Rapid Screening of Cognitive Change in Patients with Questionable Dementia Using the Memory Impairment Screen and the Isaacs Set Test

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OBJECTIVES: To assess the efficacy of combining the Memory Impairment Screen (MIS) and the Isaacs Set Test (IST) in predicting short-term development of dementia in a group of people with questionable dementia (QD) at baseline.

DESIGN: Performances of the weighted sum of MIS and IST and the $\ll$ or $\gg$ rule were compared with each other and with the Mini-Mental State Examination.

SETTING: Database of the Regional Network for Diagnostic Aid and Management of Patients with Cognitive Impairment in the Franche-Comté geographical area in France.

PARTICIPANTS: A cohort of 106 patients aged 65 and older with QD were followed up for a mean of 14.9 months (range 6–24 months).

MEASUREMENTS: Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for the combination of these two tests.

RESULTS: The weighted sum had a sensitivity of 0.74 and a specificity of 0.84. The $\ll$ or $\gg$ rule (MIS <6 or IST <25) had a sensitivity of 0.74 and a specificity of 0.81. When range values were applied, low scores on the MIS and the IST (MIS <6 and IST <25) led to a high probability of dementia, whereas high scores (MIS >7 and IST >29) suggested a high probability of remaining dementia-free in the study follow-up.

CONCLUSION: This quickly performed tool (5 minutes) is simple to use and score. When including cutscores (MIS <6 or IST <25) or range values, this test could be considered a useful screening procedure for all types of dementias. **J Am Geriatr Soc 57:703–708, 2009.**

Key words: dementia screening; questionable dementia

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Early detection of dementia is important for optimal management and optimal outcomes for patients and their families.[1] Neuropsychological tests may be useful in the identification of cognitive impairment that occurs in patients at risk for developing dementia over a wide spectrum of pathologies.[2] These tests should be validated in comparison with a diagnostic reference standard and applied not only to patients with and without dementia, but also to those with questionable impairment.[1,3] In patients with ambiguous impairment or questionable dementia (QD) it is more important to predict their cognitive outcome than to discriminate them from normal controls.[4]

An effective screening tool should initially be able to identify cognitive impairment of any etiology while being statistically reliable.[3] This type of screening tool should also permit referring clinicians to better describe a patient's symptom profile after a brief consultation.[3] Brief screening tests that assess memory and executive functions have demonstrated good performance in detecting mild dementia in a case–control approach.[5,6]

In a previously reported study,[6] the combination of the Memory Impairment Screen (MIS)[7] and the Isaacs Set Test (IST),[8] which assessed memory and executive functions in 5 minutes, was found to be more sensitive than the Mini-Mental State Examination (MMSE)[9] in screening all types of dementia at the mild stage. The limitation of this case–control study could be that it did not include patients with QD.

The aim of this study was to assess the efficacy of combining the MIS and the IST in predicting short-term outcomes of patients with QD and to compare its performance with that of the MMSE.

METHOD

Participants

The study was conducted in a cohort of patients aged 66 to 89 who attended local memory impairment consultation centers between November 2003 and December 2007. Pa-

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tients were consecutively recruited through the database of the Regional Network for Diagnostic Aid and Management of Patients with Cognitive Impairment in the Franche-Comté geographical area (Rapid-Fr network).[6]

A multidisciplinary team that conducted a neurological assessment, a neuropsychological evaluation, blood tests, and a neuroradiological analysis evaluated the clinical diagnosis of each patient. A diagnosis of QD was made based on the following criteria: presence of cognitive complaints that originated from the patients or their referent; impairment in one or more cognitive tests but insufficiently severe to interfere with daily activities assessed using four instrumental activities of daily living (IADLs) (ability to use the telephone, independence in transportation, self-administration of medication, ability to handle financial affairs);[10] a Clinical Dementia Rating (CDR)[11] score of 0.5; and absence of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM IV), criteria for dementia.[12]

