MEASURING EVERYDAY COGNITIVE FUNCTIONING
How useful is the IQCODE for discriminating between AD, MCI and subjective memory complaints?
ABSTRACT

Background: Informant questionnaires may be useful in diagnosing early dementia. Conflicting results were found when these questionnaires were used to differentiate mild cognitive impairment (MCI) from healthy elderly subjects. We evaluated the ability of the most commonly used informant questionnaire, the informant questionnaire on cognitive decline in the elderly (IQCODE), to discriminate between Alzheimer’s disease (AD), mild cognitive impairment (MCI) and subjective memory complaints (SMC).

Methods: Informants of 180 AD patients, 59 MCI patients and 89 SMC subjects who visited the Alzheimer Center of the VU University Medical Center between 2004 and 2007 completed the short Dutch version of the IQCODE. Logistic regression and receiver operating characteristic curves were used to evaluate the diagnostic ability of the IQCODE. Results: The IQCODE was able to differentiate AD from MCI and SMC, but was not able to differentiate SMC from MCI. Conclusions: The IQCODE may be helpful in diagnosing AD, but is of limited use in differentiating MCI from SMC.
INTRODUCTION

Alzheimer’s disease (AD) is the most common cause of dementia worldwide. AD is generally thought to be preceded by a prodromal phase, usually referred to as Mild Cognitive Impairment (MCI). This stage forms a continuum between normal cognitive functioning and Alzheimer's disease. Recognizing MCI may contribute to an early diagnosis of AD, since MCI patients are at increased risk of developing AD.

Patients in the early phases of cognitive decline are often referred to memory clinics. Screening tests, such as the mini mental state examination (MMSE), are commonly used in these settings. Informant-based instruments could be used to complement the diagnostic process, since informants, such as spouses or children, can provide relevant information about decline in everyday functioning or everyday cognition. However, standardized and validated informant instruments are less frequently encountered than cognitive tests. Nonetheless, several informant questionnaires are available; the informant questionnaire of cognitive decline of the elderly (IQCODE) is a reliable questionnaire and is currently the most widely used informant instrument. The original IQCODE consists of 26 items, aimed at everyday cognitive functioning. The items of the IQCODE are for example related to everyday memory and instrumental activities of daily living. A short version of 16 items with comparable psychometric qualities is also available. The questionnaire has been validated in numerous languages and countries.

A number of investigators have evaluated the quality of the IQCODE as a screening questionnaire in community samples. According to these studies, the IQCODE performs at least as well as cognitive screening tests such as the MMSE. Moreover, an important advantage of the IQCODE over the MMSE is that it is not being affected by patient's premorbid intelligence or education. Other investigators have suggested that the combination of the IQCODE with a cognitive screening test produces the highest accuracy rates.

Despite this widespread research in community samples, only a limited number of studies have investigated the use of the IQCODE in a memory clinic population. In this setting, the IQCODE also seems to be able to differentiate between dementia patients and elderly without cognitive deficits. The accuracy values of the IQCODE vary, with sensitivity values of 0.74 to 0.90 and specificity values of 0.39 to 0.71. Several studies included MCI patients. These studies have conflicting results: According to Isella et al. and Ehrensperger et al. healthy elderly can be distinguished from MCI patients, whereas Dutra de Abreu et al. could not confirm these findings. These previous studies used healthy elderly as a control group. However, since these subjects are not likely to visit a memory clinic, a study with a realistic control group is necessary.
The aim of the current study is to evaluate the ability of the IQCODE to discriminate between persons with AD, MCI and subjective memory complaints (SMC). SMC refers to the subjects who had memory complaints, but in whom no objective cognitive impairment was found. The comparison between these groups is highly relevant for a memory clinic setting, as these groups are frequently encountered and differentiation is difficult. We hypothesized to find differences on the IQCODE between all study groups.

METHODS

Patients

From the cohort of patients who visited the Alzheimer Center of the VU University Medical Center between 2004 and 2007, all consecutive patients diagnosed with probable AD, MCI or SMC and of whom the caregiver completed an IQCODE were included in the study.

