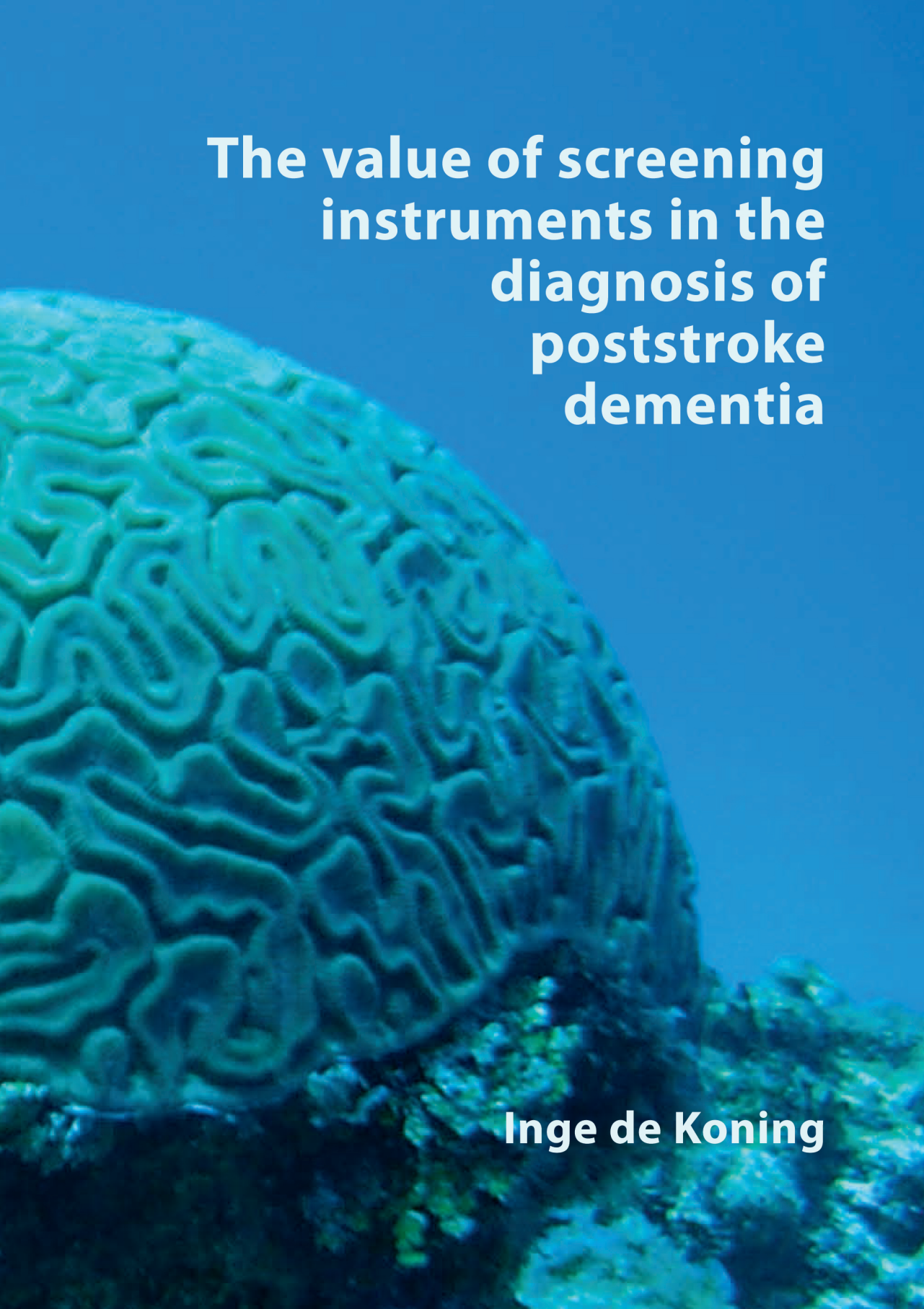
The value of screening instruments in the diagnosis of poststroke dementia



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The Value of Screening Instruments in the Diagnosis of Poststroke Dementia

De waarde van screening instrumenten bij de diagnose van dementie na een beroerte

Proefschrift

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Voor mijn ouders

Siertje Reinders & Johan de Koning

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General introduction

Chapter 1

Stroke is a major cause of morbidity in the industrialized world. It often results not only in physical disability, but also in significant cognitive impairment or dementia. Between 10 and 40% of patients with a recent stroke develop dementia.[1-4] Although stroke was already recognized as an important cause of dementia more than one hundred years ago, research on determinants of poststroke dementia and the cognitive profile of dementia after a stroke has strongly intensified during the last decade.

The diagnosis of dementia after a stroke is complex and poses clinicians for several problems. Poststroke dementia is a clinical entity with very heterogeneous cognitive disturbances, that may be characterized as cortical or subcortical, or a combination of the two. Furthermore, cognitive functioning may be hampered by the somatic symptoms that often accompany a stroke. In clinical practice, cognitive screening instruments take an important place, either to select patients who need further neuropsychological testing or as a diagnostic test in patients with obvious dementia. Most existing screening instruments that are used in a clinical setting, however, are developed to detect dementia compatible with Alzheimer's disease and their value in detecting dementia after stroke is less well known.

In this thesis, I describe and discuss the diagnosis of dementia after stroke, with emphasis on the value of screening instruments in the diagnosis of poststroke dementia. I will use the terms dementia after stroke and poststroke dementia for any type of dementia that occurs after a stroke, irrespective of its presumed cause.

In the prospective hospital-based part of the Dutch Vascular Factors in Dementia study, we examined 300 consecutive stroke patients in the acute phase of stroke. We investigated which clinically relevant and easily obtainable variables in the acute phase predicted the presence of dementia three to nine months after the event (*chapter 2*). An overview of the value of existing dementia screening instruments in the diagnosis of poststroke dementia is presented in *chapter 3*. We determined the feasibility and value of the CAMCOG and the MMSE in screening for poststroke dementia (*chapter 4*), and describe the development of a new screening instrument, the R-CAMCOG, a shorter, and easier to administer test, based on the original CAMCOG in *chapter 5*. The external validation of the R-CAMCOG was performed in a new prospective study of 121 stroke patients (*chapter 6*). The usefulness of the R-CAMCOG, was compared with the MMSE, an internationally widely used and acknowledged screening instrument in *chapter 7*. Finally, I will discuss the main findings and methodological aspects in *chapter 8* and summarize our findings in *chapter 9*.

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Simple clinical variables as predictors for dementia after stroke

Chapter 2

ABSTRACT

Background. It has been estimated that 10 to 40% of patients who suffer a stroke become demented. The mechanisms underlying poststroke dementia or the independent effect of vascular risk factors are not yet completely understood. In view of the high incidence of dementia after a stroke and the progress in the development of therapeutic agents it is important to early select stroke patients with a high risk of dementia. We studied whether easily obtainable clinical information after acute stroke is useful in predicting poststroke dementia.