For all patients with QD, the diagnosis at the follow-up visit was considered the main outcome. Conversion to dementia (converters) was defined according to the following criteria: progressive worsening of cognitive function at follow-up severe enough to affect IADLs[12] and progression of CDR score from 0.5 to 1. Standard criteria were used for diagnosis of Alzheimer's disease (AD),[13] vascular dementia (VaD),[14] dementia with Lewy bodies,[15] and frontotemporal dementia.[16] To avoid a diagnostic circularity, dementia was defined independently of the score results on the MIS, IST, and MMSE. Patients were considered not to have dementia (nonconverters) if their cognitive function remained stable or improved and they scored 0.5 or 0 on the CDR.

To limit the risk of including patients who may have had dementia at the baseline, only patients with QD who progressed to dementia at least 6 months after their baseline assessment[17] and remained without dementia at least 12 months after baseline were enrolled. Patients who were followed up for more than 24 months were not included in this study. It was not considered feasible to attempt to predict long-term outcome based only on brief assessment tests.

Exclusion criteria were craniocerebral trauma, stroke within 3 months from the beginning of the study, acute neurological or somatic pathologies, or progressive psychiatric illness except for major depression. The ethics committee of Besançon University Hospital gave their official approval to conduct the study, and all participants gave their informed consent for study inclusion.

Neuropsychological Evaluation

All participants first underwent the two screening tests (MIS, IST; Appendix A) and then the MMSE. In addition, they all underwent a complete neuropsychological battery of tests, as described previously.[6] Major depression was diagnosed using the DSM-IV depression scale.[12] All participants underwent the same neuropsychological battery at baseline and at follow-up.

Statistical Analysis

Continuous variables were compared using the Student *t*-test, and categorical data were analyzed using the chi-square test.

The ability of the combination of the MIS and the IST to predict the presence or absence of dementia (as a dichotomous outcome) was investigated using the weighted sum rule and the logical "or" rule.[18]

With the weighted sum rule, a logistic regression was performed to combine the MIS and IST scores, yielding a score on a new scale. The optimal cutoff score was derived from a receiver operating characteristic (ROC) analysis[18] to discriminate between converters and nonconverters. Individuals with baseline QD with a total MIS-IST score less than the optimal cutoff were considered to be nonconverters, and those assigned a value equal or higher were considered as converters.

With the logical "or" rule combination, the optimal cutoffs were calculated by combining all possible scores for the MIS and the IST. Individuals with baseline QD were considered to be converters if the MIS or IST score was positive (abnormal) and nonconverters if both tests scores were negative (normal).

To maximize the accuracy of prediction, range values were also used. In this procedure, two combinations of MIS and IST were calculated so as to have no false positives and no false negatives, respectively.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)[18] of the MIS-IST combination and MMSE were calculated. Sensitivities and specificities were compared using the McNemar test.[18] The area under the ROC curves[18] was used to measure the overall accuracy of discrimination between converters and nonconverters for each screening tests. $P < .05$ was considered statistically significant for all above analyses.

All computations were performed using Stata software release 8.0 (Stata Corp, College Station, TX).

RESULTS

Participant Characteristics

During the study period, 362 patients with QD were consecutively recruited through the database of the Rapid-Fr Network. Of these, 212 (59%) were not followed up and 150 (41%) were followed up. A cohort of 106 patients were followed up for 6 to 24 months (mean 14.9 ± 4.5). There was no significant difference in age, sex, or depression rate between patients with QD who were followed and those who were not. The patients with QD who were followed were less educated and had better memory performance on the Buschke Cued Recall Test (BCRT).[19] They did not differ on any other neuropsychological tests (Table 1).

To ensure that patients with QD who were followed were within the normal and dementia categories, their cognitive performance was compared with that of 266 patients with cognitive complaints but no dementia (CDR = 0) and those of 207 patients with mild dementia (CDR = 1) who attended the local memory impairment consultation centers over the same study period. The patients with QD performed significantly lower than the group with no dementia and significantly better than the group with mild dementia on all neuropsychological tests (Table 1).

