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Retrospective identification and characterization of Mild Cognitive Impairment from a prospective population cohort

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Key words: MCI, diagnosis, cohort studies, gender, dementia, ApoE, cardiovascular disorder

ABSTRACT

Objectives: Mild Cognitive Impairment (MCI) case-finding criteria have low specificity in general population studies. The present study retrospectively identifies cases of MCI and determines baseline criteria giving the highest discriminability. The ability of these criteria to increase current case-detection specificity is estimated.

Design: A population-based cohort was recruited from electoral rolls from three French cities. Clinical and environmental characteristics were evaluated at baseline and 2 and 4 year follow-up. The clinical characterisitics of incident cases of dementia were examined retrospectively .

Participants: 8919 persons over 65 without dementia (60.8% women). The mean age (SD) of the participants was 74.2 (5.6) for men and 74.4 (5.6) for women.

Results: 320 persons (3.6%) were retrospectively classified as MCI at baseline. This MCI group had poorer performance on all cognitive tests compared to the rest of the cohort and a sub-sample undergoing MRI were found to have more white matter hyperintensities. The group were also characterized by the presence of an ApoE 4 genotype (OR=2.17 CI 1.44-3.29 for men; OR=2.27 CI 1.59-3.24 for women), and IADL loss (OR=1.72 CI 1.01-3.0 for men and OR=1.49 CI 0.97-2.3 for women). Women with MCI also had high depressive symptomatology (OR=1.96; CI 1.34-2.87), anticholinergic drug use (OR=1.59; CI 1.05-2.28) and low BMI (OR=1.54; CI 1.05-2.28) and men a history of stroke (OR=2.17 CI 1.16-4.05) and glycemia (OR=1.72 CI 1.13-2.71). Addition of these characteristics to conventional MCI definitions increases their specificity.

Conclusions: This general population study employing a retrospective method for classifying persons with MCI identified gender-specific non-cognitive clinical variables which may increase specificity.

OBJECTIVES

The concept of Mild Cognitive Impairment (MCI) is widely used to describe a group at high-risk of dementia with a view to earlier therapeutic intervention. Case detection criteria for MCI were initially based on cases referred to specialist units and demonstrated relatively high levels of predictive validity[1]. However, MCI is not by definition a very disabling condition, so most cases do not consult specialists and present more often in general practice. It is thus best characterized from observations derived from general population studies. A number of cohort studies which have involved clinical verification of MCI cases by neurologists have concluded that many persons considered clinically to be MCI and at high risk of dementia are not identified by the clinic-based algorithms currently used[2-5] and that furthermore of those that are identified as MCI, the majority do not develop dementia even after 8 years of follow-up.[2, 5-8] There is thus clearly a need to refine case detection procedures for MCI within the general population setting.

MCI refers fundamentally to a recent decline in cognitive performance which cannot be reliably established by reference to a single neuropsychological examination even when age and education adjusted standardization data are available. Moreover neuropsychological studies associated with measures of hippocampal atrophy, as well as post-mortem observations of neurofibrillary pathology in the medial temporal lobes, suggest that MCI is not a separate diagnostic entity but a state mid-way between normal ageing and dementia[9,10] requiring the identification of clinical cut-off points rather than the establishment of independent biological markers. The methodology generally used to validate MCI criteria, the prospective estimation of rates of evolution towards dementia, has demonstrated current criteria to have high sensitivity but

very poor specificity with inacceptable rates of false positives[5-8]. The principal problem is thus that small changes in cognitive functioning, while very sensitive indicators of MCI tend to be highly non-specific, giving false positive too high to be currently applicable in intervention studies. Numerous studies have attempted to improve detection rates by modifying the type and number of tests and their cut-off[3,7], but there has been little attempt to examine the possible contribution of non-cognitive correlates of MCI as supporting diagnostic criteria.

The present study, based on a large multi-centre prospective population study of brain ageing, aims to combine both retrospective and prospective designs to provide a more clinically meaningful 'gold standard' for MCI caseness, and thus suggest clinical characteristics other than the MCI cognitive criteria likely to increase specificity. In this study 'true' cases of MCI are operationally defined by retrospective examination of individual trajectories as persons with no dementia who will receive within the next four years a diagnosis of dementia by a neurologist. This group are referred to as Dem-MCI. We examine the clinical characteristics of this group in the years preceding the dementia to establish principal discriminating characteristics, and then compare the performance of the algorithms thus derived with existing case identification procedures. The study focuses on non-cognitive features of MCI which may be used to improve specificity levels.