Methods. From 1993 to 1996 we studied a prospective and consecutive hospital-based cohort of 291 acute stroke patients. The diagnosis of dementia at 3 to 9 months after the onset of stroke was based on the results of an extensive neuropsychological examination, clinical presentation, information from a close relative and the score on the Blessed dementia scale. A final judgment of cognitive functioning was made by a diagnostic panel consisting of two neurologists, a neuropsychologist and a trained physician. For the assessment of dementia, the criteria of the DSM-III-R were used. We performed multiple logistic regression analyses to determine which variables were independently associated with dementia after stroke. We then constructed a final prediction model consisting of clinically and statistically significant and consistent variables.

Results. Of the 291 patients, 62 (21%) were demented. The final model for early prediction of poststroke dementia included age, sex, years of education, previous stroke, white matter lesions on CT scan, neglect, hemorrhage on CT scan, mean arterial blood pressure, and atrial fibrillation. ROC analysis showed that the area under the curve for this model was 0.82, with a high specificity and a moderate sensitivity (resp. 95% and 37%), at the 50% threshold of the diagnostic probabilities (positive predictive value: 70%, negative predictive value: 85%).

Conclusions. Easily available clinical variables, obtained shortly after acute stroke, can be used to predict poststroke dementia.

INTRODUCTION

Cerebrovascular disease is one of the most important causes of dementia in Europe and North America.[2 3] Several studies have estimated that 10 to 40% of patients who suffered a stroke become demented.[4-7] The mechanisms underlying poststroke dementia or the independent effect of vascular risk factors, however, are not yet completely understood. In view of the high incidence of dementia after a stroke and progresses in the development of therapeutic strategies it is important to be able to early select stroke patients with a high risk of dementia for further diagnostic work up, to facilitate appropriate medical attendance or medical therapy.

The results of recent studies regarding the possible associations of stroke and subsequent dementia are ambiguous,[7-11] which may be explained by differences in study population, study design, or the definition of dementia. We conducted a study with emphasis on clinical detail. The study was based on a prospective hospital-based cohort of 291 well-defined stroke patients who were examined extensively on somatic and cognitive features. Its aim was pragmatic; it should answer the question whether clinical information that is easily obtainable in the acute phase of stroke is useful in predicting poststroke dementia.

PATIENTS AND METHODS

Patients

Patients were recruited from the Rotterdam Stroke Databank, a prospective registry of patients with a transient ischemic attack (TIA), ischemic stroke or primary intracerebral hemorrhage, admitted to the Department of Neurology of a large university hospital. From March 1, 1993 until January 15, 1996, all patients who met the criteria for enrolment in The Dutch Vascular Factors in Dementia Study were entered consecutively.[6] Patients had to be 55 years or over, and had a TIA with neurological signs on examination, an ischemic stroke or intracerebral hemorrhage. Patients were excluded when a reliable assessment of dementia could not be made because of aphasia (i.e. a score less than 3 on the Aphasia Severity Rating Scale from the Boston Diagnostic Aphasia Examination [BDAE]),[12] severe sensory handicaps (e.g. deafness or blindness), persistent impairment in consciousness, severe psychiatric symptoms, or insufficient command of the Dutch language. Additional exclusions were a TIA without neurological signs, concomitant primary cerebral disorder or severe co-morbidity with a short life expectancy. Informed consent was obtained from all patients or from close relatives in case of impaired judgment.

For the present study we excluded patients with a pre-existent moderate or severe dementia.

Procedure

The clinical and demographic characteristics of the patients at baseline were assessed immediately after admission to the hospital. We obtained detailed information on demographic variables, cardiovascular risk factors, stroke characteristics, and premorbid mental and physical status. In addition to a full neurological examination, ancillary investigations consisted of standardized blood tests, chest x-ray, computed tomographic

scanning and/or magnetic resonance imaging of the brain, duplex scanning of the carotid arteries, and a cardiac analysis.

Demographic characteristics

Demographic characteristics included age, sex, and education, which was categorized by the number of years of schooling completed.

Cardiovascular risk factors

Hypertension was defined as previously diagnosed and treated hypertension or hypertension at casual reading during admission, but al least 24 hours after onset of symptoms (e.g. systolic pressure (SBP) >180 mmHg and/or diastolic pressure (DBP) >110 Hg). We also calculated the mean arterial blood pressure (MAP) through the standard formula DBP + 1/3*(SBP –DBP). Diabetes was defined as previously diagnosed and treated diabetes or a fasting glucose ≥7 mmol/L. Hypercholesterolemia was defined as a previously diagnosed and treated hypercholesterolemia, a serum cholesterol ≥6.0, or a serum cholesterol/HDL ratio >5.5.

Previous and present vascular diseases

These data included peripheral vascular disease (e.g. intermittent claudication or peripheral vascular surgery), previous hemorrhagic or ischemic stroke, cardiac disease (e.g. angina pectoris, myocardial infarction, coronary artery bypass grafting, congestive heart failure, and atrial fibrillation).

Type of stroke

Type of stroke was categorized as TIA, ischemic stroke or primary intracerebral hemorrhage, and site of stroke was noted as right or left hemispheric or infratentorial. Etiology of stroke was classified according to the TOAST criteria.[13]

Premorbid and present cognitive functioning

Premorbid cognitive functioning was established by a careful interview with a close relative and the score on the Blessed dementia scale.[14] Severity of dementia was assessed with the Blessed Dementia Scale, e.g. a score of >4 indicates moderate dementia, a score of >6 severe dementia.

Neuropsychological examination

An extensive neuropsychological examination was carried out in all patients in whom there was any suspicion of dementia or cognitive decline. If patients were not testable due to cognitive deficits or in case they refused further co-operation, the extensive neuropsychological evaluation was not performed. In some patients only a limited number of tests could be administered. The extensive neuropsychological examination consisted of an intelligence test, either the shortened version of the Groninger Intelligence Test,[15] a Dutch intelligence test, or when this was not administrable Raven's Coloured Matrices,[16] a non-verbal intelligence test. The shortened form of the Boston Naming Test (CERAD)[17] was used to examine word-finding difficulties. Memory was evaluated with Word List Memory (CERAD),[17] and the Rivermead Behavioural Memory Test.[18] We used Digit Span forward and backward (WAIS)[19] to assess the span of immediate verbal recall, but also as a measure for

attentional capacity. Parts of the Trail Making Test,[20] and the Stroop Color Word Test[21] too were used to examine attention. Scores on verbal fluency (animals, occupations, letter B), Stroop Color Word Test part III,[21] Trail Making Test B,[20] served as indication for the level of executive functioning. Proverbs and similarities (WAIS)[19] provided a measure for abstraction and verbal concept formation. Visuo-constructive ability was examined by copying the drawing of a circle, diamond, two overlapping rectangles and a cube (CERAD).[17] Visual perception and spatial orientation were examined by Judgment of Line Orientation.[22]

