Clinically Presenting Mild Cognitive Impairment (MCI): Variable Presentations and Their Outcomes

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BACKGROUND

Amnestic-MCI is a valuable research construct and patients typically progress to AD at 10-15% annually (Petersen's criteria using the WMS-R, LM II impairment ≥1.5 SD).[1] Amnestic deficits on other episodic memory tests may also identify MCI patients who will progress to AD. The significance of impairments in non-memory domains or purely subjective cognitive complaints is uncertain.

OBJECTIVES

Baseline characteristics and annualized conversion to Alzheimer disease [AD] in 3 MCI subtypes and in patients with subjective memory loss [SML] were evaluated.

METHODS

133 subjects with the diagnosis of MCI or SML were identified in the Baylor College of Medicine Alzheimer's Disease and Memory Disorders Center prospective, longitudinal cohort.[2] All subjects underwent an evaluation by a neurologist and completed a standardized dementia workup. A detailed history and interview with the patient and informant, neurological and physical examinations, a neuroimaging study, psychometric testing, and screening laboratory studies were performed as part of the initial visit. We employ a comprehensive battery of neuropsychological tests to assess all patients, described elsewhere.[2] Subjects were classified into one of three types of MCI: **amnestic MCI [A-MCI]** if logical memory delayed recall score (LM II) on the WMS-R was ≥1.5 SD below an education adjusted norm[1,3] or visual reproduction delayed recall score (VR II) on the WMS-R was ≥1.5 SD below age corrected norms; **amnestic-subthreshold MCI [AS-MCI]** if memory was normal on WMS-R but impaired by ADAS-cog word list delayed recall ≥1.5 SD, age 55-69, 6+ errors, age 70-74, 7+ errors, age 75-89, 8+ errors[4]; or **non-amnestic MCI [NA-MCI]** if a non-memory cognitive domain was impaired ≥1.5 SD. We used the standard two paragraphs of the WMS-R LM task and averaged the score, as opposed to the single paragraph used by Petersen et al. General cognitive function was normal and activities of daily living were preserved by clinician's judgment based upon neuropsycholgical test results, a structured interview with the patient and an informant, and Lawton and Brody ADL assessment at the baseline. The A-MCI and AS-MCI subtypes were defined by the presence of a salient memory component either alone or in conjunction with other cognitive- domain impairments but of insufficient severity to constitute a second domain (<1.5 SD from normal). Likewise the NA-MCI cases were defined by the presence of impairment in one or more non-memory cognitive domains which, in the absence of memory impairment, does not meet criteria for dementia. The **subjective memory loss [SML]** group had a normal psychometric battery with no test ≥1.5 SD from normal, but complained of a memory problem.

We analyzed baseline demographic and psychometric characteristics and the last diagnosis for those subjects who returned for annual follow-up examinations in order to assess conversions to AD and non-AD dementia. We calculated the conversion rate to dementia in those subjects who came for follow-up visits at 2, 3, and 4 years in the 3 MCI subgroups. Mean follow-up time overall was was 3.3± 2.2 years.

Table 1. Cumulative Number of Annual FU Visits by Group

	All	A-MCI	AS-MCI	NA-MCI	SML
# of subjects	133	38	20	48	27
1 year	76	26	8	25	17
2 year	52	23	8	14	9
3 year	41	17	6	12	6
4 year	32	15	3	9	5
No follow-up	57	12	12	23	10
Mean FU time (SD)	3.3 (2.2)	4.2 (2.4)	3.1 (1.6)	2.8 * (1.9)	2.7 (2.2)

FU [Follow-up]; A-MCI [Amnestic MCI]; AS-MCI [Amnestic Subthreshold MCI]; NA-MCI [Non-Amnestic MCI]; SML [Subjective Memory Loss].

*p<0.05.

Relevant statistical comparisons were made for baseline characteristics between the A-MCI subjects and the other three groups. We used Cox regression to determine significant predictors of time to conversion to AD.

Psychometric testing included but was not limited to the Mini-Mental Status Examination (MMSE), the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), the Wechsler Memory Scale-Revised (WMS-R) logical memory and visual reproduction subtests, Clinical Dementia Rating Scale (CDR), and the Rey Osterrieth Complex Figure Test (Rey-O).

Covariates: Age, education, gender, ApoE epsilon4 allele, duration of symptoms at initial visit; history of diabetes, psychiatric symptoms, or hypertension.

RESULTS

Table 2. Baseline Subject Characteristics

	All	A-MCI	AS-MCI	NA-MCI	SML
# of subjects	133	38	20	48	27
Male [%]	44	26	65 **	42	56 *
Age [yrs]	69 (9.7)	73 (8.5)	67 * (9.6)	70 (9.6)	67 * (10.4)
Education [yrs]	16 (3.1)	15 (3.2)	15 (3.6)	16 (3.3)	16 (2.5)
Hypertension [%]	39	27	60 *	43	31
APOE ε4 carriers [%]	43	69	33 *	40 *	19 ***

Mean (SD) for all continuous variables.

For all statistical comparisons, referent group = Amnestic MCI; *p<0.05; **p<0.01; ***p<0.001; otherwise p=NS.