PARTICIPANTS

Subjects for the present study were recruited randomly from the electoral roles of three French cities (Bordeaux, Dijon and Montpellier) between 1999 and 2001 as part of a multi-site cohort study of community-dwelling persons aged 65 years and over (the Three City Study). Subjects

were interviewed initially either at a study centre or in their own homes if disabled. The cohort was followed up twice at two year intervals. Given that cognitive impairment may commence up to 20 years before the diagnosis of dementia[11], this four-year window was considered adequate to capture a true MCI group. The mortality rate over the four year follow-up was 6.8 %. The study design has been described in detail elsewhere[12]. The study protocol was approved by the Ethical Committee of the University-Hospital of Bicêtre (France) and written informed consent was obtained from each participant. The present analysis is carried out on 8919 subjects (60.8% female) at base-line who did not have dementia. The mean age (SD) of the sample was 74.2 (5.6) for men and 74.4 (5.6) for women.

DESIGN

Socio-demographic and clinical variables

A standardized interview included questions relating to socio-demographic characteristics, physical activities, weight and height. Information was also obtained on exposure to anaesthesia in the preceding year, subjectively evaluated health (six items relating to inhabitual difficulties in everyday activities, related to learning, calculating, language and orientation), sleep quality, herpes infections, subjective report of appetite loss, self-reported social isolation, current alcohol consumption, and tobacco use. Past history of stroke was validated by medical records. Blood pressure was measured twice during the interview using a digital electronic tensiometer OMRON M4. Subjects were considered as hypertensive if mean systolic blood pressure was 160mm Hg or higher or mean diastolic blood pressure was 95mm Hg or higher or they were on antihypertensive medication. Fasting blood samples were taken for cholesterol and glucose levels and apolipoprotein E status. Hypercholesterolemia was defined as fasting blood CST $\geq$ 6.2 mmol/l

and diabetes as treated diabetes or fasting blood glucose 7.0 mmol/l. Subjects with hypertension, obesity, high triglycerides, low HDL cholesterol and either impaired fasting glucose or diagnosed diabetes were classified as having metabolic syndrome. Cardiovascular antecedents included history of myocardial infarction, coronary surgery, coronary angioplasty and arterial surgery of the legs due to arteritis in inferior limbs. Impairment in the performance of everyday activities was assessed with the Instrumental Activities of Daily Living Scale (IADL), impairment being defined as difficulty with at least one IADL[13].

Past history of head trauma, respiratory disease, cancer, hypertension, hypercholesterolemia, diabetes, stroke, asthma, angina pectoris was established according to standardized questions with additional information where necessary from general practitioners. For persons who reported the occurrence of vascular events during follow-up, further medical data were obtained from general practitioners, specialists and hospital records. The interview also included an inventory of all drugs used during the preceding month, noting those with potential anticholinergic effects according to previously established criteria[14], and past as well as present use of hormonal replacement therapy (HRT). Medical prescriptions and, where feasible, the medications themselves were seen by the interviewer. Depressive symptomatology was assessed by the Center for Epidemiological Studies-Depression scale (CES-D)[15] with a >16 cut-off point indicating a high level of symptomatology. A short cognitive battery included Trail Making tests A and B assessing psychomotor speed and executive function[16], the immediate and delayed recall of the 5-word Test of Dubois[17], The Benton Visual Retention Test (BVRT)[18] and the Isaacs Set Test (Isaacs)of verbal fluency[19].