Diagnosis of dementia

The diagnosis of dementia at 3 to 9 months after the onset of stroke was based on the results of an extensive neuropsychological examination, clinical presentation, information from a close relative and the score on the Blessed dementia scale. A final judgment of cognitive functioning was made by a diagnostic panel consisting of two neurologists, a neuropsychologist and a trained physician. For the assessment of dementia, the criteria of the DSM-III-R[1] were used. A further sub-classification of dementia was made according to the research criteria of the NINDS-AIREN international workshop.[23]

STATISTICAL ANALYSIS

To determine the clinical correlates of dementia in relation to stroke, we compared the characteristics of demented and not-demented patients using chi-square analyses or Student's t-test where appropriate. We performed a multiple logistic regression analysis with all variables that were statistically significant ($p<0.10$) in the univariate analyses. Then, we excluded variables with a large number of missing values or overlapping measures, and constructed a model, that was based on variables that were considered to have a consistent and clinically relevant association with poststroke dementia, as judged from previous studies and clinical experience. In this way, we avoided the pitfalls of stepwise selection procedures.[24]

RESULTS

The number and origin of patients excluded from the study population is represented in Figure 1. From the 825 patients registered in the Rotterdam Stroke Databank, approximately a quarter was younger than 55 years of age, 15% died within three months after stroke onset, 5% had a transient ischemic attack without any sign on neurological examination, and another 5% had severe aphasia. One tenth was excluded for various other reasons (e.g. moved out of the region, did not speak Dutch, or had a short life expectancy due to other diseases), and 5% did not give informed consent. Of the 300 remaining patients, 9 had a moderate or severe dementia before the most recent stroke and were excluded from the present study. Overall, 21% of the patients were demented 3 to 9 months after stroke.

The demographic characteristics of the 291 study patients are summarized in Table 1. The demented patients were on average 5 years older than not-demented patients and had on average 1.6 years less education. There were no differences between demented and not-demented patients with regard to the presence of hypertension and diabetes.

Table 1. Demographic variables and vascular riskfactors

	Demented (N=62)	Not-demented (N=229)	Total studygroup (N=291)	P
Age *	73.4 (7.2)	68.2 (8.0)	69.3 (8.1)	<0.001
Years of education*	7.4 (3.1)	9.0 (3.0)	8.7 (3.1)	<0.001
Female sex	31 (50)	84 (37)	115 (40)	0.06
Hypertension	51 (82)	202 (88)	253 (87)	0.22
Systolic blood pressure*	167.1 (29.4)	170.7 (30.0)	170.0 (29.9)	0.39
MAP*	118.5 (18.5)	121.1 (18.6)	120.6 (18.6)	0.33
Diastolic blood pressure*	94.2 (15.6)	96.3 (16.2)	95.9 (16.1)	0.37
Diabetes	16 (26)	50 (22)	66 (23)	0.51
Hyperlipidemia	38 (61)	171 (75)	209 (72)	0.04
Total cholesterol*	5.53 (1.3)	6.27 (1.2)	6.11 (1.2)	<0.001
Peripheral vascular disease	3 (5)	33 (14)	36 (12)	0.04
Atrial fibrillation	15 (24)	30 (13)	45 (15)	0.03
Angina pectoris	13 (21)	28 (12)	41 (14)	0.08
Congestive heart failure	6 (10)	12 (5)	18 (6)	0.20
Myocardial infarction	8 (13)	37 (16)	45 (15)	0.53
CABG	2 (3)	14 (6)	16 (6)	0.38
Previous stroke	21 (34)	42 (18)	63 (22)	0.008
Smoking	16 (26)	88 (38)	104 (36)	0.07
Alcohol consumption	17 (27)	109 (48)	126 (43)	0.004

Values are number of patients with percentages in parentheses
*Values are means with standard deviations in parentheses
MAP: mean arterial bloodpressure DBP + 1/3 x (SBP –DBP)
CABG: coronary artery bypass graft

Serum cholesterol level was inversely related to dementia three to nine months after stroke (p<0.001). Atrial fibrillation, previous stroke and use of alcohol were significantly associated with the presence of dementia. Table 2 shows the stroke features in both groups. About three-quarters of the patients suffered an ischemic stroke. Of the patients presenting with TIA, only 3 (7%) became demented three to nine months after stroke. Of the patients with an ischemic stroke 46 (22%) were demented, whereas 13 (37%) patients with an intracerebral hemorrhage were demented at 3 to 9 months. White matter lesions were present in about half of the demented patients, but only in one fifth of the not-demented patients. Demented patients suffered more often from an ischemic stroke as a consequence of a cardiac embolism (27% vs. 17%), whereas in the not-demented group large artery atherosclerosis and small vessel disease were more frequent. Neglect in the acute phase was strongly associated with dementia 3 to 9 months after stroke.

We performed a multiple regression analysis in which we included all variables that were associated with dementia in the univariate analyses (p<0.10). Because our main purpose was to establish which easily obtainable clinical information in acute stroke predicts poststroke

