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The Informant Questionnaire on Cognitive Decline in the Elderly Individuals in Screening Mild Cognitive Impairment With or Without Functional Impairment

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Abstract

The Informant Questionnaire on Cognitive Decline in the Elderly individuals (IQCODE) is a reliable, validated informant-based instrument. Most of the studies well support the validity of the IQCODE in dementia screening, but the sensitivity of the rating scale at the early stage during the course of dementia is limited. In this study, we investigate the utility of the IQCODE for patients with mild cognitive impairment (MCI) and the discriminative power of the IQCODE in patients having MCI with and without functional impairment. The samples included mild Alzheimer disease (AD, N = 280), MCI ([N = 657], further divided into 2 subgroups: patients with MCI having functional impairment [MCI-fi, N = 357] and patients having MCI without functional impairment [MCI-fn, N = 300]), and normal cognition (NC, N = 274). The IQCODE, Mini-Mental State Examination (MMSE), and other neuropsychological tests were administered to all participants. Logistic regression and receiver—operating characteristic (ROC) curves were used to evaluate the diagnostic ability of the IQCODE, compared to the MMSE. The optimal cutoff scores of the IQCODE were 3.19 for the MCI (sensitivity/specificity: 0.979/0.714) and MCI-fn (0.900/0.817), 3.25 for the MCI-fi (0.978/0.701), and 3.31 for mild AD (0.893/0.779), while the MMSE was identical, that is 26, for both MCI and its functional normal and functional impaired subgroups (0.892/0.755, 0.867/0.745, and 0.913/0.745, respectively) and 24 for mild AD (0.807/0.836). The discriminating accuracy of the IQCODE was slightly superior to that of the MMSE but did not reach statistical significance. Our study suggests that the IQCODE might be useful in screening for MCI, with hierarchical scores indicating functional normal or impaired.

Keywords

mild cognitive impairment, Alzheimer disease, screening test, informant-based questionnaire

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Introduction

For more than a decade, there has been a growing interest in the transition state of the cognitive changes between normal aging and dementia or, more specifically, Alzheimer disease (AD).[1] Clinical dementia diagnosis is based on the quantification of the patient's cognitive deficits and also on impairment in the activities of daily living (ADLs). This quantification provides the possibility that we may be able to identify the earliest clinical features of the illnesses before cognitive and functional impairment is evident. Toward this end, the concept of mild cognitive impairment (MCI) has been evolved to capture this predementia phase of cognitive dysfunction.[2] The MCI is defined as a slight impairment in the cognitive function (typically memory) with normal function or only minimal abnormal complex instrumental ADLs (IADLs).[3]

Previous longitudinal studies showed that participants with MCI having early functional changes experienced a more rapid cognitive decline than their functionally intact MCI peers. In addition, the restriction of IADLs was associated with a much lower chance of reversibility to normal cognition.[4,5] Evidence from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study demonstrated that baseline informant-reported functional deficits were associated with a 4-fold increase in conversion to dementia during long-term follow-up.[6] These findings suggest that the restrictions in IADLs in patients with MCI have a strong diagnostic and predictive value for subsequent

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dementia. Thus, identifying participants with MCI having early functional changes is clinically important.

To date, several performance-based measures have been proposed as screening instruments for MCI[7-10]; however, in general, these neuropsychological screening tests do not account for the functional change in early cognitive impairment. Therefore, besides neuropsychological evaluation, further assessment of functional status is necessary to make a diagnosis for cognitive impairment. Informant-based measures, capturing the subtle change in both cognition and function in one time, provide an alternative approach for assessing cognitive as well as functional decline.

The IQCODE is a reliable, validated informant-based instrument and has been widely adopted by clinical researchers across different cultures and languages.[11] The questionnaire addresses everyday memory and function including short-term and long-term memory, orientation in time and space, financial awareness, learning, and executive skills. Most of the studies well support the validity of the IQCODE in dementia screening, but the sensitivity of the rating scale at the early stage during the course of dementia is limited.[12] Recently, some studies have shown that patients with MCI and patients with early dementia can be ideally detected by IQCODE,[13,14] whereas others could not confirm these findings.[15,16]

The primary aim of our study was to investigate the utility of the IQCODE for patients with MCI and the discriminative power of the IQCODE in patients having MCI with and without functional impairment.