To ensure that differences in the scores on neuropsychological tests did not reflect the older age of the group with mild dementia, a sample that included 90% of the patients was selected at random from this group to match

Table 1. Baseline Characteristics of the Patients According to Diagnosis

Characteristic	QD (CDR = 0.5)			
	Followed Up n = 106	Not Followed Up n = 212	No Dementia (CDR = 0) n = 266	Mild Dementia (CDR = 1) n = 207
Age, mean ± SD	75.7 ± 5.0	75.4 ± 5.4	75.5 ± 5.5	77.6 ± 5.3
Male, n (%)	44 (41.5)	74 (34.9)	112 (42.1)	85 (41.1)
Education ≥12 years, n (%)	9 (8.5)*,†	37 (17.6)	66 (24.9)	30 (14.6)
Depression, n (%)	11 (10.4)‡	25 (11.8)	15 (5.6)	5 (2.4)
Memory Impairment Screen score, mean ± SD (range 0–8)	6.7 ± 1.3*,†,‡	6.3 ± 1.7	7.4 ± 0.9	4.8 ± 2.0
Isaacs Set Test score, mean ± SD	28.1 ± 5.7†,‡	27.2 ± 5.8	32.6 ± 6.0	24.3 ± 5.8
Mini-Mental State Examination score, mean ± SD (range 0–30)	25.2 ± 2.7†,‡	25.0 ± 2.2	27.1 ± 2.0	23.1 ± 2.3
Buschke Cued Recall Test score, mean ± SD (range 0–48)				
Free recall	16.8 ± 6.1*,†,‡	15.4 ± 5.6	23.8 ± 5.7	9.4 ± 4.5
Total recall	40.9 ± 5.1*,†,‡	38.4 ± 5.9	44.9 ± 2.5	29.4 ± 7.9
Trail-Making Test score, mean ± SD				
Part A (range 0–150)	72.4 ± 31.7†,‡	75.7 ± 34.6	52.1 ± 20.2	91.5 ± 39.3
Part B (range 0–300)	241.8 ± 79.7†,‡	246.5 ± 76.2	156.7 ± 63.4	269.5 ± 60.3
Picture naming score, mean ± SD (range 0–30)	28.4 ± 2.2†,‡	28.2 ± 2.2	29.3 ± 1.3	27.1 ± 3.1
Copy score, mean ± SD (range 0–6)	5.4 ± 1.0†,‡	5.5 ± 1.0	5.8 ± 0.5	5.0 ± 1.6

* Significantly different from the group with questionable dementia (QD) that was lost to follow-up.
† Significantly lower than the group without dementia.
‡ Significantly higher than the group with mild dementia.
SD = standard deviation.

by age the group of patients with QD that was followed. The results showed the same higher performances for patients with QD as the mild dementia group.

Of the 106 patients with QD examined at follow-up, 38 (36%) converted to dementia at a mild stage (CDR = 1), and 68 remained free of dementia. Of the converter patients, 20 had AD, five had mixed dementia (AD and VaD), five had dementia with Lewy bodies, four had VaD, one had frontotemporal dementia, and three had other dementia. Of the nonconverters, 57 still had QD (CDR = 0.5), and 11 had reverted to normal (CDR = 0) at follow-up.

Demographic and cognitive characteristics of converters and nonconverters are presented in Table 2. The age ($P = .24$), the sex ratio ($P = .61$), the level of education ($P = .57$) and the frequency of depression ($P = .46$) at baseline were similar between groups. The converter group performed worse than the nonconverter group on the MIS ($P < .001$), the IST ($P < .001$), and the free recall ($P < .001$) and total recall ($P < .038$) of the BCRT. Performances of the two groups did not differ on any of the neuropsychological tests (Table 2).

