairment: a 2-year follow-up study. Dement Geriatr Cogn Disord 2005;19:113–119.

21 Backman L, Jones S, Berger AK, Laukka EJ, Small BJ: Multiple cognitive deficits during transition to Alzheimer's disease. J Intern Med 2004;256:195–204.

22 Bozoki A, Giordani B, Heidebrink JL, Berent S, Foster NL: Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. Arch Neurol 2001; 68:411–416.

23 Dilling H, Mombour W, Schmidt MH, Schulte-Markwort E (eds): Weltgesundheitsorganisation: Internationale Klassifikation psychischer Störungen, ICD-10 Kapitel V (F) Forschungskriterien. Bern, Huber, 1994.

24 Palmer K, Baeckman L, Winblad B, Fratiglioni L: Detection of Alzheimer's disease and dementia in the preclinical phase: population-based cohort study. BMJ 2003;326:245–249.

25 Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, Mellits ED, Clark C: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989;29:1159–1165.

26 Morris JC, Edland S, Clark C, Galasko D, Koss E, Mohs R, van Belle G, Fillenbaum G, Heyman A: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). IV. Rating of cognitive change in the longitudinal assessment of probable Alzheimer's disease. Neurology 1993;43:2457–2465.

27 Welsh K, Butters N, Hughes J, Mohs R, Heyman A: Detection of abnormal memory decline in mild cases of Alzheimer's disease using CERAD neuropsychological measures. Arch Neurol 1991;48:278–281.

28 Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, Heyman A: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). V. A normative study of the neuropsychological battery. Neurology 1994;44:609–614.

29 Thalmann B, Monsch AU, Schneitter M, et al: CERAD-Neuropsychological battery – A minimal data set to be used as a common assessment tool of dementia. Neurobiol Aging 1998;19:9.

30 Thalmann B, Monsch AU, Schneitter M, et al: The CERAD neuropsychological assessment battery (CERAD-NAB): a minimal data set as a common tool for German-speaking Europe. Neurobiol Aging 2000;21:20.

31 Shulman KI, Shedletsky R, Silver IL: The challenge of time: clock-drawing and cognitive function in the elderly. Int J Geriatr Psychiatry 1993;1:135–140.

32 Morris JC: The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–2414.

33 Morris JC, Ernesto C, Schafer K, Coats M, Leon S, Sano M, Thal LJ, Woodbury P: Clinical Dementia Rating training and reliability in multicenter studies: the Alzheimer's Disease Cooperative Study experience. Neurology 1997;48:1508–1510.

34 Petersen R (ed): Conceptual Overview. Mild Cognitive Impairment, Aging to Alzheimer's Disease. Oxford, Oxford University Press, 2003.

35 Hindmarch I, Lehfeld H, de Jongh P, Erzigkeit H: The Bayer Activities of Daily Living (B-ADL) Scale. Dement Geriatr Cogn Disord 1998;9(suppl 2):20–26.

36 Norton MC, Tschanz JA, Fan X, Plassman BL, Welsh-Bohmer KA, West N, Wyse BW, Breitner JC: Telephone adaptation of the modified Mini-Mental State Exam (T3MS). The Cache County Study. Neuropsychiatry Neuropsychol Behav Neurol 1999;12:270–276.

37 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939–944.

38 Alexopoulos P, Perneczky R, Cramer B, Grimmer T, Kurz A: Validation of a short telephone test (T3MS) for the diagnosis of cognitive impairment (in German). Fortschr Neurol Psychiatr. DOI: 10.1055/s-2005-915568.
39 Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC: Mild cognitive impairment – beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. J Intern Med 2004;256:240–246.
40 Schmand B, Jonker C, Geerlings MI, Lindeboom J: Subjective memory complaints in the elderly: depressive symptoms and future dementia. Br J Psychiatry 1997;171:373–376.
41 Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC: Subclassifications for mild cognitive impairment: prevalence and predictive validity. Psychol Med 2003;33:1029–1038.
42 Fisk JD, Merry HR, Rockwood K: Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. Neurology 2003;61:1179–1184.
43 Ritchie K, Touchon J: Mild cognitive impairment: conceptual basis and current nosological status. Lancet 2000;355:225–228.
44 Wentzel C, Rockwood K, MacKnight C, Hachinski V, Hogan DB, Feldman H, Ostbye T, Wolfson C, Gauthier S, Verreault R, McDowell I: Progression of impairment in patients with vascular cognitive impairment without dementia. Neurology 2001;57:714–716.
45 Ingles JL, Wentzel C, Fisk JD, Rockwood K: Neuropsychological predictors of incident dementia in patients with vascular cognitive impairment without dementia. Stroke 2002;33:1999–2002.
46 Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, Galasko D, Jin S, Kaye J, Levey A, Pfeiffer E, Sano M, van Dyck CH, Thal LJ, Alzheimer's Disease Cooperative Study Group: Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352:2379–2388.