In a sub-sample (the Montpellier cohort) MRI structural imaging was performed on every second subject under 85 years at baseline (717 subjects) using fast multislice double echo T2-weighted 2D axial acquisition, 4 mm thick slices, with 0.4 mm between slice spacing covering the whole brain (30 slices, the upper slice passing through the brain vertex). Fast SPGR 3D T1-weighted axial acquisition, with 2 excitations; 124 slices (1mm thick). White matter lesion volume was estimated using a semi-automatic method[20]. Areas of supratensorial white matter hyperintensity (WMH) were segmented on T2 sequences using MRIcro software. A first layer of region of interest (ROIs) corresponding to WMH was created by a semi-automated technique based on intensity thresholding. A second layer of ROIs was then manually outlined on each slide by gross contouring of all WMH. The intersection of the first and second layer was then manually inspected and automatic total volume of WMH obtained. An experienced reader examined all scans. Another experienced neurologist examined 80 randomly chosen scans to asses inter-rater reliability. Inter-reader and intrareader-intraclass correlations coefficients showed good to excellent agreement (0.79 and 0.95 respectively) . Total WMH was calculated as a function of total brain volume, and as the population distribution is highly skewed, data was divided into quartiles.

Diagnosis of Dementia

A preliminary diagnosis and classification of dementia at each follow-up examination was made by the 3C study local clinical investigators according to DSM-IV criteria[21] and validated by a national panel of neurologists independently of the 3C investigators. The date of onset of dementia was the date of the follow-up interview when dementia was diagnosed. Subjects diagnosed with dementia at baseline were excluded from this analysis. For comparison purposes a diagnosis of MCI according to currently used criteria was also made using the revised

algorithm (MCI-R) based on cross-sectional evaluation, which has been proposed by an international consensus group[22]. Given the highly abnormal distribution of test scores 'cognitive dysfunction' is defined as being in the lowest quartile on one of the cognitive tests used, adjusted by age and education rather than by standard deviations. This cut-off was found to have included all the subsequent dementia cases. On the only cognitive test for which log normalization was possible (verbal fluency) this cut-off was observed to correspond to >1 SD below the mean of the cohort.

Statistical analyses

Univariate comparisons were carried out using t-tests and chi-squared where relevant. Backward, stepwise logistic regression was carried out on variables found to be significant on univariate analysis. A correlation matrix was used to check colinearity (r>0.80). Hazard ratios (HRs) for the incidence of dementia were estimated using Cox proportional hazard models adjusted for the covariates age, education level and centre across MCI groups, based on results of the stepwise logistic regression. Interactions between variables were examined on this same cohort in a previous report where we found significant interaction with sex on a large number of variables, justifying our decision to examine risk profiles separately for men and women[23]. We have thus stratified our present analyses by sex. Statistical analyses were carried out with SPSS for Windows NT, version 17.0.

RESULTS

Within this sample 320 persons (192 women) without dementia at baseline were diagnosed with dementia at one of the two follow-up examinations. This Dem-MCI group, are older than the

comparison group (77.8 (SD=5.73) and 74 (SD=5.49) years respectively). Table 1 compares the clinical characteristics of the Dem-MCI group at baseline with those who did not develop dementia. Dem-MCI subjects were found to differ on a number of clinical and socio-demographic characteristics; notably higher age, lower education, ApoE ε4 genotype, depressive symptomatology, poor subjective health, more socially isolated, loss of appetite, difficulty with IADLs, non-use of hormonal replacement therapy, history of glycemia or diabetes, stroke or cardiovascular disease, low BMI and greater use of drugs with anticholinergic effects. The Dem-MCI group had poorer performance on all cognitive tests compared to the rest of the cohort. In the Dem-MCI group 75.3% had a subjective cognitive complaint compared to 66.7% of the non-MCI population. For comparison purposes we applied the conventional MCI-R criteria based on a statistical definition of poor cognitive performance at baseline (lowest quartile on one of the cognitive tests) to the two groups. This MCI-R group represents 42 % (n=3747) of the sample. The criteria identified 66.2% of our Dem-MCI group but also classified 41.9% of the normal population as MCI. The MCI-R group were younger than the Dem-MCI group (74.63 SD=5.8 versus 77.87 SD=5.73, $p<0.001$) and had a higher percentage with medium levels of education 60.3% versus 42.5%, $p<0.001$) although such comparisons are questionable given that the MCI-R group contained 204 Dem-MCI subjects. Significant differences between the Dem-MCI group and the rest of the Montpellier cohort in total white matter lesion volume were found to be significant in a regression model adjusting for the other significant variables when men and women are combined, but numbers were too small to examine this separately for the two sexes (OR=1.5 [CI: 1.05- 2.13]).