Performance of the Weighted Sum Rule

The baseline scores of the MIS and the IST of the 38 converters and the 68 nonconverters were used as predictors. The logistic regression model for this combination was as follows:

$$\text{Log}(P/1 - P) = 12.91 - 1.19 \times \text{MIS} - 0.20 \times \text{IST}$$

Where P was the probability of patients converted to dementia, MIS was the MIS score, and IST was the IST score.

A test cutoff score of -0.23 was considered to be the optimal cutoff point. The sensitivity (i.e., the number of converters with a total MIS-IST score ≥ -0.23) and the specificity (i.e., the number of nonconverters with a total MIS-IST score < -0.23) of the weighted sum were 0.74 and 0.84, respectively. At the prevalence rate of 25%, the PPV and the NPV were 0.61 and 0.91, respectively. The area under the ROC curve for this model (0.857) was significantly greater than the MMSE (0.590) ($P < .001$).

Performance of the "Or" Rule

Combining a cutoff score of less than 6 on the MIS and less than 25 on the IST produced the optimal combination of sensitivity (0.74) and specificity (0.81). The sensitivity of the "or" rule was similar to that of the MMSE, using an optimal cutoff score of less than 27 (0.74 vs 0.76) ($P = .80$), and the specificity was significantly greater (0.81 vs 0.40) ($P < .001$).

When range values were applied, of all the patients who scored positive on both tests (MIS < 6 and IST < 25), five were converters and none were nonconverters, whereas of those scoring higher on both tests (MIS > 7 and IST > 29), 11 were nonconverters and none were converters.

DISCUSSION

This study was conducted to assess the accuracy of the MIS-IST combination to discriminate between patients with QD, those who converted to dementia from those who remained free of dementia, over a short period of time. The results indicate that the performances of the weighted sum rule were similar to those of the "or" rule in terms of sensitivity (0.74 for both combinations) and specificity (0.84 and 0.81, respectively). Whatever the method used for combining the MIS and the IST, it was found more effective than the MMSE.

Table 2. Characteristics of Nonconverters and Converters with Questionable Dementia (QD) at Baseline and Follow-Up

Characteristic	Nonconverters* n = 68		Converters† n = 38	
	Baseline	Follow-Up	Baseline	Follow-Up
Age, mean ± SD	75.2 ± 5.0	76.4 ± 5.0	76.4 ± 4.8	77.3 ± 4.7
Male, n (%)	27 (39.7)	27 (39.7)	17 (44.7)	17 (44.7)
Education ≥12 years, n (%)	5 (7.4)	5 (7.4)	4 (10.5)	4 (10.5)
Depression, n (%)	7 (10.3)	2 (2.9)	4 (10.5)	2 (5.3)
Weighted sum, mean ± SD	−1.6 ± 1.4‡	−1.8 ± 1.9§	0.8 ± 1.9¶	2.2 ± 2.4
Memory Impairment Screen score, mean ± SD (range 0–8)	7.2 ± 0.9‡	7.3 ± 0.9§	5.8 ± 1.5	5.1 ± 1.9
Isaacs Set Test score, mean ± SD	29.4 ± 5.3‡	30.0 ± 6.0§	25.8 ± 5.7	23.2 ± 5.8
Mini-Mental State Examination score, mean ± SD (range 0–30)	25.5 ± 2.7	25.4 ± 2.5§	24.6 ± 2.8¶	22.2 ± 3.4
Buschke Cued Recall Test score, mean ± SD (range 0–48)				
Free recall	18.4 ± 6.1‡	19.2 ± 6.3§	14.1 ± 5.1¶	9.2 ± 5.6
Total recall	41.6 ± 4.8‡	42.4 ± 5.4§	39.5 ± 5.4¶	32.1 ± 7.4
Trail-Making Test score, mean ± SD				
Part A (range 0–150)	70.1 ± 33.1	71.9 ± 31.9§	76.7 ± 29.1¶	96.7 ± 39.1
Part B (range 0–300)	232.9 ± 83.2	230.5 ± 81.2§	257.6 ± 71.3	279.4 ± 47.9
Picture naming score, mean ± SD (range 0–30)	28.5 ± 1.9	28.8 ± 1.6§	28.2 ± 2.6	27.1 ± 3.0
Copy score, mean ± SD (range 0–6)	5.6 ± 0.9	5.6 ± 1.0§	5.2 ± 1.3	4.7 ± 1.9
Instrumental activity of daily living score, mean ± SD (range 0–4)	0.2 ± 0.5	0.2 ± 0.5§	0.5 ± 0.8¶	1.4 ± 1.1