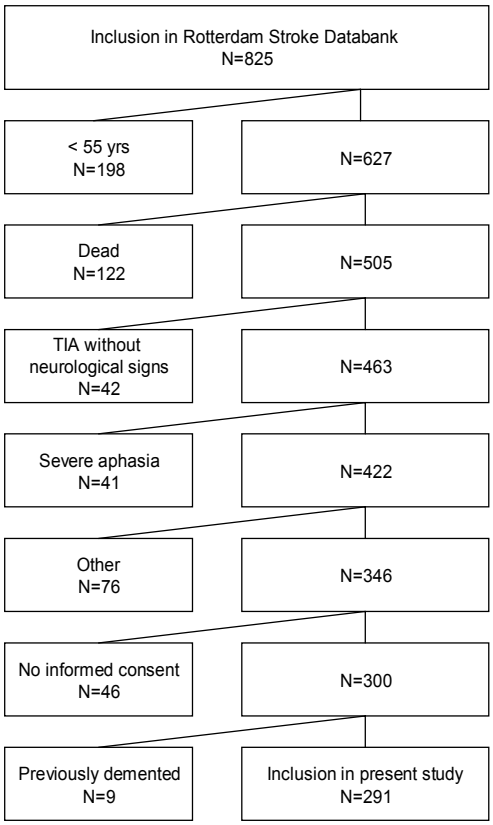

Figure 1. Selection of patients for the present study

Table 2. Stroke features in demented and not-demented patients

	Demented (N=62)	Not-demented (N=229)	Total studygroup (N=291)	P
Type of stroke				
TIA	3 (5)	43 (19)	46 (16)	
Ischemic stroke	46 (74)	164 (71)	210 (72)	
Intracerebral hemorrhage	13 (21)	22 (10)	35 (12)	0.004
Site of stroke				
Right hemisphere	32 (52)	104 (45)	136 (47)	
Left hemisphere	18 (29)	100 (44)	118 (40)	
Infratentorial	12 (19)	25 (11)	37 (13)	0.06
Clinical features				
Lowered consciousness	6 (10)	8 (4)	14 (5)	0.05
Neglect	24 (39)	36 (16)	60 (21)	<0.001
Aphasia	9 (15)	32 (14)	41 (14)	0.81
White matter lesions	28 (45)	44 (19)	72 (25)	<0.001
Cause of ischemic stroke				
Large artery atherosclerosis	9 (18)	49 (24)	58 (23)	
Cardiac embolism	13 (27)	35 (17)	48 (19)	
Small vessel disease	11 (22)	67 (32)	78 (30)	
Other	1 (2)	11 (5)	12 (5)	
Incomplete investigation	15 (31)	45 (22)	60 (23)	0.20

dementia, we constructed a clinically sensible model. We therefore first included variables that were associated ($p<0.1$) with the presence of dementia in the univariate analyses, e.g. age, years of education, sex, cholesterol level, atrial fibrillation, angina pectoris, congestive heart failure, previous stroke, smoking, use of alcohol, type of stroke, site of stroke, lowered consciousness level, neglect, white matter lesions, and hemorrhage. Next, we added variables that did not reach significance in the univariate analysis but were regarded as clinically sensible based on the results of previous studies or clinical experience. The final model, the clinically sensible model, consisted of the following prognostic factors: age, sex, years of education, previous stroke, presence of leukoaraiosis on CT, neglect, MAP, atrial fibrillation, and hemorrhagic stroke. ROC analysis showed that the diagnostic accuracy of this model was 0.82, with a high specificity and a moderate sensitivity (resp. 95% and 37%), at the 50% threshold of the diagnostic probabilities (positive predictive value: 70%, negative predictive value: 85%).

Table 3. Predictors of poststroke dementia in a multiple regression model

	Odds ratio (95% CI)
Age*	1.06 (1.0 – 1.1)
Years of education*	0.9 (0.8 – 1.0)
Female sex†	1.3 (0.7 – 2.6)
MAP (mmHg) ‡	0.98 (0.96 – 1.0)
White matter lesions †	3.0 (1.7 – 5.3)
Neglect†	3.1 (1.5 – 6.3)
Previous stroke	2.1 (1.0 - 4.4)
Hemorrhagic stroke†	2.3 (0.9 – 5.6)
Atrial fibrillation†	2.4 (1.0 – 5.6)

* odds ratio per year increase, † odds ratio: presence of variable ‡ odds ratio per unit increase

DISCUSSION

We investigated in a carefully examined hospital-based stroke population whether commonly available clinical variables are useful in predicting the presence of dementia 3 to 9 months after a stroke. In univariate analyses we found strong associations with age, years of education, sex, level of cholesterol (inverse relation), congestive heart failure, atrial fibrillation, previous stroke, alcohol consumption, neglect, type of stroke, cause of ischemic stroke, and white matter lesions on CT scan. We constructed a clinically sensible model, based on significant variables in univariate analyses and clinically relevant variables. This model, which included age, sex, years of education, white matter lesions on CT, neglect, intracerebral hemorrhage, MAP, and atrial fibrillation as risk factors for the presence of poststroke dementia, had an acceptable diagnostic accuracy.

Several prospective hospital-based studies have been conducted to unravel the question which patients are at risk for dementia after stroke. The results of these studies, however, are ambiguous. This is likely due to differences in study populations, definitions of concepts, different methods, or the use of different criteria for the diagnosis of dementia. Our purpose

was to design a pragmatic and feasible prognostic model with clinical variables that are easy to obtain in patients with acute stroke.

As we wanted to establish the relationship between a stroke and the development of poststroke dementia, we excluded patients with a previously diagnosed moderate or severe dementia (3%) to preclude confounding. The majority of these patients had a diagnosis of probable Alzheimer's disease. We did not exclude patients with pre-existent mild dementia or cognitive impairment, as more subtle cognitive disturbances may easily be overlooked either by patients or their relatives or by the attending physicians. The proportion of all patients with pre-existent dementia in our study (7%) is somewhat lower than in previous studies.[4 7 25 26] There are, however, large variations in the numbers of pre-existent dementia in these studies, probably due to selection or recruitment bias. Dementia was present in 21.3% of the remaining patients in the present study. The large variation in the prevalence of poststroke dementia in previous studies, ranging from 6% to 32%,[10 27] is due to differences in study design, particularly the in- and exclusion criteria, the information on which the diagnosis of dementia was based and the criteria for dementia used. The strength of our study is that we performed an extensive neuropsychological examination in each patient with any suspicion of cognitive decline. Furthermore, we conducted a careful interview with the patient and a close informant to establish the severity of cognitive decline, onset and course.

The diagnosis was made three to nine months after stroke to overcome acute and transient symptoms. In a multidisciplinary diagnostic panel the diagnosis was based on the results of an extensive neuropsychological examination, and information from an interview with the patient and a close informant.

In accordance with most other studies, we found that advancing age,[7 8 10 11] and years of education[7 8 10 11] were related to the presence of dementia in univariate analyses. Female sex was related to the presence of poststroke dementia in our study, but only Barba et al. have reported this before.[7]

Some well-established vascular risk factors, such as hypertension, diabetes mellitus, myocardial infarction, and smoking were not related to poststroke dementia in our sample. Some previous studies did find a relation with diabetes,[8 9] or smoking,[10] but others did not. Although hypertension is a known vascular risk factor, there are no studies that report a direct association with poststroke dementia. However, our study indicates a protective effect of increased blood pressure, perhaps because low bloodpressure leads to relative hypoperfusion and more cerebral damage in this category of patients. In our study, level of cholesterol was inversely related to the presence of dementia. Demented patients had on average a lower cholesterol level than not-demented patients (5.4 mmol/L vs. 6.3 mmol/L). One study also found that hypercholesterolemia was a more frequent symptom among not-demented patients,[10] but others did not.[7 8 11] An explanation for our finding may be that demented patients were older whilst the level of cholesterol is known to be inversely related with age. Another explanation may be that not-demented patients have a higher body weight, simply because they eat more. However, after adjustment for body weight or age, the relationship between cholesterol level and poststroke dementia remained intact. Interestingly, in the study of Dyker et al, low cholesterol levels were an adverse prognostic factor for survival in acute stroke patients.[28] In our opinion, the association between lower level of cholesterol and increased risk of dementia may be real, albeit unexplained, and needs to be investigated in explorative studies. However, as we could not find a plausible

explanation for the association between level of cholesterol and poststroke dementia, and taking into account the conflicting results of other studies, we cannot exclude that the association of level of cholesterol with poststroke dementia in our study may be due to a yet unknown confounding mechanism.