Table 1 here

Stepwise logistic regression was used to identify principal non-cognitive clinical characteristics taking into account confounding effects from the other variables (Table 2) for men and women independantly. From this analysis it was observed that the significant discriminating clinical characteristics of the Dem-MCI group at baseline are in descending order for men ApoE ε 4 genotype and stroke, difficulties with IADL and glycemia. For women they are ApoE ε 4 genotype, depression, use of drugs with anticholinergic properties and low BMI.

Table 2 here

Finally, a Cox model stratified by gender and adjusted for age, education and study centre was used to establish hazard ratios for conventional MCI-R criteria alone compared to the same criteria supplemented by factors identified from this study (see Table 3) in order to assess the impact on specificity of an additional non-cognitive factor added to current MCI-R criteria. Specificity for MCI-R criteria alone is 60%, rising to 92% with the addition of ApoE ε 4 for men and women and to 97% in men with either history of stroke or IADL difficulties and to 93% in women with depressive symptomatology and 95% with anticholinergic drug use. Receiver Operating Characteristics curves were calculated (Table 3) showing no significant loss of discriminability (area under the curve AUC) with improved specificity.

DISCUSSION

In this study we have chosen to substitute the usual definition of MCI based on cross-sectional statistical criteria for cognitive dysfunction by a pragmatic definition which comes closer to the

clinical meaning of this concept, that is, non-demented elderly persons in a pre-dementia phase (Dem-MCI). Comparing our Dem-MCI cases at baseline with the remainder of the non-demented population we found, not surprisingly, significant differences on all the cognitive domains tested. Our principal interest here, however, are the non-cognitive differences which might increase the specificity of currently used algorithms. This population study included a large array of clinical variables allowing us to explore a greater number of risk factors than in most previous population studies. We observe above all that Dem- MCI subjects are characterized by a large number of cerebro and cardio vascular risk factors and additionally high levels of depressive symptomatology, IADL difficulties, anticholinergic drug use and non-use of hormonal replacement therapy in women.

Our observations are in agreement with the findings of the Framingham heart study which has previously documented high rates of cardiovascular risk factors in the years preceding onset of MCI and dementia, related in particular to carotid atherosclerosis and subsequent white matter lesions, silent infarcts and stroke[24]. Based on the Montpellier imaging data, Dem-MCI is also characterized by greater white matter lesion volume as observed elsewhere [25, 26] which in turn has been previously associated with increased levels of circulating beta-amyloid peptide[20]. White matter lesion volume may in fact be a further candidate for algorithm modification but unfortunately we were unable to include it in the final model in this analysis as data was only available for one centre. Furthermore, white matter lesions in the hippocampus and medial temporal areas as opposed to total volume may have been a more sensitive predictor of dementia. Regional analysis on this data set is currently being undertaken.

As indicated by our previous research, risk factors for MCI to dementia are not the same for men and women [23] suggesting that future research should perhaps construct separate criteria for MCI by sex. This would also have important implications for the planning of intervention programmes. The principal question which we aimed to address in the present report was whether by adding any of these non-cognitive variables to conventionally used MCI-R criteria we might improve their specificity in predicting dementia onset without significantly lowering overall discriminability. Our results show that specificity levels may be improved by including ApoE ε 4 genotype for both men and women. Including stroke and IADL difficulties in MCI algorithms for men and depression and anticholinergic drug use in women would appear to greatly improve detection rates. It is of particular interest to note that two of the significant precursors for women (depression and anticholinergic drug use) are potentially reversible at the present time. This is not the case for men. With regard to the improvement of current criteria, this analysis strongly suggests that increasing difficulty with IADLs should not be an exclusion criteria for MCI as it has in the past, but on the contrary an inclusion criterion. IADL loss in MCI is likely to be much more subtle than in dementia, probably principally related to difficulties in executive skills and action sequencing rather than psychomotor impairment. We have used loss of one or more IADLs as a criterion based on previous research on frailty in this population [27]. This may have been too low a threshold and may have also included persons with disability due to confounding causes such as stroke or cardiac disorders. There is a clear need to develop specific scales for the detection of IADL change in MCI.

