Revised Criteria for Mild Cognitive Impairment: Validation within a Longitudinal Population Study.

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'Revised Criteria for Mild Cognitive Impairment (MCI-R): Validation within a longitudinal population study'

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Abstract

Background: Mild Cognitive impairment (MCI) refers to the transitional zone between normal ageing and dementia. Current criteria perform poorly within the general population setting. Revisions have been proposed based on results obtained from clinical and epidemiological studies.

Objective: To evaluate revised diagnostic criteria for Mild Cognitive Impairment (MCI-R) incorporating changes in activity level and non-mnesic cognitive functioning.

Method: MCI-R subjects were recruited from a representative network of general practitioners in the south of France. A computerized neuropsychometric examination was given. At 2 years follow-up a diagnosis of dementia was made by a neurologist using DSM III-R criteria and without knowledge of the results of the cognitive testing. Rate of conversion to incident dementia were assessed by Receiver Operating Characteristics (ROC) analysis.

Results: MCI-R prevalence was found to be 16.6% using revised criteria. Significantly better prediction of transition to dementia (AUC=0.80, sensibility: 95 %, specificity: 66%) was obtained with MCI-R than with the previous MCI criteria (AUC=0.48, sensibility: 5 %, specificity: 91 %). Predictive power was found to increase when MCI sub-types were combined.

Conclusion: Incorporating the possibility of change in activity level and alteration of non-mnesic cognitive functions have been found to ameliorate the original algorithm and better define subjects converting to dementia. This definition may be applicable to both clinical and population research.

The identification of cases of sub-clinical cognitive impairment at high risk of evolving towards dementia is important both for early treatment and protection of the individual. The concept of Mild Cognitive Impairment (MCI) [1] is now widely used to describe this high-risk group[2-6] and numerous large-scale research programmes have now been undertaken with a view to providing treatment. As mild cases of cognitive disorder more commonly present initially to the general practitioner than to the specialist, it is important that diagnostic criteria perform adequately within this setting. Previous attempts to apply MCI criteria in general practice have been disappointing; the algorithm giving variable predictive validity with regard to the identification of dementia converters[7, 8]. A recent consensus conference held in Stockholm[9] provided an opportunity for clinicians and researchers working in the field of MCI to compare data sets and to propose modifications to the existing criteria which might improve screening accuracy, especially in the general population setting. Essentially, the new criteria allow for the inclusion of cognitive deficits other than memory dysfunction, and also recognise that MCI may be associated with early and subtle changes in ability perform tasks of everyday living. The aim of the present study is to evaluate the performance of these revised criteria within a longitudinal population study.

Methods

Sample

The subjects included in the present study were over 60 years of age and recruited from a representative general practitioner research network as part of the Eugeria longitudinal study of cognitive aging described in detail elsewhere (Ritchie et al) [10]. The population-based network is representative of general practice in the Montpellier

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region in the south of France, and includes urban and rural areas and subjects living in institutions. An intensive training course in psychogeriatric screening and application of criteria for senile dementia according to the diagnostic and statistical manual, 3 rd ed., revised (DSM III- R)[11] was given to the 63 general practitioners in the network. 833 subjects representing all subjects without dementia over 60 were recruited into the study in the first year. At baseline dementia cases were excluded by the general practitioners. A proxy questionnaire on cognitive functioning over the past year was sent to all subjects. This screening instrument, Détérioration Cognitive Observée (DECO) has been shown in previous study to be highly sensitive to early changes in cognitive functioning due to various cause[12]. It is based on the degree of change in cognitive functioning over the last year, as estimated by a proxy who had at least monthly contact with the subject over the past 3 years. Of these subjects, 308 subjects with cognitive complaints verified by proxies at base-line were identified. These persons were considered by an observer to have shown some degree of observable deterioration in at least one area of cognitive functioning over the past year and also to have a subjective cognitive complaint of declining ability (DECO score of less than 38).

These subjects were followed over a further 2 years along with a random sample (n=64) of the remaining subjects without cognitive complaints.

Instruments

Neuropsychological assessment

Subjects were visited in their homes and given a computerized neuropsychometric examination, ECO (Examen Cognitif par Ordinateur)[13]. ECO assesses primary memory, verbal and visuospatial secondary memory, language skills (word and syntax comprehension, naming, verbal fluency), visuospatial performance (ideational,

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ideo-motor and constructive apraxia, functional and semantic categorization of visual data, visual reasoning and form perception), and focused and divided attention (visual and auditory modalities). The development of ECO and the theoretical basis for test selection is described elsewhere[13]. Response latencies were recorded using a tactile screen.