A total of 180 patients met the criteria for probable AD, 59 for MCI and no objective cognitive deficits were found in 89 subjects. The mean age was 68.4 (SD 10.1) years. The level of education was categorized using the classification of Verhage, ranging from 1 (low) to 7 (high). The study was approved by the Ethics Committee of the VU University Medical Center and all patients gave written informed consent.

Instruments

IQCODE

The IQCODE measures changes in everyday cognitive functioning over the previous 10 years. The questionnaire is self-administered by an informant of the patient. The cognitive changes are scored on a bipolar 5-point scale, with 1 indicating ‘much improved’, 3 ‘not much change’ and 5 ‘much worse’. In this study we used the Dutch short version of the IQCODE, consisting of 16 items. The total scoring range lies between 16 and 80. In the original scoring, the ratings are averaged, composing a score between 1 and 5. An alternative approach is to sum the ratings. This approach was used in the current study and leads to a total scoring range between 16 and 80. Informants completed the IQCODE during the visit at the outpatient clinic during the time the patients underwent the examinations. Diagnoses were made independently of the IQCODE scores.

Dementia screening

All subjects underwent a standard dementia screening including medical history, informant based history, physical and neurological examination, screening laboratory tests, neuropsychological tests, MRI, EEG and the MMSE. Diagnoses were
made in a multidisciplinary consensus meeting. The NINCDS-ADRDA criteria were used for the diagnosis of probable AD and the Petersen criteria for the diagnosis of MCI.\textsuperscript{1,28,29} SMC were defined by virtue of their presentation to the memory clinic. No objective impairments were found in these patients.

**Statistical analysis**

Logistic regression analysis was used to investigate the association between the IQCODE and the risk of AD or MCI. The IQCODE was the predictor of interest and a diagnosis of AD or MCI was the dependent variable with either SMC or MCI as reference group. Associations were presented as odds ratios (OR) with 95% confidence intervals (CI). Unadjusted univariable analyses were performed followed by multivariable logistic regression with adjustment for the covariates age, gender, education and MMSE. The linearity of the associations was studied, and independent variables were categorized if they did not show a linear association with outcome. Sensitivity and 1-specificity values for both models were plotted against each other at each possible cut-off point to compose receiver operating characteristic (ROC) curves.

Since several cases contained missing item scores, we applied a multiple imputation method before conducting the logistic regression analysis. By using this method, we could allow up to 50% missing values and it was not necessary to discard any potentially relevant data. Previous reports on missing items of the IQCODE describe two to six missing responses.\textsuperscript{16} In the current study, 19.8% of the subjects had one or more missing values, with a maximum of seven missing values. The imputation method used was corrected item mean substitution (CIMS). This approach uses the effect from an individual and the effect from the question as counterweights for imputing the missing data. It was shown to be adequate for test and questionnaire data.\textsuperscript{30} We applied this imputation method five times to the incomplete data set.

Logistic regression analyses were conducted for each data file, and the results were merged using a statistical program (MI-mul). Subroutines in SPSS for CIMS and MI-mul have been made available by van Ginkel and van der Ark\textsuperscript{31} and van Ginkel.\textsuperscript{32}

Statistical analyses were performed with SPSS (version 15.0 for windows; SPSS Inc., Chicago, Ill, USA). Statistical significance was set at p < 0.05.
RESULTS

Table 1 shows the comparison of demographic and baseline variables between the study groups. Some educational levels of the Verhage classification were represented by very few patients, so we categorized education into low (1 to 4), mean (5) and high (6 and 7).