Methods

Patients

Sample is from a baseline part of China Cognition and Aging Study (China COAST). The China COAST is an ongoing longitudinal national study on MCI and dementia based on the hospital and the population with a follow-up scheduled every 1 to 2 years. The hospital-based baseline cohort includes patients with informants who visited the neurological clinic of 36 tier 3 hospitals, covering 4 municipalities and 19 provinces of China, from September 2009 to December 2009. All consecutive participants who were 55 years and older, or with complaint of cognitive impairment, or with history of stroke/TIA, and without serious visual, hearing impairment or other serious illness preventing further examination underwent a standard cognitive screening procedure. Informants were the patients' spouses or relatives who lived in the same household and reported no psychiatric or neurological disease. The outpatients who were diagnosed as MCI, mild probable AD, or normal cognition (NC) and their informants completed an IQCODE without missing items that were included in the study.

Instruments

The IQCODE is an informant-rated questionnaire developed with the goal of assessing change in the cognitive functioning over 10 years.[11] This study is based on the 16-item version and the cognitive changes are scored on a 5-point scale, with 1 indicating "much improved," 3 "not much change," and 5 "much worse." Higher scores correspond to greater cognitive decline. The ratings are averaged, composing a mean score between 1 and 5. The questionnaire takes approximately 10 minutes to administer. The IQCODE has been validated for use in Chinese.[17]

The Chinese version of ADLs (CADLs) was used to describe functional status in the study. The CADLs was developed from the Older Americans Resources and Services (OARS) ADLs.[18] The CADLs includes 6 activities of basic ADLs (bathing, dressing, toileting, transferring, continence, and feeding) and 8 activities of IADLs (using telephone, shopping, meal preparation, housekeeping, laundry, use of transportation, self-administration of drugs, and handling finances). In addition, to further detect ADLs impairment, 3 items were derived from transferring (walking outdoor, walking indoor, and walking up and down the stairs) and another 3 items (getting on to and out of bed, cutting toenails, staying at home alone) are added to compose the 20-item CADLs. The 3-point coding in the original OARS (0 = completely unable to do, 1 = with some help, and 2 = without help) was changed to 4 points in the CADLs (1 = can do it myself, 2 = have some difficulty doing but can still do it by myself, 3 = need help to do it, and 4 = cannot do it at all). The score of the CADLs is the sum of every item score, ranging from 20 to 80. The CADLs has also been validated for use in Chinese elderly individuals.[18]

Procedure

The cognitive screening procedure included medical history, informant-based history, physical and neurological examination, laboratory tests, cranial magnetic resonance imaging (MRI), and a battery of neuropsychological and functional evaluations, including the IQCODE, the Mini-Metal State Examination (MMSE),[19] the World Health Organization—University of California Los Angeles Auditory Verbal Learning Test (WHO-UCLA AVLT),[20] the Clock Drawing Test(CDT),[21] the Clinical Dementia Rating (CDR),[22] CADLs, the Neuropsychiatric Inventory (NPI),[23] the Hamilton Depression scale (HAMD),[24] and the Hachinski Ischemic Score (HIS).[25] Diagnoses were made in a consensus meeting independent of the results of the IQCODE and the MMSE. Patients with mild AD were required to meet the National Institute of Neurological Disorders and Stroke—Alzheimer's Disease and Related Disorders Association(NINCDS-ADRDA) criteria[26] and global CDR = 1. Operationally modified Petersen criteria were used for MCI,[1] including (1) memory impairment with an insidious onset complained by participants or informants; (2) objective abnormal memory function, WHO-UCLA AVLT delayed recall score at least 1.5 standard deviation (SD) below an education-adjusted norm; (3) normal general cognitive function, as determined by a clinician's judgment based on CDR (global CDR of 0.5, with at least a 0.5 in the memory domain); (4) the ADLs were required to be normal or only slightly impaired, based on the scores of CDR functional domains (ie, judgment and problem solving, community affairs, home, and