Ten summary scores representing six cognitive domains were used in the analysis.

attention: response time on a dual task

primary memory: immediate recall of names

secondary memory: (i) delayed recall of names and (ii) their associated faces

visuospatial ability: (i) response time on a visual matching tasks and (ii) number of elements correct in the copying of meaningful and meaningless figures

language: (i) mean reaction time on word and syntax comprehension, (ii) naming and (iii) verbal fluency using both phonetic and functional cues

reasoning : completion of logical visual series

Activity of daily Living assessment

 A validated activity of daily living scale (ECA)[14] with finely-graded hierarchical sub-scales was used to assess alterations in everyday functioning in collaboration with both subjects and caregivers.

Definition of cases

At 2 years follow-up a diagnosis of incident neurological disorders including dementia was carried out by a neurologist using a standardized neurological examination based on DSM III-R[11] criteria and without knowledge of the results of the cognitive testing (computerized neuropsychometric examination).

A consent form describing the aims and methods of the study was completed by all subjects. Authorization for the study was also obtained from the National Data Protection and Ethics Committees.

Criteria for MCI and MCI-R identification

MCI and MCI-R criteria were applied to base-line data. The criteria for MCI are those previously proposed by Petersen et al.[1] :

(i) presence of a subjective memory complaint

(ii) preserved general intellectual functioning (as estimated in this study by performance on a vocabulary test)

(iii) demonstration of a memory impairment by cognitive testing

(iv) intact ability to perform activities of daily living

(v) absence of dementia.

MCI-R criteria are those proposed by the Stockholm consensus group[9]. They stipulate :

 (i) presence of a cognitive complaint from either the subject and/

or a family member

 (ii) absence of dementia

(iii) change from normal functioning

(iv) decline in any area of cognitive functioning

(v) preserved overall general functioning but possibly with increasing difficulty in the performance of activities of daily living

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The definition of a significant change in cognitive performance is problematic in all studies of MCI; 1.5 standard deviations (SD) being most commonly used to define cognitive deficit within both a research and clinical context. We also found this gave the best concordance with clinical judgment (the examining neurologist was also asked to clinically classify subjects as possible MCI on the basis of the standardized interview only). Subjects classified as MCI and MCI-R demonstrated a decrement of more than 1.5 standard deviations on a memory task (MCI) or on a cognitive task (MCI-R) compared to ECO standardisation data matched by age and level of education.

MCI sub-types

The MCI-R subjects may be sub classified according to the presence or absence of a memory impairment [15]. All test scores were first converted to z scores to permit across-test comparisons taking into account differences in the relative difficulty of tests. Subjects can be designated as having amnestic MCI if they have a prominent memory impairment either alone or with other cognitive impairments (multiple domain with amnesia) or non-amnestic MCI if a single non-memory domain is impaired alone or in combination with other non-memory deficits (multiple domain without amnesia) (see figure 1).

Figure 1 here

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Analysis of data

Receiver Operating Characteristics (ROC) analysis has been used to analyze the relative predictive power of MCI and MCI-R identified to predict dementia onset in the following two years. We calculated the area under the curves (AUC) and the sensitivities and specificities for dementia for MCI, MCI-R and MCI-R sub-types.

Statistical analysis were be performed using SPSS (Statistical Package for social Science) program version 13.0. The AUCs of the MCI groups were compared using the ROCcomp procedure of STATA program version 9.0.

Results

Of the 308 subjects (30% male; 70% female) included in the study at baseline with a subjective cognitive complaint, with a mean age of 75.7 years (SD=7.8), 139 were classified as MCI-R. The revised criteria provide an estimated prevalence of 16.6% and a yearly incidence of 0.06% in the general population. All MCI-R subjects were independent for activities of daily living but many had greater difficulty than non-cognitively impaired persons in performing these activities when graded on sub-scales of performance. Approximately 32% of MCI-R subjects report increasing difficulty with at least one activity compared to 15.6% in cognitively stable subjects. The greatest difficulties reported by those MCI-R subjects later diagnosed with dementia are with Instrumental Activities of Daily Living use of the telephone (36.8%), managing money (31%) use of household appliances (22%) and one basic Activity of Daily Living, dressing (26.3%). While subjects were still able to dress appropriately, proxies reported increasing difficulty (14 %) (principally in time taken to dress or in deciding what to wear).