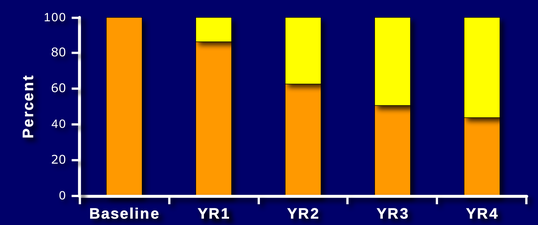
Table 3. Baseline Neuropsychological Tests

	All	A-MCI	AS-MCI	NA-MCI	SML
MMSE score	27.7 (2.9)	26.8 (3.6)	27.5 (1.7)	28.1 (1.8)	28.7 (3.9)
ADAS Delay Word Recall Errors	5.4 (2.4)	6.9 (2.0)	7.5 (1.2)	4.4 * (1.9)	3.4 *** (1.8)
Logical Memory I	20.3 (7.2)	14.7 (5.7)	21.1 ** (7.2)	22.4 *** (6.4)	24.2 *** (5.6)
Logical Memory II	13.9 (8.6)	5.3 (5.5)	16.0 *** (6.4)	17.5 *** (6.6)	19.0 *** (7.5)
Visual Reproduction I	27.9 (7.3)	23.4 (8.4)	28.7 ** (5.6)	29.0 ** (6.4)	31.8 *** (4.9)
Visual Reproduction II	18.1 (10.2)	8.7 (8.2)	20.3 *** (8.1)	21.0 *** (8.5)	25.2 *** (7.1)
Rey-Osterrieth Copy	30.4 (6.0)	31.8 (4.7)	28.7 (8.4)	28.6 * (6.1)	33.4 (3.1)
CDR Sum of Boxes	1.7 (1.3)	1.9 (1.1)	1.8 (1.3)	1.7 (1.6)	1.4 * (0.7)

Mean (SD) for all variables.

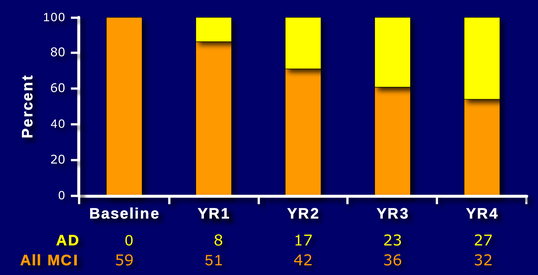
For all statistical comparisons, referent group = Amnestic MCI; *p<0.05; **p<0.01; ***p<0.001; otherwise p=NS.

Figure 1. 4-year Annualized Conversion to Dementia: All MCI with 1 year FU



56% cross-over rate by year 4 (14% per year)

Figure 2. 4-year Annualized Conversion to AD: All MCI with 1 year FU



46% cross-over rate by year 4 (11% per year)

At year 4 all but 1 subject with A-MCI or AS-MCI converted to AD in contrast to the NA-MCI subtype where there were fewer AD conversions (8/13). The non-AD conversions were to Lewy Body or Frontal Lobe Dementia. There was only one conversion to AD in the SML group and this occurred during year 1.

We used Cox regression to determine significant predictors of time to conversion to dementia and to AD controlling for symptom duration and all significant univariate variables revealed that both the APOE ε4 genotype (HR=6.2, 95% CI 1.8-21.1, p=0.004) and ADAS-cog word list delayed recall (HR=1.3, 95% CI 1.0-1.6, p=0.04) were significant predictors of conversion.

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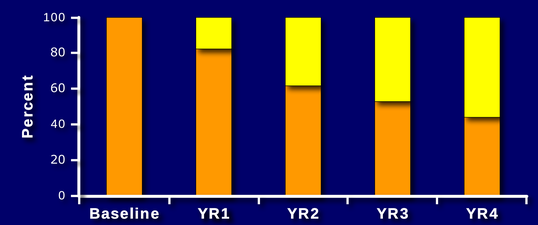
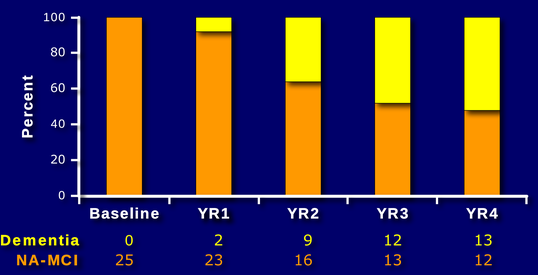
Figure 3. 4-year Annualized Conversion to AD: A-MCI and AS-MCI subtypes



56% cross-over rate by year 4 (14% per year)

Figure 4. 4-year Annualized Conversion to Dementia: NA-MCI subtype



52% cross-over rate by year 4 (13% per year)

CONCLUSION

1) **Our data suggest that all MCI subtypes are at risk of converting to dementia if the groups are defined by abnormalities on psychometric testing (≥1.5 SD from the mean).**

2) **Individuals with amnestic MCI (WMS-R, LM II ≥1.5 SD) and amnestic-subthreshold MCI (ADAS-cog impaired delayed word list recall ≥1.5 SD) had similarly high rates of conversion to AD. Delayed list recall may be a more sensitive memory criteria than delayed paragraph recall to identify those at risk for converting to AD dementia.**

3) **The ApoE epsilon4 allele remains a strong predictor for conversion to AD among multiple MCI subtypes.**

4) **Our findings are preliminary as we have variable durations of follow-up for the groups and not all subjects have been followed for 4 years.**

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