

Predictive Accuracy of MCI Subtypes for Alzheimer's Disease and Vascular Dementia in Subjects with Mild Cognitive Impairment: A 2-Year Follow-Up Study

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Key Words

Mild cognitive impairment · Predementia stage · Vascular dementia · Alzheimer's dementia · Diagnostic criteria

Abstract

Aim: The aim of this study was to investigate the prognostic accuracy of different subtypes of mild cognitive impairment (MCI): amnesic MCI, multiple domain MCI, and single non-memory domain MCI, for the development of Alzheimer's dementia (AD) and vascular dementia (VaD). **Patients:** Nondemented patients from a memory clinic cohort (n = 118), and a stroke cohort (n = 80, older than 55 years and with a cognitive impairment). **Results:** 'Multiple domain MCI' had the highest sensitivity for both AD (80.8%) and VaD (100%), and 'amnesic MCI' had the highest specificity (85.9% for AD, 100% for VaD). The positive predictive value was low for all subtypes (0.0–32.7%), whereas the negative predictive value was high (72.8–100%). **Discussion:** The subtype 'multiple domain MCI' has high sensitivity in identifying people at risk for developing AD or VaD. The predictive accuracy of the MCI subtypes was similar for both AD and VaD.

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Introduction

Mild cognitive impairment (MCI) is a term referring to persons who do not fulfill criteria for dementia, but who exhibit some form of cognitive impairment. The most common causes of MCI are age-related cognitive impairment, the predementia stages of Alzheimer's disease (AD), and vascular dementia (VaD). It has recently been proposed that specific subtypes of MCI may be useful to distinguish between these three conditions [1]. For example, subjects with isolated memory impairment (amnesic MCI) may be at increased risk of developing AD, while subjects with impairments in multiple cognitive domains (multiple domain MCI) may be at increased risk of developing VaD, and patients with a single non-memory domain impairment may be at increased risk of developing frontotemporal lobe dementia [1]. This proposal has not yet been tested in a clinical setting, but a recent population-based study failed to find support for the proposal [2].

The aim of the present study is to investigate whether 'amnesic MCI', 'multiple domain MCI', and 'single non-memory domain MCI' are diagnostic entities for the predementia stage of AD and VaD in two separate cohorts (memory clinic and stroke cohort) of subjects with MCI.

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Table 1. Cognitive domains, tests used and definition of impairment

Domains	Test	Impairment
Memory	AVLT, total words direct recall and delayed recall	score \leq 10 th percentile
Executive functioning	mean interference score SCWT, CST or TMT	score \leq 10 th percentile
Calculation	GIT	score \leq 10 th percentile
Visuospatial	GIT	score \leq 10 th percentile
Orientation	MMSE items 1 and 2 (place, person, time)	score \leq 8
Attention	MMSE item 4 (serial 7's)	score \leq 4
Praxis	MMSE item 11 (copying)	score = 0
Language	MMSE items 6, 7, 8, 9, 10 (understanding, expression, writing)	score \leq 6
Mental speed	SCWT I, CST I and II or TMT I and II	score \leq 10 th percentile

AVLT = Auditory Verbal Learning Test; SCWT = Stroop Color Word Test; CST = Concept Shifting Test; TMT = Trail Making Test; GIT = Groninger Intelligence Test; MMSE = Mini Mental State Examination.

Interference score: part III – mean (part I + part II).

As there is controversy about the emphasis of an (isolated) memory impairment in the concept MCI [3–5], we further subdivided the subtype ‘multiple domain MCI’ into: ‘multiple domain MCI with memory impairment included’ (memory+) and ‘multiple domain MCI with memory impairment excluded’ (memory–).

Patients and Methods

Patients

Two clinical cohorts of nondemented, cognitively impaired subjects were available for this study: a cohort of patients with memory complaints who contacted the Memory Clinic of the University Hospital Maastricht, and a cohort of first-ever stroke patients from the stroke unit of the same hospital. Patients from the memory clinic cohort were participants of a longitudinal study of mild cognitive impairment, which started in 1990 [6]. The stroke patients were participants of a longitudinal study called CODAS (Cognitive Disorders after Stroke) [7–9].