Depressive symptomatology is also clearly a very important co-occurring symptom as has been observed elsewhere [28,29] and has furthermore been associated with cerebral amyloid and tau

deposition[29]. Our findings suggest it is a risk factor which particularly affects women. Depression is frequently an exclusion criterion in clinical MCI trials; a practice which is clearly not justified by our results. Again further research is required to determine the specific characteristics of MCI-related depressive symptomatology and to fix cut-off points from dimensional scales. Finally to what extent is subjective complaint a useful criterion given that it is currently a central part of current definitions of MCI ? We found in fact that while 75.3% of the Dem-MCI group had a cognitive complaint at baseline, so did 66.7% of the persons who did not develop dementia at follow-up. Again this criterion appears to have very poor specificity.

The strengths of this study have been the large prospective data set which has been able to take into account almost all the known risk factors for MCI evolution towards dementia. By retrospective identification of MCI cases it has taken a non-orthodox approach which is closer to the clinical reality of MCI (that is, cognitive impairment which does develop into dementia) than has been provided by past studies using statistical criteria. There are, however, a number of limitations to our study. We do not know how many of the persons in our non-MCI group may have developed dementia more than four years later. Observations from the Montpellier data set allow us to estimate that between four and 7 year follow-up a further 2% of Dem-MCI subjects went on to develop dementia. Assuming a similar low rate in other centres it is unlikely that this may have significantly changed our results, although it is possible that slower onset cases may have different risk factors. This point remains to be clarified by future research on this cohort. Conversely we have made the assumption that subjects with dementia at four year follow-up actually had MCI at base-line. Results from the Framingham cohort suggest cognitive impairment to be present, however, 13 years before dementia onset[30] and a twin study in which only one twin developed dementia showed significant cognitive loss 20 years before diagnosis[11]. The final

question is whether we may have achieved similar results by simply changing the cognitive test cut-off point within existing MCI-R criteria. This has already been attempted within case-control studies and prospective cohorts using a wide range of neuropsychological tests [2,4,5,31,32] with the common finding that prevalence rates vary widely, (10-74% [31])with small changes to cut-off points with specificity reaching inacceptable levels over 1.5 standard deviations. Together these results have so far suggested that, in the absence of more disease-specific cognitive tests, other criteria will be necessary.

CONCLUSION

Prospective studies may provide a more clinically relevant method of identifying persons with MCI by redefining it as persons without dementia who will develop the disorder within a short time period. From this alternative MCI cohort we have been able to identify a number of gender-specific non-cognitive clinical variables which may increase the specificity of current case-finding procedures. While the limitations of our study and the need for validation in other cohorts would prevent us from recommending an immediate modification of current MCI criteria, the study suggests that that this approach may in the future be useful in informing the revision process.

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Table1

Comparison of retrospectively identified MCI cases with the non-dementia population with t test or chi-squared as appropriate % (n).

Characteristics	Dem-MCI (n=320)	Comparison group (n=8599)	p values *
Sex (% women)	60 (192)	60 .8 (5230)	0.76
Education level			
low	39.9 (126)	24.9 (2142)	
medium	42.5 (135)	56.2 (4824)	0.0001
high	17.9 (57)	18.9 (1620)	
Depressive symptomatology level (CESD>16)	24.3 (76/313)[†]	13.4 (1134)	0.0001
APOE ε4 genotype	31.6 (93/313)[†]	19.6 (1596)	0.0001
High level of glycemia, diabetes mellitus or treatment	19 (56/295)[†]	13.6 (1112)	0.0001
Hypercholesterolaemia or treatment	53.7 (161/300)[†]	57.7 (4765)	0.16
Stroke	8.9 (28/316)[†]	4 (340)	0.0001
All cardiovascular antecedents	14.1 (45)	9.3 (795)	0.048
Head trauma	8.6 (27/315)[†]	7.5 (632)	0.46
Asthma	7.5 (24/318)[†]	8 (684)	0.762
Metabolic syndrome	36.6 (113/309)[†]	33 (2752)	0.18
BMI <27	73.4 (229/312)[†]	67 (5711)	0.017
Hypertension (<160/90 mm Hg or treatment)	63.8 (204)	61.1 (5248)	0.17
Herpes	26.1 (82/314)[†]	30.3 (2586)	0.116
Alcohol (current drinkers)	79.7 (255)	79.7 (6835)	0.99
Tobacco (current or former smokers)	33.9 (108/319)[†]	38.9 (3348)	0.067
Poor subjective health	10.7 (34/318)[†]	5 (426)	0.0001