Table 1. Demographic Characteristics and Neuropsychological Variables of the Study Groups

			MCI		
	NC (n = 274)	Mild AD (n = 280)	Total (n = 657)	MCI-fn (n = 300)	MCI-fi (n = 357)
Age,years	70.08 (7.08)	69.97 (7.64)	70.87 (7.32)	70.30 (7.10)	71.34 (7.41)
Gender, %male	42.3	38.9	40.5	40.7	40.3
Education, years	6.94 (3.34)	6.75 (5.76)	7.36 (4.74)	7.13 (4.33)	7.59 (5.11)
IQCODE	3.18 (0.24)	3.67 (0.46)[b]	3.51 (0.32)[b]	3.47 (0.30)[b,c]	3.55 (0.33)[b,c,d]
MMSE	27.31 (2.71)	18.54 (0.34)[b]	22.66 (4.14)[b]	23.2 (3.80)[b,c]	22.21 (4.36)[b,c,d]
CADLs	20.00 (0.00)	24.42 (6.16)[b]	21.62 (3.79)[b]	20.00 (0.00)[b,c]	23.54 (4.49)[b,c,d]
CDT	2.88 (0.50)	1.60 (1.00)[b]	2.13 (0.95)[b,c]	2.30 (0.86)[b,c]	1.95 (1.00)[b,c,d]
AVLT immediate recall	28.04 (5.33)	14.80 (5.60)[b]	18.84 (6.91)[b,c]	19.78 (6.63)[b,c]	17.83 (7.06)[b,c,d]
AVLT delayed recall	10.21 (1.18)	4.71 (2.99)[b]	5.75 (3.37)[b,c]	6.18 (3.33)[b,c]	5.28 (3.36)[b,c,d]

Abbreviations: NC, normal cognition; AD, Alzheimer disease; MCI, mild cognitive impairment; MCI-fn, mild cognitive impairment with normal function; MCI-fi, mild cognitive impairment with function impaired; IQCODE, informant questionnaire on cognitive decline in the elderly individuals; MMSE, Mini-Mental State Examination; CADLs, Chinese version of activities of daily living; CDT, clock drawing test; AVLT, World Health Organization—University of California Los Angeles Auditory Verbal Learning Test.

[a] Data are mean standard deviation, unless otherwise stated.

[b] Compared to NC, $P < .01$.

[c] compared to patients with mild AD, $P < .01$.

[d] compared to patients with MCI-fn, $P < .01$.

hobbies) $\leq$1; (5) HIS $\leq$4 and no presentation of extensive white matter lesions and/or lacunar infarction on the MRI; (6) not sufficiently impaired, cognitively and functionally, to meet NINCDS-ADRDA criteria; and (7) without other obvious medical, neurological, or psychiatric explanations for the memory loss (with the exception of mild depression). Further, patients with MCI were divided into 2 subgroups by the CADLs score: MCI with functional impairment (ie, MCI-fi, a summed score of CADLs is 21;22 for <75 years old, 21—24 for $\geq$75 years old) and MCI with functional normal (ie, a summed score of CADLs is 20). Inclusion criteria of the NC were an overall CDR score of 0 and scores in the normal range on all battery tests.

The study was approved by the ethics committee of the Xuan Wu Hospital, Capital Medical University. Written informed consent was obtained for each participant, either directly from the patient or from his or her informant.