### Table 1. Comparison between demographic and baseline variables of the study groups.

<table>
<thead>
<tr>
<th></th>
<th>SMC (n = 89)</th>
<th>MCI (n = 59)</th>
<th>AD (n = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.6 (10.8)</td>
<td>68.1 (8.0) *</td>
<td>72.3 (8.0) *†</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>43 (48.3)</td>
<td>45 (76.3) *</td>
<td>97 (53.9)</td>
</tr>
<tr>
<td>Education ‡, n</td>
<td>30 / 24 / 35</td>
<td>24 / 19 / 16</td>
<td>83 / 49 / 48</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.6 (1.5)</td>
<td>27.3 (1.9) *</td>
<td>21.1 (4.9) *†</td>
</tr>
<tr>
<td>IQCODE</td>
<td>55.5 (5.6)</td>
<td>58.9 (7.7) *</td>
<td>66.8 (7.1) *†</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or n (%). * p < 0.05 versus patients with SMC. † p < 0.05 versus patients with MCI. ‡ education was scored as low / mean / high educational level.

The association between the MMSE, dementia and MCI was non-linear and the MMSE was therefore dichotomized for the logistic regression analyses. For the analyses which included AD patients (AD versus MCI and AD versus SMC), MMSE values were dichotomized as ≤24 or >24. For the analysis between MCI and SMC, MMSE values were dichotomized as ≤28 or >28. We used the median score for this dichotomization, since there were only a few subjects with a MMSE score of 24 and below.

The results of the logistic regression analyses are shown in Table 2. First, analyses were performed on subjects with AD and SMC. The association between the IQCODE and diagnosis remained significant after adjustment for age, gender, education and MMSE. When considering these odds ratios, one should bear in mind that these represent the odds ratio for an increased IQCODE score of one point. Table 1 shows a mean difference of 11 points between AD and SMC. This would lead to a practical odds ratio of 16.46 (1.2911). Second, we performed logistic regression analyses on patients with SMC and MCI. The association with the IQCODE lost significance after adjustment for covariates. Third, logistic regression analyses were performed on patients with AD and MCI. The IQCODE remained associated with AD after adjustment for covariates.

ROC curves are shown in Figures 1-3. Figure 1 shows ROC curves for both the unadjusted (model 1) and adjusted (model 2) model for AD versus SMC. The Area under the curve (AUC) for the unadjusted model was 0.89 (95% CI, 0.85-0.93)
Table 2. Results of logistic regression analyses for the IQCODE.

<table>
<thead>
<tr>
<th></th>
<th>Model 1 OR (95% CI)</th>
<th>p</th>
<th>Model 2 OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD versus SMC</td>
<td>1.30 (1.22-1.38)</td>
<td>&lt;.001</td>
<td>1.29 (1.18-1.42)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MCI versus SMC</td>
<td>1.09 (1.03-1.15)</td>
<td>.004</td>
<td>1.06 (1.00-1.13)</td>
<td>.063</td>
</tr>
<tr>
<td>AD versus MCI</td>
<td>1.17 (1.11-1.23)</td>
<td>&lt;.001</td>
<td>1.14 (1.06-1.22)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Data are presented as odds ratios (95% CI) for one step increase in the IQCODE sum score.
Model 1: univariable, Model 2: adjusted for age, gender, education and MMSE.

Figure 1. ROC curves for AD versus SMC.
Model 1: IQCODE, Model 2: IQCODE with age, gender, education and MMSE.

Figure 2. ROC curves for MCI versus SMC.
Model 1: IQCODE, Model 2: IQCODE with age, gender, education and MMSE.

Figure 3. ROC curves for AD versus MCI.
Model 1: IQCODE, Model 2: IQCODE with age, gender, education and MMSE.
and 0.98 (95% CI, 0.96-0.99) for the adjusted model. The ROC curves for MCI versus SMC are shown in Figure 2. The AUC was 0.68 (95% CI, 0.59-0.77) for the unadjusted model and 0.81 (95% CI, 0.74-0.88) for the adjusted model. Figure 3 shows the ROC curve for AD versus MCI, with an AUC of 0.78 (95% CI 0.72-0.85) for the unadjusted model, and 0.93 (95% CI 0.89-0.96) for the adjusted model. The internal consistency of the IQCODE was high (Cronbach's alpha = 0.93). The correlation between the IQCODE and MMSE was moderate, with a value of 0.60.