Neglect in the acute phase proved a strong independent prognostic factor for poststroke dementia 3 to 9 months after a stroke. When neglect was still present at the time of the neuropsychological examination, and scores on some tests were influenced by the hemi-inattention, we judged the results of other tests on the same cognitive domain. The presence of neglect therefore did not confound the diagnosis of dementia. Only a few other studies have included neglect as a clinical variable.

As in most other studies we excluded patients with a moderate or severe aphasia, because this would hinder a reliable judgment of cognitive functioning. The presence of mild aphasia was not related to poststroke dementia in our study, which is in agreement with the study of Tatemichi et al.[8] Other studies reported an association between aphasia and poststroke dementia, but this can be explained by different in- and exclusion criteria. In one study, all aphasic patients, including patients with a severe aphasia were analyzed.[9] whereas in another, severe aphasia served as an exclusion criterion, but this was only judged on clinical grounds.[10]

Previous stroke is a frequently found clinical determinant of poststroke dementia,[8 10 29] which was confirmed by our data. Atrial fibrillation has been reported as an independent risk factor for dementia in several studies,[9 25] also confirmed by our results.[30] In our study, poststroke dementia was related to the site and type of stroke, but not to the cause of ischemic stroke. We found an increased risk for dementia in patients with an intracerebral hemorrhage, whereas patients with a TIA had a considerable lower risk of dementia. Left hemispheric stroke was associated with a lower risk of dementia, which refutes the findings of other studies.[8 10] The presence of white matter lesions on CT scan was associated with an increased risk of poststroke dementia, in accordance with previous studies.[11 31 32]

The predictors of poststroke dementia in our final multiple regression model are variables that are easy to assess and obtained on a routine basis in most neurological departments. This makes the model feasible and of practical value in predicting poststroke dementia. A drawback of the model, reflecting our focus on clinical variables, is the absence of other determinants, such as biochemical markers, or detailed MRI variables, which may also be strong predictors of poststroke dementia.[33] Furthermore, although the diagnosis of dementia was carefully made by a multidisciplinary panel, the dementia syndrome and type of dementia were not pathologically verified, which possibly led to misclassification of the type of dementia. Of course, this prediction model should be evaluated in a new independent dataset before it is used routinely.

Despite these limitations, the present study may provide more insight in the clinical determinants of poststroke dementia and may stimulate further research into its underlying mechanisms.

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The value of screening instruments in the diagnosis of poststroke dementia

Chapter 3

ABSTRACT

Brief dementia screening instruments, or mental status tests are frequently used to screen for cognitive impairment. We discuss the strengths and weaknesses of existing mental status tests in dementia screening in general. Most screening instruments that are used in clinical practice are developed to detect dementia compatible with Alzheimer's disease and their value in detecting dementia after stroke is less well known. A stroke may cause both cortical and subcortical deficits and the clinical expression of poststroke dementia is different from that of Alzheimer's disease. Existing brief mental status tests have limited value in this patient group because they tend to ignore specific problems which may occur in stroke patients. Some expanded screening instruments, like the CAMCOG, are more useful and have additional diagnostic value. With the growing interest in research for vascular factors in dementia over the past years, however, a specific screening instrument for poststroke dementia would be a valuable contribution.

INTRODUCTION

With the aging of the population in industrialized countries, the prevalence of dementia has increased dramatically in the past 20 years and is expected to continue to increase further during the early 21st century, placing a heavy burden on public health care resources. The most important cause of dementia is Alzheimer's disease, followed by cerebrovascular diseases.[1 2] Although recent studies suggest that various vascular mechanisms also play a significant role in Alzheimer's disease, the clinical expression and management of vascular dementia and Alzheimer's disease are usually very different. Early detection and differentiation of dementia is important from a psychosocial point of view and with respect to management of the dementia syndrome.

Cognitive deterioration is by definition a central feature of dementia and the diagnosis of dementia therefore completely relies on the assessment of cognitive functioning. A clinical investigation, which includes an interview with the patient and a close informant, is important, but psychometric assessment of cognitive functioning is necessary in many cases to support clinical judgment and quantify the cognitive deficits. Brief screening instruments, or mental status tests, can provide insight in the presence of cognitive impairment in a quick and convenient way and are frequently used to screen for cognitive impairment. Although these tests do not provide the same amount and type of information as a full neuropsychological examination, they may be used for selecting patients in whom such an extended neuropsychological examination is deemed necessary. For many seriously impaired patients, the mental status examination may not only be the examination of choice, but may also be the only examination that can be made of these patients' neuropsychological condition. Mental status tests by no means replace formal testing; rather do they serve another goal.

In this review, we will briefly describe the clinical differences between Alzheimer's disease and vascular dementia, especially poststroke dementia, and discuss the diagnostic criteria. It is beyond the scope of this article to review all dementia screening tests, but we will discuss the strengths and weaknesses of these tests in general. Furthermore, we will evaluate the factors that have to be taken into account when screening for cognitive impairment after stroke. We will discuss the feasibility of existing tests in stroke patients and their ability to differentiate between dementia in Alzheimer's disease and vascular dementia, in particular dementia after stroke.

DEMENTIA

Dementia is an acquired clinical syndrome with cognitive deterioration as a central feature. It has various underlying causes, but Alzheimer's disease and vascular dementia are most common. Dementia caused by Alzheimer's disease is a typical cortical dementia and is characterized by memory deficits and decline of at least one other cognitive function in comparison with the patient's previous level of functioning as determined by a history of decline in performance and by abnormalities noted from clinical examination and neuropsychological tests. The diagnosis of dementia cannot be made when consciousness is impaired by delirium, drowsiness, stupor or coma, or when other clinical abnormalities

prevent adequate evaluation of mental status beside the presence of dementia.[3 4] According to the DSM-III-R, but not the NINCDS/ADRDA criteria, the cognitive deficits should be severe enough to interfere with daily functioning. To fulfil the criteria for Alzheimer's disease of the DSM-III-R and NINCDS/ADRDA the dementia must have an insidious onset and a gradual progressive course, and all other possible causes for dementia must be excluded.