Statistical Analyses

Characteristics of the 3 diagnostic groups (ie, NC, MCI, and mild AD group) were compared using analysis of variance and chi-square tests, and the correlations between measures and demographic variables were calculated using Pearson correlation coefficients. We used multivariate linear regression to examine the IQCODE and MMSE scores, while adjusting for age, education, and gender. Receiver—operating characteristic (ROC) curves were constructed to determine the ability of the IQCODE to discriminate 4 planned comparisons of interest: (1) the NC versus MCI, (2) the NC versus MCI-fn, (3) the NC versus MCI-fi, and (4) the NC versus mild AD. To provide a standard for comparison, the ROC curve for the MMSE was also produced. The sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) of the IQCODE and MMSE were calculated. The confidence intervals (CIs) for sensitivities and specificities were calculated following Clopper and Pearson method.[27] The area under the ROC curves (AUCs) were used as an overall index of performance of the screening tests. The AUCs and their standard errors were calculated using the Wilcoxon method described by Hanley and McNeil[28] and the differences between areas compared using the method of Hanley and McNeil.

All statistical analyses were executed with the SPSS 16.0 (SPSS Inc; Chicago, Illinois) package. Statistical significance was set at $P < .05$.

Result

Demographic Characteristics of the 3 Groups

Demographic characteristics and scores on the key study measures (represented by mean $\pm$ SD) of participants with NC, MCI, and mild AD are described in Table 1. There were no statistical differences among the 3 groups with regard to age, gender, and years of education of the participants (for each $P > .05$).

Correlations Between Demographic Variables and Test Scores of IQCODE and MMSE

The IQOCDE and MMSE scores were significantly correlated to each other in all the 3 diagnostic groups ($r = -.156$ for the NC group, $-.158$ for the MCI group, and $-.449$ for the mild AD group; for each $P < .001$).

In the NC group, the IQCODE and MMSE scores were all significantly correlated with age ($r = .178$ and $-.167$ respectively; $P < .001$) and years of education($r = -.141$ and .635 respectively; $P < .001$). Gender had no significant effect on the 2-scale scores. Impact of age and education on the IQCODE and the MMSE scores was further analyzed. The result of linear regression analysis showed that the IQCODE score was influenced by age ($R^2 = .032$, β coefficient = .178, $P = .003$), but