DISCUSSION

In this study we investigated whether the IQCODE was able to differentiate between AD, MCI and SMC. We found that the IQCODE was able to differentiate AD from both SMC and MCI, but could not discern between MCI and SMC.

The ability of the IQCODE to discriminate AD is in line with previous studies.\textsuperscript{12,22,24} The IQCODE was not able to discriminate MCI, which is in contrast with the findings of Isella \textit{et al.}\textsuperscript{26} and Ehrensperger \textit{et al.}\textsuperscript{25} However, these studies used healthy subjects as controls, instead of people with SMC. This could lead to an overestimation of the diagnostic accuracy, as healthy controls are not likely to visit a memory clinic.\textsuperscript{33} Secondly, no adjustment for covariates was made in the analyses, so it is possible that the results were biased by confounding variables. This is a plausible explanation, since we found that the association was lost after adjustment for covariates.

We found the diagnostic ability of the IQCODE to be moderate. The power to discriminate between AD and SMC or MCI showed a major increase when the IQCODE was supplemented with age, sex, education and the MMSE score as predictors. This corresponds to the findings of previous studies.\textsuperscript{12,17,19,20} However, it is important to take into account that in the current study, as in most other studies, diagnoses were not made independently of the MMSE score. This bias will have contributed to the high sensitivity and specificity values. We therefore also provided sensitivity and specificity values for the IQCODE as a sole predictor.

It must be noted that a diagnosis of dementia is also not entirely independent of the IQCODE either, even though diagnoses were made independently of the IQCODE score. This is caused by the fact that the diagnostic criteria of dementia require a decline in social and occupational functioning.\textsuperscript{34} It is therefore to be expected that patient with AD will perform worse on a scale measuring everyday cognitive functioning. In addition, an important difference between MCI and AD is that MCI patients should have no difficulties in everyday functioning.\textsuperscript{29} Our findings support the MCI criteria and are therefore not entirely unexpected.
However, according to recent insights, MCI patients may report difficulties concerning complex day-to-day activities. It remains unclear what these activities are, but one can think of activities such as using a computer, or a mobile telephone. Such advanced activities are not covered in the IQCODE questionnaire. The low complexity of the IQCODE items might explain why the IQCODE was not able to discriminate MCI. A questionnaire consisting of more complex IADL items could be able to distinguish between the groups and could possibly indicate those patients prone to develop AD.

This is the first study which investigated the level of effectiveness of the IQCODE in discriminating between SMC, MCI and AD. One of the strengths of this study was the application of CIMS for missing items. Other studies excluded cases with too many missing item scores. By using CIMS none of the cases with missing item scores had to be excluded, so selection bias was minimized. The relatively large size of the samples is another important strength of this study. Limitations of the current study include the substantial amount of missing data. Even though we dealt with these missing items in the best possible way, in clinical practice missing items should be avoided when possible. Furthermore, due to the cross-sectional design no follow-up data were available. We did not have reliable information on which informant completed the IQCODE. Possible differences between different types of informants could therefore not be investigated. Another limitation of the current study is that subtypes of MCI were not identified. It might be possible that the IQCODE’s sensitivity differs for subtypes of MCI. A limitation of the SMC control group is that memory complaints can be an early sign of cognitive decline, in particular in highly educated elderly subjects. Even though SMC is a clinically relevant control group, this choice could possibly have led to a slight underestimation of the diagnostic properties of the IQCODE.

In conclusion, the IQCODE is an easy, self-administered informant questionnaire, which is useful to differentiate AD from MCI and SMC. However, its ability to identify MCI is limited, as the IQCODE could not distinguish MCI from SMC. Future studies could investigate whether different types of informants provide reliable information and whether subsets of items (e.g. memory or instrumental activities of daily living) differ in their diagnostic ability.

ACKNOWLEDGEMENT

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