The dementia syndrome associated with cerebrovascular disease, vascular dementia, has a variety of etiologies and is the most important cause of dementia after Alzheimer's disease. The causes include one or multiple infarcts, a single strategic infarct, small vessel disease, hemorrhagic strokes and hypoperfusion. Poststroke dementia is a heterogeneous syndrome and there may be deficits in any cognitive domain. The dementia syndrome may be classified as subcortical in some and cortical in others, while a combination of cortical and subcortical deficits is also possible. A combination of Alzheimer's disease with vascular dementia is also known.

Research criteria for vascular dementia have been designed by the NINDS-AIREN International Workshop[5] and consist of: presence of a dementia syndrome and cerebrovascular disease and a relationship between those two disorders. The criteria for a dementia syndrome are adopted from the World Health Organization (WHO) and are defined as a cognitive decline from a previous higher level of functioning and manifested by impairment of memory and two or more other cognitive domains. These domains include orientation, attention, language, visuo-spatial functions, executive functions, motor control and praxis, preferably established by clinical examination and documented by neuropsychological testing. The deficits should be severe enough to interfere with daily living. Exclusion criteria for dementia include cases with disturbed consciousness, delirium, psychosis, severe aphasia or major sensorimotor impairment precluding neuropsychological testing. The presence of cerebrovascular disease is defined by the presence of focal signs on neurological examination consistent with stroke, and evidence of relevant cerebrovascular disease by brain imaging. A relationship between cerebrovascular disease and dementia may be inferred when dementia onset is within three months after stroke, of a history of abrupt deterioration in cognitive functions, of fluctuating, stepwise progression of cognitive deficits.

DEMENTIA SCREENING TESTS

A dementia screening test is a psychometric test that ideally should give an objective and standardized judgment of present cognitive functioning and has to be able to differentiate adequately between normal and impaired cognitive functioning. Psychometric tests should provide a quantitative observation that satisfies the demands of reliability, which refers to the consistency and reproducibility of a result, and validity, which addresses the question whether the test measures the relevant abnormality. Another important issue is the diagnostic accuracy of a test, which reflects the test's ability to correctly classify patients. The sensitivity, i.e. the ability of a test to detect subjects with true cognitive deterioration, and specificity, the ability to correctly identify the absence of cognitive deterioration, should be satisfactory. The desirable ratio of sensitivity and specificity can differ depending on the setting. Sensitivity is generally considered to be of primary importance when screening

for the presence of cognitive impairment. The relative hazards of false negative errors are thought to be greater than those of false positive errors. In most settings, it is more important not to miss patients with true cognitive deterioration, than to misclassify a patient without cognitive impairment, which may only lead to unnecessary follow up testing. Though specificity is of secondary importance in a screening situation, moderately high specificity is needed to make cognitive screening useful and informative.

Apart from the concerns of reliability, validity and diagnostic accuracy, efficiency and cost effectiveness are given high priority in screening for dementia. The screening instruments have to be relatively brief and easy to administer.

GENERAL REMARKS REGARDING DEMENTIA SCREENING INSTRUMENTS

Dementia screening instruments that are used in clinical practice are similar in many ways. Each test is a subset from a larger set of items. Most brief screening instruments have been developed for the detection of dementia of the Alzheimer type and focus on orientation, memory and higher cortical functions like aphasia, apraxia and agnosia. In the past, several mental status tests have been developed for this purpose, such as the Mini Mental State Examination (MMSE),[6] Mental Status Questionnaire (MSQ),[7] Short Portable Mental Status Questionnaire (SPMSQ),[8] Cognitive Capacity Screening Examination (CCSE),[9] and the Short Blessed Test.[10] The MMSE, which is by far the most widely used screening instrument for dementia, has proven to be a reliable and valid screening instrument in large epidemiological studies of dementia. It is also a frequently used screening instrument in clinical settings, and although it has obvious benefits in screening for cognitive impairment, several serious limitations have been noted.[11] Most studies with respect to reliability and validity of brief mental status tests concerns the MMSE, but the benefits and weaknesses are probably valid for all brief mental screening tests. Strengths of dementia screening tests are that they are brief, inexpensive and easy to administer. Obviously the administration and interpretation of these tests requires less training and need not necessarily be performed by a neuropsychologist. An additional benefit of brief screening instruments is that they tend to be less unpleasant and intrusive for older patients. Mental status tests are generally able to differentiate dementia from pseudodementia, a pattern of dysfunctional behavior that closely resembles dementia. Reported weaknesses concern the influence of age, education and (socio)cultural variables on testscores. Previous studies suggest that age and education are associated with dementia,[12-15] and also with the performance on the brief mental status tests.[16-18] Poorly educated elderly people are much more likely to fail on these tests. Cultural differences influence test performance and increase the risk of false positive scores.[19 20] Apart from these sociodemographic factors there are several other variables responsible for false positive errors: somatic illness (e.g. diabetes mellitus, Parkinson' s disease or stroke) and depression are related to lower scores on mental status tests.[21] It is also suggested that sensory handicaps, in particular visual problems, influence testscores.[22] A common critique is that most brief screening instruments are not sensitive enough to detect mild cognitive impairment: they are suitable to discriminate between moderate dementia and normal cognitive functioning, but not in separating mildly demented patients from normal subjects.[23] These tests also are less suitable to determine the stage of deterioration.[11 19] Other

limitations of brief screening tests is that they are relatively insensitive to focal brain lesions, right hemisphere dysfunction, and dementia with frontal lobe involvement.[11 17 19 24]

The above mentioned weaknesses of brief mental status tests have led to the adjustment of existing tests and the development of more comprehensive screening instruments. Teng and Chui made an effort to compensate for the weaknesses of the MMSE and developed an expanded version of the MMSE, the modified Mini-Mental State (3MS).[25] This modified version contains the items of the original MMSE but were given a different weight, and items such as abstraction and wordfluency were added. Research with the 3MS has been limited. Sofar, only slightly better sensitivity than the MMSE but no other significant improvements have been reported. The CAMCOG is the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX), a standardized instrument for the diagnosis and grading of dementia.[26] In addition to the MMSE items the CAMCOG contains measures such as recognition, abstraction, praxis, and wordfluency. Lindeboom et al. reviewed some psychometric properties of the CAMCOG and found that is was stable and reliable and differentiated well between normal cognitive functioning and mild cognitive impairment.[27] A disadvantage of the CAMCOG is, however, that it does not differentiate very well in older patients or patients with a low level of education.[27 28] Two other tests deserve mention here: The Neurobehavioral Cognitive Status Examination (NCSE)[29] and Mattis Dementia Rating Scale (MDRS).[30] These tests are also classified as screening instrument, although the items are arranged in a different manner. An interesting feature of both scales is that, instead of giving the items in the usual ascending order of difficulty, the most difficult item is given first as a screen. This instruction can save time in a screening examination, but on the other hand one study with the NCSE indicates that the screen items produce a relatively high false negative rate and it is recommended that all items are administered.[31] The NCSE is a general screening instrument for cognitive dysfunction and the findings are not summarized in a total score, but in a profile of scores. The NCSE is sensitive to the presence of cognitive dysfunction, but there is also moderate overdiagnosis of cognitive dysfunction in the elderly patient.[32 33] Furthermore, it is suggested that the NCSE is equal in its sensitivity, specificity, and diagnostic accuracy in a geriatric population to the shorter MMSE.[33] The MDRS is particularly sensitive to the cognitive changes that characterize dementia of the Alzheimer's type, with the areas of testing: attention, initiation and perseveration, construction, conceptual reasoning and memory. The total score is accurate in differentiating mild and moderate dementia from normal subjects,[34 35] but the MDRS may not be sensitive enough to assess mild dementia in high functioning patients.[36] Age and education have been found to effects the total score of the MDRS.