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Receiver Operating Characteristics (ROC) analysis showed that significantly better prediction (AUC=0.80) was obtained with MCI-R than with the previous MCI criteria (AUC=0.48) (table 2). 84 % of the persons developing dementia, had at least one functional deficit at base-line. The mean cognitive test scores for the MCI-R are given in Table 1.

Table 1, here

Subjects were classified according to MCI-R sub-type. 76 subjects had a predominant memory deficit (the memory deficit alone being 1.5 SD greater than for age and education matched controls) and were classified as amnestic MCI-R. 63 subjects had significantly lower scores (1.5 SD) on the non-memory tests or had multiple domain deficits in which numerous cognitive deficits of more than 1.5 SD were found. Given the small numbers in these two categories it was not feasible to examine the predictive validity of each of these sub-types so they have been classified together as non-amnestic MCI-R. ROC analysis shows that whereas taken alone both groups have worse predictive power (AUC=0.73 amnestic; AUC=0.26 non-amnestic); the highest prediction to dementia is obtained when the sub-types are combined (AUC=0.80) (see table 2, appendix 1).

Table 2 here

The AUC of MCI and MCI-R groups are significatively different (chi2=50.19, p<0.00001), The AUC of MCI et amnestic MCI-R groups are also significatively different (chi2=17.75, p<0.00001).

Discussion

In a previous study we have shown that currently used MCI criteria emphasizing a relatively isolated memory impairment applied to general population research have poor predictive validity for the onset of dementia within the general practice setting [2]. However, this previous study also found that subjects with a cognitive complaint verified by a proxy have a higher conversion rate to senile dementia (18% incidence over three years) than that observed in the general population. This suggests that mild cognitive dysfunction is an important risk factor for dementia, but that MCI criteria require modification if they are to have high prognostic value within the general population setting.

This study has applied revised MCI criteria proposed by an international expert group in Stockholm in 2003 within a longitudinal population study of sub-clinical cognitive deficit. The revised criteria perform significantly better than the original algorithm due to the inclusion of a criterion relating to increasing difficulty in performance of everyday tasks without loss of autonomy. The study furthermore suggests that these changes are most likely to be observed in pre-dementia in the areas of use of telephone, dressing, use of money and household appliances and that future diagnostic interviews should focus on these areas, noting however that these activities are not lost, but performed with increasing difficulty. Previous study

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have suggested that MCI subjects show mild impairments of everyday functioning when using sensitive measures[16-19].

Secondly, the revised criteria include cognitive deficits other than memory allowing us to classify MCI subjects as predominantly amnestic multiple domain, and non-amnestic as given in figure 1. While non-amnestic MCI was found to be a poor predictor of two-year dementia conversion, combined with amnestic MCI-R it gives maximum predictive validity. It is thus clear that extension of the original MCI criteria to a larger range of cognitive functions gives higher sensitivity and better dementia prediction (using the former criteria 63 subjects would not have been detected). Amnestic difficulties are, however, clearly both more common and less likely to be benign. The validity of this type of sub-classification will depend of course on the tests used – it being generally accepted that the more tests one uses, the more one sees multiple domain deficits and specialist judgement is clearly required to make this discrimination with clinical accuracy. Previous studies have shown that cognitive deficits other than memory were involved in the detection of presenile dementia [6, 20-23].

There is a fragility of the MCI concept when one attempts to operationalize it strictly in terms of test performance. Numerous attempts have been made to develop MCI screening tests which may screen independently of comprehensive clinical assessment, and not surprisingly their discriminability is relatively poor [2, 7].

The aim of the paper has been to establish a global definition which may be applicable for both clinical and population research, and not to validate a clinical dementia prediction instrument. While modifications to the original algorithm have been found to better define subjects converting to dementia, results also point to the complexity of operationalizing this definition in terms of neuropsychological tests.