* Patients with QD who did not convert to dementia during the 6 to 24 months of follow-up.
† Patients with QD who converted to dementia during the 6 to 24 months of follow-up.
‡ Significant difference between nonconverters and converters at baseline.
§ Significant difference between nonconverters and converters at follow-up.
¶ Significant difference between baseline and follow-up.
SD = standard deviation.

All patients with QD were followed-up with after a short period. One of the problems related to the short mean time until follow-up was that the patients with QD who converted to dementia in less than 12 months may have had dementia at baseline. This could have led to an overestimation of the sensitivity and the NPV,[20] although it was verified that patients with QD who converted rapidly to dementia had similar cognitive performance at baseline to that of those who converted at least 12 months after the follow-up period. Otherwise, it was also verified that the entire converter group had better cognitive performance at baseline than the group with mild dementia. Last, because a short version of the IADL was used, not all daily activities could be assessed with accuracy. Nevertheless, the results demonstrated that the baseline mean IADL score of the converters was similar to that of the nonconvertors (Table 2).

Another problem was that some of the patients with QD who were classified as nonconverters, might have developed dementia after a longer follow-up. This could have led to an underestimation of the specificity and the PPV.[20] For example, if patients with QD who were classified as nonconverters but were followed-up with in less than 18 months had been excluded from this study, the specificity of the MIS-IST pairing would have increased from 0.81 to 0.88 for the "or" rule and from 0.84 to 1.00 for the weighted sum rule. Moreover, 11 of the nonconverters, reverted to normal, and for this subgroup of patients, the specificity was better than for those who remained QD (0.91 vs 0.79).

Weighted sum based on logistic regression is often used as a method of combining two or more tests scores[21] but requires complex calculations difficult to use in general daily practice.[21] In contrast, the logical "or" rule is a simpler method.[6,18,21] An interesting result of this study was that the optimal cutoff scores (MIS < 6 or IST < 25) found with the "or" rule for discriminating between converters and nonconverters were similar to those used in a previous study for screening mild dementia.[6] This appears to be important, because for routine use in clinical practice, a screening test must be quick to administer but also simple to use and score.[1]

For these reasons, the MIS-IST combination seems to us more practical than other screenings tests such as the MMSE,[9] the Montreal Cognitive Assessment,[22] or the Demenz-Detektion,[23] on which clinicians have to separately analyze subscores in addition to the total composite score.

Also interesting is that non-AD was not excluded from the primary outcome.[24] The MIS-IST pairing, by covering episodic verbal memory and executive function, is able to detect signs of cognitive impairment that may be observed in various types of dementia and not only in AD.[3] Last, depressive patients were not excluded because this is a factor that may be associated with early dementia.[25]

QD has been defined as a broad category of patients neither clearly demented nor healthy.[11] QD and Mild cognitive impairment (MCI) overlap.[26] The term QD was chosen, because the study population was recruited from memory consultation centers and not from a community

sample. Patients presenting to a memory consultation are at high risk of conversion to dementia. This may explain the high conversion rate (36%) found in this study. Nevertheless, 10% of the patients with QD reverted to normal, confirming the heterogeneity of this population.[4]

The main limitation of this study was the low proportion (29%) of follow-up of the QD population recruited in the Rapid-Fr network. Twelve percent were followed-up with before 6 months or after 24 months and were therefore excluded from this study. There were 59% of patients who did not return to the memory consultation, although in the Rapid-Fr network, these patients were advised that it was required that they be reexamined every 6 months or at least once a year. It could not be verified, for ethical reasons, why these patients did not return. All of the patients with QD who were followed-up with had a lower level of education than those who were not. Both groups had similar cognitive performances on all tests except for memory, on which the patients with QD who were followed-up with were better. They did not differ significantly in terms of age, sex, or depression rate (Table 1). It is unlikely that these differences could have contributed to any overestimation of the results.