CONSIDERATIONS FOR DEMENTIA SCREENING AFTER STROKE

As mentioned, dementia screening instruments that are used in clinical practice are usually developed to detect cognitive deficits compatible with Alzheimer's disease. Aspects of cognitive functioning, like slowing of intellectual functioning, abstraction, retrieval, and recognition, and visuo-spatial abilities are less well measured. This means that these short tests a priori seem less suitable for detecting subcortical dementia caused by Parkinson's disease, normal pressure hydrocephalus, progressive supranuclear palsy, Binswanger disease or dementia that may have both cortical and subcortical deficits like dementia after

Table 1. Comparison of different dementia screening instruments regarding dementia in general and poststroke dementia in particular

	Dementia screening tasks in general		***Considerations for dementia screening in stroke patients***
	Strengths	**Weaknesses**	
Brief mental status tests			
(e.g. MMSE, MSQ, SPMSQ, CCSE, Short Blessed test)	– Brief, inexpensive and easy to administer. – Less unpleasant and intrusive for older patients than longer tests. – Generally able to differentiate between moderate dementia and normal cognitive functioning.	– Testscores are influenced by demographic and cultural factors. – Somatic illness and sensory handicaps influence the scores. – Not sensitive enough to discriminate between mild cognitive impairment from normal cognitive functioning. – Not suitable for staging dementia. – Generally not able to differentiate between different types of dementia.	– Developed to detect cognitive deficits compatible with Alzheimer's disease, and contain no or little subcortical elements. – Verbally based, and therefore underestimating consequences of left hemispheric lesions and possibly overestimating consequences of right hemispheric lesion.
Extended mental status tests			
3MS	– Relatively brief, and easy to administer. – By adding and weighing items a broader range of cognitive abilities can be tested than with the MMSE.	– Focus is still on cortical deficits.	– Despite the addition and weighing of items only slightly more sensitive than the MMSE in a stroke population
CAMCOG	– Reliable and valid. – Able to differentiate between mild cognitive impairment and normal cognition. – Can be used for grading dementia. – Comprehensive and allows a judgment of a large number of cognitive domains.	– Moderate influence of age and educational level. – Despite the addition of 'subcortical' items, emphasis is still on deficits compatible with AD.	– Restricted number of 'subcortical' items. – Constructional tasks (drawing and praxis) may be a problem in patients with a paresis. – Has additional diagnostic value in dementia screening in stroke population.
NCSE	– Comprehensive and assesses several areas of cognitive function. – Screen items can be a timesaver. – Highly sensitive to cognitive dysfunctioning.	– Tends to overdiagnose the cognitive deterioration in the elderly. – Equal in its sensitivity, specificity, and diagnostic accuracy in a geriatric population to the MMSE.	– Absence of timed tasks. – Tends to overdiagnose 'organic' deterioration, and may therefore be less suitable in screening for dementia in a stroke population.
MDRS	– Able to differentiate patients with mild and moderate dementia from normal subjects. – Screen may be a timesaver. – Can be used for staging dementia.	– Not sensitive enough to assess mild dementia in high functioning patients. – Moderate influence of age and level of education.	– Especially developed to detect cognitive deficits compatible with AD, with emphasis on orientation, memory, and abstraction. – The absence of timed tasks and other subcortical items makes this test not appropriate for the purpose of screening for poststroke dementia.

MMSE = Mini Mental State Examination, MSQ = Mental State Questionnaire, SPMSQ = Short Portable Mental State Questionnaire, CCSE = Cognitive Capacity Screening Examination, 3MS = Modified version of the Mini Mental State Examination, NCSE = Neurobehavioral Cognitive Status Examination, MDRS = Mattis Dementia Rating Scale, AD = Alzheimer's disease.

stroke. Moreover, existing dementia screening instruments predominantly contain verbally mediated items that tend to exaggerate the extent of cognitive deficits in patients with a left hemispheric stroke. Likewise, tests that emphasize verbal capacities may underestimate the consequences of right hemispheric lesions.[24 37 38] In patients with a stroke, in particular a left hemispheric stroke, a paresis can prevent a good performance at items that appeal to constructional abilities. Moreover, subtests that refer to praxis, frequently accompanying aphasia, can raise problems for stroke patients. In patients with a right-sided hemispheric stroke neglect can be a confounding factor in testscores.

With the fast growing interest in research for vascular factors in dementia over the past years, the need for specific screening instruments has emerged. To our knowledge, no new screening instruments have been developed for detection of poststroke dementia yet and all studies use existing screening instruments for dementia. The MMSE is still a frequently used mental status test in patients with a recent stroke, but has several disadvantages due to its emphasis on language and focus on cortical functions. However, Tatemichi et al. used the MMSE as a screening instrument and found that the MMSE can be of use when adjustments are made for the false positive rates.[39] Still, the absence of tasks sensitive to subcortical dysfunction, may make the MMSE a useful, but not ideal screening instrument for patients with a recent stroke. The 3MS seems more suitable for the detection of subcortical pathology than the MMSE. Grace et al. compared the original MMSE and the modified version in a stroke population and found that the 3MS en MMSE had a similar overall classification accuracy, which was adequate for patients with left hemispheric strokes and poor for patients with right sided strokes.[40] The authors, however, believe that the 3MS is a clinically more useful screening instrument in stroke patients because its false negative rate is lower and it demonstrated a higher sensitivity in a stroke population.