Collectively results point to certain cognitive domains as being particularly vulnerable, however, individual subjects show wide variation in patterns of deficit and rates of change across time such that it is difficult to diagnose MCI in the absence of a specialist review of the cognitive data. Further research is needed to examine the relationship across time between neuropsychological and functional test performance and clinical diagnosis of MCI. This new MCI algorithm functions only at a syndrome level, permitting the early identification of persons at risk of cognitive decline without being able to specify the nature of the underlying neuro-cognitive disorder. At present levels of knowledge it would seem unwise to attempt detection of Alzheimer's disease specifically, or to differentiate AD from other diseases such as Lewy body disease given the heterogeneity of these disorders.

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Competing of interest : none

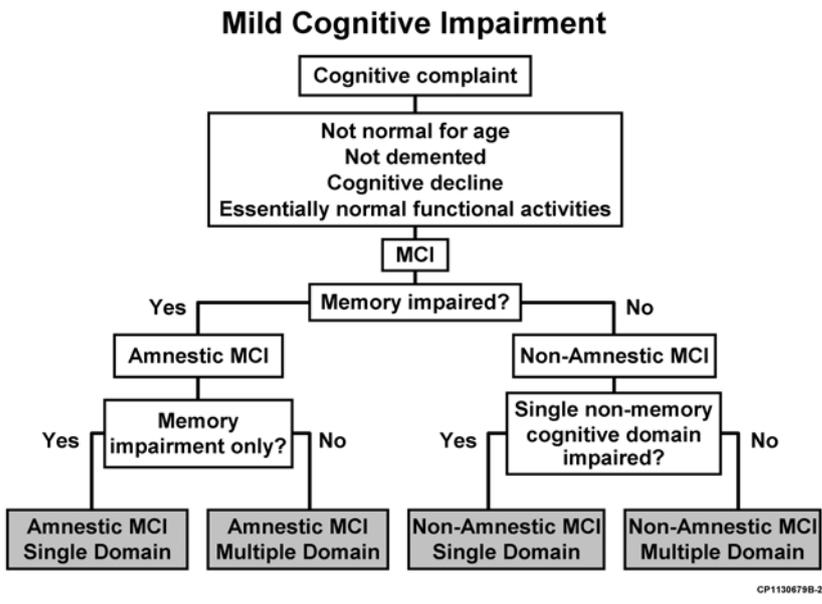## Mild Cognitive Impairment

Figure 1. Flow-chart : Amnestic and non amnestic MCI subjects.

Table1. Mean (SD) cognitive test scores for normal and MCI-R groups two years before neurological diagnosis

	Normal group n=64	MCI-R group n=139
Attention		
Mean reaction time on double task	19.94 (4.49)	26.22 (8.28)
Primary memory		
Immediate recall of name list	5.42 (1.37)	3.95 (1.83)
Secondary memory		
Delayed recall of names	5.48 (1.80)	3.16 (2.22)
Delayed recall of faces recalled	7.96 (1.24)	6.57 (2.10)
Visuospatial ability		
Mean reaction time on total visual analysis	36.44 (6.60)	47.59 (11.57)
Copying tasks	23.95 (0.21)	21.95 (4.27)
Language		
Naming total correct	9.54 (0.68)	8.38 (1.79)
Fluency total	39.01 (10.98)	23.80 (11.36)
Reaction time word and syntax comprehension	17.81 (4.92)	28.07 (10.34)
Reasoning		
Logical series total correct	1.45 (1.09)	0.57 (0.83)

Table 2. Receiver Operating Characteristics (ROC) analyses of the discriminability of MCI, MCI-R and

MCI-R sub-types (amnestic and non-amnestic) for the prediction of dementia after 2 years.

Classification	n	AUC	SE	Asymptotic Significance	95 % CI	Sensitivity %	Specifivity %
MCI	23	0.48	0.07	0.84	0.34-0.62	5	91
MCI-R	139	0.80	0.04	0.001	0.71-0.89	95	66
Sub-types :							
Non amnestic MCI-R	63	0.26	0.07	0.005	0.11-0.40	23	30
Amnestic MCI-R	76	0.73	0.07	0.005	0.59-0.88	77	70

AUC: Area Under the Curve, SE: Standard Error

Appendix 1 : Subjects number in each groups (MCI-R, not MCI-R, no baseline cognitive complaint) used in the ROC analysis.

	MCI-R	Not MCI-R	No baseline cognitive complaint	Total
Converted to dementia	18	1	0	19
Not converted to dementia	121 †	168 ‡	64 §	353
Total	139	169	64	372

†: 15 dead, 6 unable; ‡ : 3 dead; §: 1 unable