Inclusion criteria for this study were: age older than 55 years, a cognitive impairment affecting at least 1 out of 9 cognitive domains (see below), no interference with daily activities (based on a questionnaire for the informant), and follow-up longer than 2 years. Exclusion criteria were dementia at baseline (defined according to DSM-IV), an MMSE score $<$ 15 (to ensure valid neuropsychological testing), and the presence of any somatic or psychiatric disorder that could be related to the cognitive impairment, except a first-ever stroke in the CODAS cohort. Patients from the memory clinic cohort were excluded if they had cerebrovascular disorders, defined by a score on the Hachinski Ischemic Scale of 5 or higher [10]. In the CODAS cohort, patients with a previous stroke or a stroke in the cerebellum or brainstem were excluded.

Patients from the MCI cohort who were excluded because the follow-up period was too short ($n = 44$) were older than the included patients, but MMSE scores, sex ratio and level of education were not different. Patients from the stroke cohort who were excluded because the follow-up period was too short ($n = 34$) were older and had lower baseline MMSE scores than the included patients, but sex ratios and level of education were not different.

Method

Patients from the longitudinal MCI study were tested at baseline and 24 months later. Patients from the CODAS study were tested at 1, 6, 12, and 24 months after stroke. This report used the data from the baseline and 24 months’ assessments.

Cognitive Domains

Table 1 presents the cognitive domains investigated. The neuropsychological tests used have been described extensively in earlier reports [7, 8, 11].

The choice of the domains studied was based on the criteria for VaD proposed by the National Institute of Neurological Disorders and Strokes – Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) [12]. ‘Memory’ was evaluated with the Auditory Verbal Learning Test [13]; ‘executive functioning’ with a combination of the interference score of the Stroop Color Word Test (SCWT) [14] and with the interference score of either the Concept Shifting Test (CST) [15] or the Trail Making Test (TMT) [16]; ‘calculation’ and ‘visuospatial abilities’ with subscales of the Groninger Intelligence Scale [17], and ‘orientation’, ‘attention’, ‘praxis’, and ‘language’ with subtests of the MMSE [18]. In addition to the 8 cognitive domains, we included also tests to assess ‘mental speed’, as this aspect may be of relevance according to previous studies [7, 19]. ‘Mental speed’ was evaluated with a combination of the scores of the first part of the SCWT [14] and with the scores on the first and second part of either the CST [15] or the TMT [16]. Both cohorts were administered the same neuropsychological battery with one exception: patients from the memory clinic cohort

Table 2. Demographic characteristics of the two cohorts

	Memory-clinic cohort	Stroke cohort
n	118	80
Age (mean, SD)	64.8 (7.5)	70.4 (7.8)*
Level of education, % low	23.7	56.3*
Sex, % female	48.3	55.0
MMSE score (mean, SD)	27.3 (2.2)	26.3 (2.4)*

* $p < 0.05$.

completed the TMT, whereas patients from the CODAS study completed the CST. Because the TMT and CST measure the same cognitive function and are highly correlated it was valid to assess the tests in each single cohort [15]. The performance of both cohorts was compared with that of a normative group from the Maastricht Aging Study [11]. The aim of this study was to investigate factors that predispose to normal cognitive aging in a cohort of healthy elderly volunteers from the southern part of the Netherlands. Normative data from this study were stratified according to age, sex, and educational level. Individual test scores were converted to standard Z scores, in order to define impairment in the cognitive functions, using the means and standard deviations of the normative data (test score patient – mean norm group)/SD norm group.

Diagnosis of Dementia

At 24 months, and without knowledge of the baseline data, two experienced clinicians independently evaluated patients regarding a diagnosis of dementia according to the DSM-IV criteria [20], based on available data, such as information about medical history, test performance, structured interview with an informant, and a clinical observation. Interference in daily activities due to cognitive impairments was evaluated by means of questionnaires about daily activities that were completed by the informant [21]. The diagnosis of AD was based on the National Institute for Neurological and Communicative Disorders and Stroke-Alzheimers Disease and Related Disorders Association (NINCDS-ADRDA) criteria and the diagnosis of VaD was based on the NINDS-AIREN criteria.

If there was a discrepancy in diagnosis a consensus meeting was arranged. If no consensus could be reached the patient was considered not demented. Agreement between the two clinicians was high ($\kappa = 0.88$; $p = 0.01$).