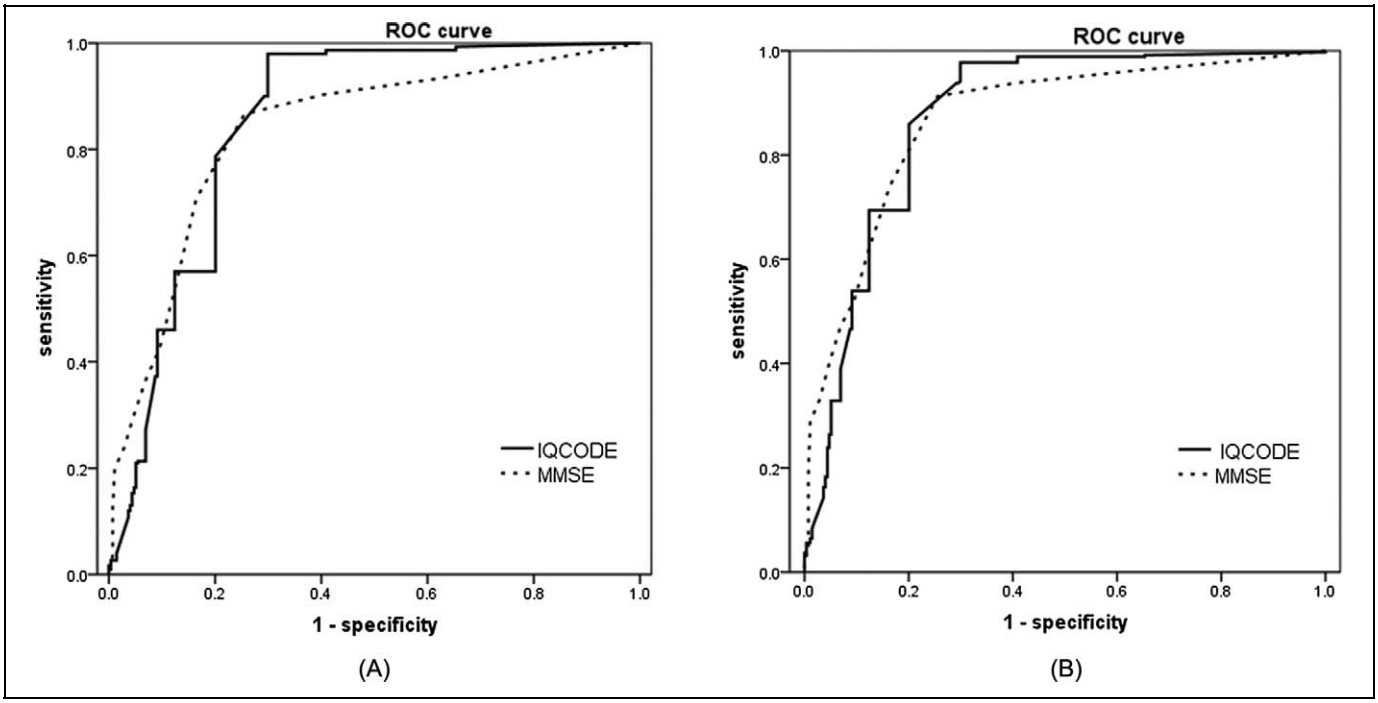

Figure 1. Receiver—operating characteristic curves for the informant questionnaire on cognitive decline in the elderly individuals and the Mini-Mental State Examination as screening tests for (A) mild cognitive impairment without functional impairment and (B) mild cognitive impairment with functional impairment.

Table 2. Diagnostic Performance of the Informant Questionnaire on Cognitive Decline in the Elderly Individuals and Mini-Mental State Examination

	Sen.(95% CI)	Spec.(95% CI)	PPV	NPV	AUC (95%CI)	Cutoff Point
NC versus MCI						
IQCODE	97.9 (97.7-98.1)	71.4 (69.8-73.0)	89.3	93.2	0.865 (0.834-0.895)	3.19
MMSE	89.2 (88.5-89.9)	75.5 (74.1-76.9)	89.3	74.2	0.854 (0.838-0.890)	26
NC versus MCI-fn						
IQCODE	90.0 (88.9-91.0)	81.7 (80.0-83.4)	77.1	86.6	0.852 (0.818-0.885)	3.19
MMSE	86.7 (85.4-88.0)	74.5 (73.4-77.6)	79.1	81.5	0.835 (0.801-0.869)	26
NC versus MCI-fi						
IQCODE	97.8 (97.6-98.0)	70.1 (68.5-71.7)	81.0	96.0	0.875 (0.845-0.906)	3.25
MMSE	91.3 (90.4-92.1)	74.5 (73.6-77.4)	82.9	87.0	0.870 (0.841-0.899)	26
NC versus mild AD						
IQCODE	89.3 (88.2-90.4)	77.9 (76.6-79.2)	82.8	88.1	0.901 (0.875-0.928)	3.31
MMSE	80.7 (78.9-82.5)	83.6 (82.6-84.6)	83.3	80.9	0.905 (0.88-0.93)	24

Abbreviations: IQCODE, informant questionnaire on cognitive decline in the elderly individuals; MMSE, Mini-Mental State Examination; MCI, mild cognitive impairment; AD, Alzheimer disease; Sen, sensitivity; Spec, specificity; CI, confidence interval; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

the rate of decline increased only 0.036 points per 10 years of age. Education had no significant additional impact on the IQCODE when the influence of age was controlled. In contrast, the MMSE score was more strongly associated with education ($R^2 = .529$, β coefficient = .608, $P < .001$).

Correlations Between Neuropsychological Performance and Test Scores of IQCODE and MMSE

In the cognitive impairment group (ie, MCI and mild AD), IQCODE and MMSE scores were significantly correlated with AVLT immediate recall ($r = -.422$ and .657, respectively; $P < .001$), AVLT delayed recall ($r = -.364$ and .544, respectively; $P < .001$), CDT($r = -.385$ and .669, respectively; $P < .001$), and CADLs ($r = .579$ and $-.675$, respectively; $P < .001$).