Insomnia	27.2 (70/257)†	25.4 (1937)	0.509
Social isolation	43.1 (138)	35.5 (3045)	0.005
Recent appetite loss (< 3 months)	21.5 (68/317)†	13.1 (1120)	0.0001
Anticholinergic drug use	12.8 (41)	7.5 (646)	0.03
Hospitalisation for cancer	1.3 (4)	1.7 (148)	0.523
Anaesthesia	33.3 (99/297)†	31.1 (2507)	0.921
Difficulty with at least 1 IADL	23.8 (75/315)†	9 (769)	0.0001
Difficulty with at least 1 ADL (except incontinence)	0.6 (2/318) †	0.9 (81)	0.563
Hormone Replacement Therapy (past or current)	20.7 (37)	31 (1561)	0.003
Verbal Fluency (Isaacs) median	55 (171)	27.2 (2302)	0.0001
Visuospatial memory (Benton)median	53.1 (164)	34.2 (2889)	0.0001
Trail making B median time	44.8 (121)	24.1 (1944)	0.0001
Immediate and delayed memory (Dubois)median	11.5 (35)	4.5 (407)	0.0001
Subjective cognitive complaint (%)	75.3 (241)	66.7 (5718)	0.0001

† Discrepancies in % reported due to missing values

Table 2

Stepwise backward logistic regression for clinical characteristics discriminating the Dem- MCI group independantly for men and women.

MEN

Variables	Beta coefficient	Wald	p	OR 95 % IC *
APOE ε4 genotype	0.77	16.61	< 0.001	2.17 [1.44-3.29]
Stroke	0.77	5.94	0.015	2.17 [1.16-4.05]
IADL	0.54	4.02	0.040	1.72 [1.01-3.00]
Glycemia	0.56	6.36	0.012	1.72 [1.13-2.71]

*Model adjusted by age, education level, centre

WOMEN

Variables	Beta coefficient	Wald	p	OR 95 % IC *
APOE ε4 genotype	0.82	20.63	< 0.001	2.27 [1.59-3.24]
Depression (cesdt>16)	0.67	12.25	< 0.001	1.96 [1.34-2.87]
Anticholinergic drugs	0.46	4.15	0.041	1.59 [1.05-2.28]
low BMI	0.43	3.39	0.027	1.54 [1.05-2.28]
IADL	0.40	3.39	0.065	1.49 [0.97-2.30]

*Model adjusted by age, education level, centre

Table 3

Cox proportional hazards model for transition to dementia comparing specificity of conventional MCI-R criteria when additional clinical characteristics are added

MEN

	Roc curves		Cox models			
MCI Groups	Specificity %	AUC	Beta coefficient	Wald	p	Hazard Ratios 95 % IC *
MCI -R	60	0.642	1.10	32.61	<0.001	3.01 [2.1-4.4]
MCI-R+APOE ε4	92	0.566	1.27	30.83	<0.001	3.58 [2.3-5.6]
MCI-R+stroke	97	0.531	1.42	20.13	<0.001	4.15 [2.2-7.7]
MCI-R+IADL	97	0.564	1.52	34.73	<0.001	4.57 [2.5-7.6]

*Cox models adjusted by age, education level, centre
AUC: Area Under the Curve

WOMEN

	Roc curves		Cox models			
MCI Groups	Specificity %	AUC	Beta coefficient	Wald	p	Hazard Ratios 95 % IC *
MCI -R	60	0.604	0.76	23.35	<0.001	2.1 [1.6-2.9]
MCI-R+anticholinergic drug	95	0.553	0.83	13.70	<0.001	2.3 [1.5-3.5]
MCI-R+APOE ε4	92	0.531	1.03	27.28	<0.001	2.8 [1.9-4.1]
MCI-R+depression	93	0.561	1.02	28.53	<0.001	2.8 [1.9-4.1]

*Cox models adjusted by age, education level, centre
AUC: Area Under the Curve