Diagnosis of MCI

MCI was defined if patients had: (1) an impairment in at least 1 of the 9 cognitive domains; (2) no interference in daily activities; (3) no dementia according to the DSM-IV. A cognitive impairment was defined as a score lower than the 10th percentile of the z scores, based on the norm scores, compared to the norm group (equivalent of 1.28 SD below the norm scores) or an MMSE score lower than 80% of the maximum score on the relevant scale.

The descriptions proposed by Petersen et al. [1] were used to subclassify MCI. Patients were classified as ‘amnesic MCI’ if they had a memory impairment, but were performing otherwise well (z score > 1.28 compared to the norm group) on other indexes of cognitive function. Patients were classified as ‘multiple domain MCI’ if they had impairments on 2 or more domains. This latter concept corre-

sponds with that of Cognitive Impairment No Dementia (CIND) [5, 22, 23]. Moreover we made a subclassification in ‘multiple domain MCI memory+’ if patients had impairments on 2 or more domains, one of which was memory impairment and ‘multiple domain MCI memory-’ if patients had impairments on 2 or more domains but no memory impairment. Patients were classified as ‘single non-memory domain MCI’ if they had an impairment in a single domain other than memory.

Statistical Analyses

Descriptive statistics were used for the demographic variables and the number of patients that became demented. Baseline differences between the two groups with regard to the number of cognitive impairments were tested with a chi-square test or t test. The validity and predictive value of MCI subtype as being diagnostic for the development of dementia were determined with sensitivity, specificity, and predictive values. Analyses were performed with the Statistical Package for Social Sciences version 10 (SPSS-10) for Macintosh.

Results

In total 118 patients from the memory clinic cohort and 80 patients from the stroke cohort were included in this study. Patients from the stroke cohort had a lower educational level, were older, and had lower baseline MMSE score than patients from the memory clinic cohort (table 2).

At baseline compared with patients from the memory clinic cohort, patients from the stroke cohort more often had an impairment in calculation ($\chi^2 = 16.3$, d.f. = 1, $p = 0.01$), visuospatial functioning ($\chi^2 = 14.3$, d.f. = 1, $p = 0.01$), attention ($\chi^2 = 8.8$, d.f. = 1, $p = 0.01$), language ($\chi^2 = 8.7$, d.f. = 1, $p = 0.01$), and praxis ($\chi^2 = 15.2$, d.f. = 1, $p = 0.01$), but less often an impairment in memory ($\chi^2 = 34.4$, d.f. = 1, $p = 0.01$) (fig. 1).

In both cohorts most patients (63.5 and 73.8%, respectively) had ‘multiple domain MCI’ (table 3).

In the memory clinic cohort, 26 patients were classified as demented (22.0%) at follow-up, all being diagnosed with AD according to the NINCDS-ADRDA. In the stroke cohort only 5 patients had dementia at follow-up (6.3%), all of whom were diagnosed with VaD according to the NINDS-AIREN criteria.

The sensitivity and specificity of the four MCI subtypes for the diagnosis of either AD or VaD 2 years later are presented in table 4. The subtype ‘multiple domain MCI’ had high sensitivity for the development of both AD and VaD. Specificity rates were highest for the amnesic type in both cohorts. For all MCI subtypes the positive predictive value was low (range 0.0–32.7%), but the negative predictive value was higher for all MCI subtypes (range 72.8–100%).