Results of the ROC Analyses

The ROC curves for the IQCODE and the MMSE as measures for discriminating MCI with and without function impairment from NC are shown in Figure 1. The discriminating accuracy of the IQCODE was slightly superior to that of the MMSE (AUC

0.865 vs 0.854 for MCI, 0.852 vs 0.835 for MCI-fn, and 0.875 vs 0.870 for MCI-fi). However, this difference was not statistically significant.

Sensitivity, specificity, and PPV and NPV obtained at the best cutoff points for the 2 screening tools are shown in Table 2. The cutoff score for the IQCODE was different difference between the MCI-fn and the MCI-fi group (3.19 and 3.25, respectively), while for the MMSE it was identical, that is 26, in both the MCI group and its 2 subgroups.

Discussion

In the present study, we assessed the validity of the IQCODE in patients with MCI, subtyped on whether functional impairment exists, and compared to NC and patients with mild AD. Cutoff scores to classify patients at different cognitive decline levels were provided: an IQCODE score <3.19 is considered as cognitive normal, while values >3.31 indicate patients with frank mild AD; intermediate scores between 3.19 and 3.31 may indicate a diagnosis of MCI. It is noteworthy that within that scope, an IQCODE score >3.25 (ie, 3.26 ~ 3.31) suggests MCI-fi.

We found that the cutoff score of the IQCODE could differentiate between the MCI-fi and MCI-fn, while the MMSE only provided identical cutoff score for the 2 subgroups. There are some explanations for the difference: first, the questions of the IQCODE focus primarily on discrete everyday function dependent on the specific cognitive abilities often affected by dementia, such as handling personal finances, going shopping, and so on. This may increase sensitivity to very subtle changes that occur in the early or preclinical stages of dementia, where an affected individual still generally maintains his or her independence of function in daily life. Second, the unique aspect of the IQCODE is that it specifically assesses cognitive and functional change from the previous cognitive level that is one of the major criteria required for the clinical diagnosis of MCI. Third, the influences of education and age have been shown to be negligible on IQCODE scores. Additionally, the IQCODE proved acceptable to informants and was quick and easy to use. This study supports the utility of the IQCODE that it provides, the possibility of a simple and applicable way to detect cognitive and/or functional impaired patients with MCI.

There are some strengths to this study. To our knowledge, few studies have tried to use a single screening instrument to differentiate MCI from the aspect of whether the functional deficits exist. Currently, MCI is dominantly subtyped on a cognitive basis as amnestic versus nonamnestic and single domain versus multiple domain. There is also emerging literature on subtyping MCI according to the presence of clinical feature,[29] likely etiology,[30] neuroimaging findings,[31] genetic features,[32] or progression rate.[33] Data from the ADNI show that patients with MCI having impaired IADLs exhibited more widespread gray matter thinning in frontal and parietal lobe brain regions, and a higher rate of progression to probable AD over a 2-year follow-up period than MCI with intact IADLs,[34] suggesting that the MCI-fi could be a beginning of AD. For this reason, we divided the MCI group into 2 subgroups, according to the functional evaluation by the informants. In addition, this study utilized a large sample (particularly the cognitive impairment sample) that likely provided relatively good statistical power for detecting the group differences and relationships between the cognitive measures and the IQCODE.

There are some caveats of the present study. First, as this was a baseline study, it could be argued that the presence of deficits of cognition coupled with impaired everyday function would probably misclassify MCI and AD. Although this is possible, it should be noted that the characteristics of our MCI group were comparable with those of the MCI group reported by Petersen.[1] That is, the diagnoses were provided according to the well-recognized neuropsychological criteria, and the sample might be minimally biased. Second, although only close informants who reported no psychiatric/neurological disease were included, we did not examine the quality of the relationship and mental health of the informant.[12] Therefore, in our future study, we will examine the effect of informant's stress on the IQCODE ratings for patients with MCI with different functional levels.

In conclusion, this study provides the evidence that IQCODE is useful to classify patients at different cognitive status, especially the patients with MCI with or without functional impairment. This may contribute to better identifying those who are at greater risk for further cognitive decline.

Declaration of Conflicting Interests

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