Another limitation was that the PPV for the "or" rule and the weighted sum were modest at a 25% base rate (0.56 and 0.61, respectively). The PPV is usually low when the prevalence of the disease is low,[27] but it can also be overestimated depending on the populations investigated.[27] Therefore, a good PPV must be interpreted with caution before being communicated to clinicians.[28] In addition to the problem mentioned with the PPV, the generalization of statistical study results applied to clinical practice remain difficult.[28] Therefore, to lessen this difficulty, it is suggested that clinicians also include range values,[3] which were calculated in this study so as to have no false positives and no false negatives. The results of the current study showed that only converters ($n = 5$) failed both tests (MIS < 6 and IST < 25) and that only nonconverters ($n = 11$) obtained high scores on both tests (MIS > 7 and IST > 29). Although this was accurate in 100% (16/16), range values could be performed for only 15% (16/106) of the group with QD. Nevertheless, when range values are applied to patients with CDR scores of 0 and 1 used in this study to compare QD cognitive performance (Table 1), 55 patients with mild dementia scored positive on both tests but none with no dementia. In contrast, 117 patients with no dementia scored high on both tests, compared with only five in the group with mild dementia.

The results of this study, obtained from patients with QD who were recruited from memory consultations, cannot be routinely applied to primary care settings. Although the role of dementia screening in primary care still remains debated, screening is frequently proposed as a first stage in the diagnostic procedure, with specialized consultations conducted in a second stage.[5] Although a negative screen may reassure patients who are concerned about cognitive decline, the distress caused by a false positive result could be a possible limitation of this procedure.[3] Administration of a second cognitive screening within 2 weeks to 3 months was proposed to reduce the false-positive rate.[29] This technique needs to be further developed so as to avoid unnecessarily longer and more costly testing in patients without dementia.[29] Prospective studies are warranted to establish the optimal delay for a repeated screening assessment. General practitioners are currently the best professionals to administer this second screen. When considering positive results, they can, without prejudging the diagnosis, routinely begin their research of curable pathologies. Even when rare, diagnosis and treatment of these curable pathologies remains of primary interest for early screening.[30] Based on their knowledge of the clinical and family context general practitioners are also in the best position to subsequently decide and propose a specialized consultation for their patients.

The MIS-IST pairing is quick (5 minutes) and simple to use and score. When including cutscore (MIS < 6 or IST < 25) or range values, this test could be considered a useful screening procedure for all types of dementias.

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APPENDIX A

The Memory Impairment Screen (MIS)

The MIS is a 4-minute, four-item delayed free- and cued-recall memory test.

1. The subject is informed that he or she must learn four words from different semantic categories.

2. The subject is asked to read the four words out loud.

3. The subject is asked to locate, point to, and read out the word once the examiner has given the semantic cue (e.g., "Read out and point to the name of the animal").

4. The words are then hidden.

5. After an interfering task (counting backwards from 100) lasting at least 2 minutes, the subject is invited to reproduce the words learned in any order over 20 seconds (free recall).

6. A cued recall is proposed for any words not mentioned by free recall: the examiner repeat the semantic cue (e.g., "What was the name of the animal?").

Grading: For each word, the score for a correct answer by free recall is 2 points and for cued recall, 1 point. The total MIS score (total MIS $= (2 \times \text{free}) + \text{cued}$) ranges from 0 to 8.

The Isaacs Set Test (IST)

The IST is a 1-minute verbal category fluency task.

Subject must orally produce as many words as possible for the following categories within 15 seconds: colors, animals, fruits, and cities.

Grading: The total number of items named produces the score (any repeated words or intrusions are not included).