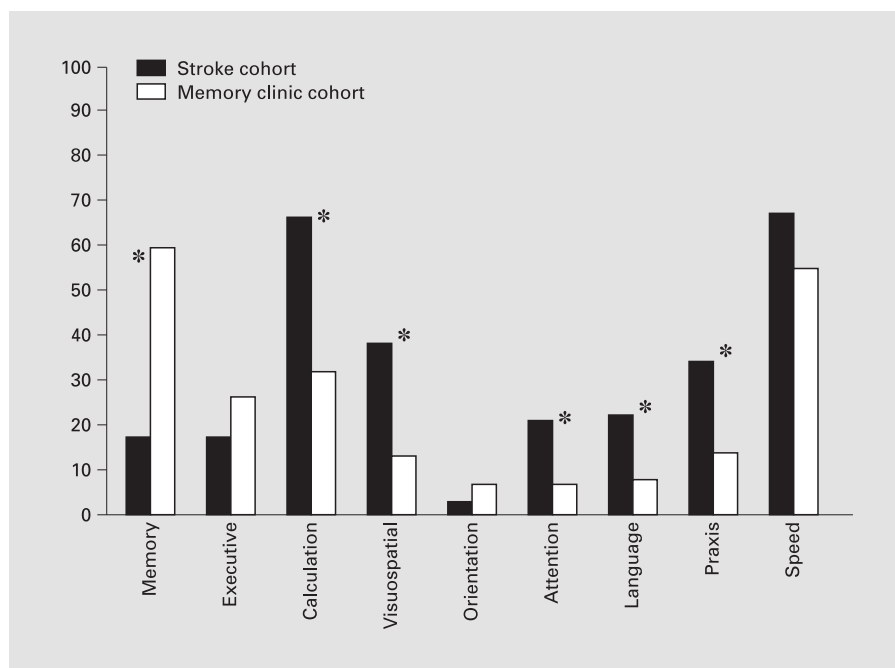


Fig. 1. Percentages of patients with an impairment.

Table 3. Distribution of patients according to different MCI subtypes

	Amnesic MCI	Multiple domains MCI			Single non-memory
		all	memory+	memory-	
Memory clinic cohort	17 (14.4%)	75 (63.5%)	52 (44.1%)	23 (19.5%)	26 (22.0%)
Without dementia at follow-up	13	54	35	19	25
With AD at follow-up	4	21	17	4	1
Stroke cohort	0	59 (73.8%)	13 (16.3%)	46 (57.5%)	21 (26.2%)
Without dementia at follow-up	0	54	11	43	21
With VaD at follow-up	0	5	2	3	0

To investigate which individual cognitive domain had the highest predictive value we did a post hoc analysis into the predictive values for the development of either AD or VaD of each separate domain. Orientation had the highest positive predictive value for the development of AD (PPV = 62.5%, CI = 0.29–0.96) and memory had the highest negative predictive value for the development of AD (NPV = 91.5%, CI = 0.84–0.99). For the development of VaD, attention had the highest positive predictive value (PPV = 18.0%, CI = 0.00–0.36), and both mental speed and executive functioning had the highest negative predictive value (NPV_{speed} = 100% CI = 1.0–1.0 and NPV_{executive} = 100%, CI = 1.0–1.0).

Discussion

This is the first study to establish the prognostic value of the different MCI subtypes in a clinical population [1]. In the memory clinic cohort, the ‘multiple domain MCI’ subtype was the most prevalent, and the ‘amnesic MCI’ subtype the least. This suggests that isolated memory impairment is rare and that the amnesic MCI subtype has limited applicability in clinical practice, unlike ‘multiple domain MCI’, which would appear to be a more relevant subtype [5]. Indeed, ‘amnesic MCI’ had a low sensitivity as a prognostic test for the development of AD, whereas ‘multiple domain MCI’ had a high sensitivity.

Table 4. Sensitivity and specificity for the four MCI subtypes for the development of either AD or VaD

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
<i>Memory clinic cohort</i>				
Amnesic MCI	15.4% (0.02–0.29)	85.9% (0.79–0.93)	23.5% (0.03–0.44)	78.2% (0.7–0.86)
Multiple domains all	80.8% (0.66–0.96)	41.3% (0.31–0.51)	28.0% (0.18–0.38)	88.4% (0.79–0.98)
Multiple domains MCI memory+	65.4% (0.47–0.84)	61.9% (0.52–0.72)	32.7% (0.20–0.45)	86.4% (0.78–0.95)
Multiple domains MCI memory–	15.4% (0.02–0.29)	79.3% (0.71–0.88)	17.3% (0.02–0.33)	76.8% (0.68–0.85)
Single non-memory MCI	3.8% (0.0–0.11)	72.8% (0.64–0.82)	3.8% (0.0–0.11)	72.8% (0.64–0.82)
<i>Stroke cohort</i>				
Amnesic MCI	0.0% (0.0–0.0)	100% (1.0–1.0)	0.0% (0.0–0.0)	93.8% (0.88–0.99)
Multiple domains all	100% (1.0–1.0)	28.0% (0.18–0.38)	8.5% (0.01–0.16)	100% (1.0–1.0)
Multiple domains MCI memory+	40.0% (0.0–0.83)	85.3% (0.77–0.93)	15.4% (0.0–0.35)	95.5% (0.91–1.0)
Multiple domains MCI memory–	60.0% (0.17–1.03)	42.7% (0.31–0.54)	6.5% (0.0–0.14)	94.1% (0.86–1.02)
Single non-memory MCI	0.0% (0.0–0.0)	73.8% (0.62–0.82)	0.0% (0.0–0.0)	92.1% (0.84–0.99)
CI = Confidence interval.				

Other investigators also found MCI or related concepts such as CIND to be valid with regard to the development of dementia (mostly AD) [5, 22–24]. The low positive predictive value of the MCI subtypes found in our study may be because of the small number of cases of dementia diagnosed and the short follow-up. The results suggest that this subtype classification of MCI is of limited clinical relevance. The negative predictive value of these subtypes was high, the highest being for ‘multiple domain MCI’. This indicates that if patients are not diagnosed as ‘multiple domain MCI’, the chance of them becoming demented is low.

In the stroke cohort ‘multiple domain MCI’ was the most common subtype and ‘amnesic MCI’ the least. ‘Multiple domain MCI’ had the highest sensitivity and ‘amnesic MCI’ had the highest specificity for the pre-dementia stage of VaD. In their study of stroke patients, Ballard et al. [25] did not find MCI and other related concepts to be useful as indicators of the transition phase to dementia after stroke. Despite of these negative results, nondemented patients with cerebrovascular diseases and with mild cognitive deficits are at increased risk of developing dementia [22, 23, 26–28].

In both cohorts, the ‘multiple domain MCI’ subtype was the most prevalent. Also others found that the cognitive profile of patients in the predementia stage is characterized by multiple domains impaired, which accords with the concept of CIND [5, 22, 23]. We further divided this concept and found that in the stroke cohort, ‘multiple domain MCI memory–’ was more than 3 times more prevalent than the ‘multiple domain MCI memory+’. These findings suggest that the cognitive profile of patients with cerebrovascular disease differs from that of patients with other disorders. This is in line with the analysis of the individual cognitive domains in which patients from the MCI cohort had more often memory deficits. In combination with our finding that memory deficits had the highest negative predictive value, patients without a memory deficit had thus a lower chance of becoming demented than patients with a memory deficit. In the stroke cohort patients without executive functioning or without mental speed deficits had a lower chance of becoming demented compared to patients with these deficits. Busse et al. [2] failed to find relation between MCI subtypes and the development of dementia, which may be because they used a population-based design in which

subjects with neurological disorders were excluded. As a result, subjects who were at higher risk of developing VaD were underrepresented [2].

This study has some shortcomings. Firstly, patients from the two cohorts visited the hospital for different reasons: patients from the memory cohort had memory complaints whereas patients from the stroke cohort had had a stroke. However, despite these differences in referral, the groups were similar with regard to cognitive functioning (MMSE score at baseline differed only 1 point), and inclusion and exclusion criteria. Secondly, the patients in the stroke cohort were tested four times, and those in the memory clinic cohort only two times, which may have led to differences caused by a learning effect. However, as dementia was primarily diagnosed on the basis of the clinical assessment, we consider this effect to be of limited relevance in our study. Thirdly, we diagnosed MCI and its subtypes based on psychometric definitions and not in combination with a clinical judgment. This is in contrast with the clinical diagnosis of MCI, as described by Petersen et al. [1]. Moreover, we did not take memory complaints into consideration, which means we may have overestimated the number of patients with MCI because other studies have shown that the prevalence of MCI increases when subjective cognitive complaints are not taken into consideration [2, 29]. Fourthly, because few

patients were diagnosed with dementia, the power of the study was low, which may be a consequence of the exclusion of people with an MMSE score <15. Lastly, the follow-up period was relatively short, which could have led to an underestimation of the positive predictive value of the various subtypes of MCI.

In conclusion, the subtype 'multiple domain MCI' has the highest sensitivity in predicting both AD and VaD. A high sensitivity in diagnosing patients who are at risk of developing dementia is desirable in the light of intervention possibilities.

We propose that patients who meet the diagnostic criteria of subtype 'multiple domain MCI' are in the pre-dementia stage and have a high risk of going on to develop dementia. However, the low positive predictive value indicates that other markers for the predementia stage are needed.

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