In the Dutch Vascular factors in Dementia Study the CAMCOG was used as a screening instrument.[41] Although the CAMCOG was also originally designed to diagnose primary degenerative dementia, it has an advantage over brief screening tests that it covers a broader range of cognitive functions in a relative short amount of time. It also detects mild cognitive deterioration and has few ceiling effects. We investigated the clinical utility and diagnostic accuracy of the CAMCOG in patients with a recent stroke in a prospective study by comparing the CAMCOG with a final "gold standard" judgment of cognitive functioning.[42] Despite its length and multiplicity the CAMCOG appeared well administrable in an elderly stroke population, as has been confirmed by a study of Kwa et al.[43] The CAMCOG was more sensitive and specific than the MMSE as a screening instrument for dementia in stroke patients. We found that apart from the CAMCOG score two other clinical variables independently improved the diagnostic accuracy. Patients with an intracerebral hemorrhage had approximately a three times larger risk to be demented after stroke in comparison with patients with a TIA or ischemic stroke, whereas patients with a left hemispheric stroke had a three times lower risk than patients with a right hemisphere stroke. According to our study results the CAMCOG is a feasible and accurate screening instrument for dementia in a stroke population, especially when type and site are taken into account.

CONCLUSION

With the growing interest in dementing disorders the number of brief, and more or less standardized mental status tests has strongly increased. Most of these tests, however, are similar in many aspects. They are a subset from a larger itempool, that has been constructed with Alzheimer's disease in mind. Not surprisingly most tests are sensitive to the cognitive deterioration compatible with Alzheimer's disease, especially when age and education are taken into account. Brief screening tests are not suitable to differentiate between normal cognitive functioning en mild dementia. In patients with a recent stroke there are other demands to a dementia screening test. Since a stroke may cause both cortical and subcortical deficits, the clinical expression of poststroke dementia is different from that of Alzheimer's disease. Due to the complexity and heterogeneity of the cognitive deficits a brief screening test is not informative. A screening test should contain items on more cognitive domains, and in addition to the items of brief mental tests this means that more attention should be paid tot subcortical deficits, like timed tasks and specific memory items. It may also be necessary to skip items like constructional abilities. The CAMCOG is somewhat longer and more comprehensive than regular screening tests, and seems to be an improvement, especially when other diagnostic factors are taken into account. However, instead of making adjustments to a test retrospectively, it is probably better to adjust the test itself. A screening instrument that is able to screen for dementia in a stroke population would be a valuable contribution to future research in vascular dementia.

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The CAMCOG: a useful screening instrument for dementia in stroke patients

Chapter 4

ABSTRACT

Background. Most mental screening tests focus on the detection of cognitive deficits compatible with Alzheimer's disease. Stroke patients who develop a dementia syndrome, however, constitute a more heterogeneous group with both cortical and subcortical disturbances. We assessed the diagnostic accuracy of the CAMCOG and MMSE for dementia, in patients with a recent stroke.

Methods. In patients aged 55 and over who were admitted in the Rotterdam Stroke Databank, cognitive functioning was assessed between three and nine months after the most recent stroke. The "gold standard" diagnosis of dementia was compatible with the criteria of the DSM-III-R. Independently of the diagnostic procedure, the CAMCOG and MMSE score were obtained.

Results. Of 300 consecutive patients, 71 (23.7%) were demented. Sixteen severely demented patients were not testable and excluded. The CAMCOG and MMSE score were significantly related to dementia (both $p<.0001$) in a logistic regression model. Receiver Operating Characteristic (ROC) analysis showed that the CAMCOG was a more accurate screening instrument (area under the curve CAMCOG: 0.95 vs. area under the curve MMSE: 0.90). Two other clinical variables independently improved the diagnostic accuracy of the MMSE and CAMCOG: patients with a left hemispheric lesion had a lower (OR 0.3, 95% CI: 0.1–0.7), and patients with hemorrhagic stroke had a higher chance of being demented (OR 3; 95% CI: 1–10). The effect of left hemispheric lesion as an independent diagnostic factor could not be explained by selection or its association with aphasia alone.

Conclusion. The CAMCOG is a feasible instrument in patients with a recent TIA or stroke. It is a more accurate screening tool for dementia than the MMSE, especially when type and site of stroke are taken into account.

INTRODUCTION

In patients with a recent stroke, it is important to assess cognitive deficits in a quick and convenient, but also reliable and accurate way. In the past, several mental status tests have been developed for this purpose, such as the Mini Mental State Examination (MMSE),[1] Mental Status Questionnaire (MSQ),[2] Short Portable Mental Status Questionnaire (SPMSQ),[3] Cognitive Capacity Screening Examination (CCSE),[4] Neurobehavioral Cognitive Status (NCSE),[5] and the Short Blessed Test.[6] Although these tests do not provide the same amount and type of information as a full neuropsychological examination, they may be used for selecting patients in whom such an extended neuropsychological examination is necessary. Most brief cognitive screening instruments have been developed for the detection of dementia of the Alzheimer type and focus on orientation, memory and higher cortical functions like aphasia, apraxia and agnosia. Aspects of cognitive functioning, like slowing of intellectual functioning, abstraction, retrieval and recognition, and visuo-perceptual abilities are less well measured. Stroke patients who develop dementia, however, may have deficits in any cognitive domain. The dementia syndrome may be classified as subcortical in some, and cortical in others. Previous studies in stroke populations also suggest that brief mental status tests are relatively insensitive to specific brain lesions or focal cognitive deficits.[7 8] Cognitive screening tasks predominantly contain verbally mediated items and therefore tend to exaggerate the extent of cognitive deficits in patients with left hemispheric lesions. Likewise, tests that emphasize verbal capacities may underestimate the consequences of right hemispheric lesions.[9-11] The question is whether these tests are valid tools in stroke patients.

The CAMCOG is the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX),[12] a standardized instrument for the diagnosis and grading of dementia. The CAMCOG consists of 67 items with a maximum possible score of 107 and can be divided in several subscales: orientation, expressive and comprehensive language, memory (remote, recent and learning), attention, praxis, calculation, abstraction, and perception. All items of the MMSE are also incorporated in the CAMCOG. Although the CAMCOG was also originally designed to diagnose primary degenerative dementia it has an advantage over brief screening tests in that it covers a broader range of cognitive functions in a relative short amount of time. It also detects mild cognitive deterioration and has few ceiling effects.[12] Studies of the CAMCOG have focused on the utility and validity of the complete CAMDEX.[12-15] In most of these studies the CAMCOG cut-off point of 79/80 suggested by Roth et al. seemed satisfactory for discriminating between normal subjects and demented patients.[12] Lindeboom et al. reviewed some psychometric properties of the CAMCOG and found that is was stable and reliable and differentiated well between normal cognitive functioning and mild cognitive impairment.[16] So far, little is known about the diagnostic value of the CAMCOG in a stroke population. Somatic handicaps as well as cortical disturbances such as aphasia or neglect may have a negative influence on its accuracy.

In this study, we investigated the diagnostic value of the CAMCOG as a screening instrument for poststroke dementia in comparison with the MMSE. Furthermore, we assessed the role of other clinical factors, that could confound or modify the relation between the screening test results and the presence of dementia.

SUBJECTS AND METHODS

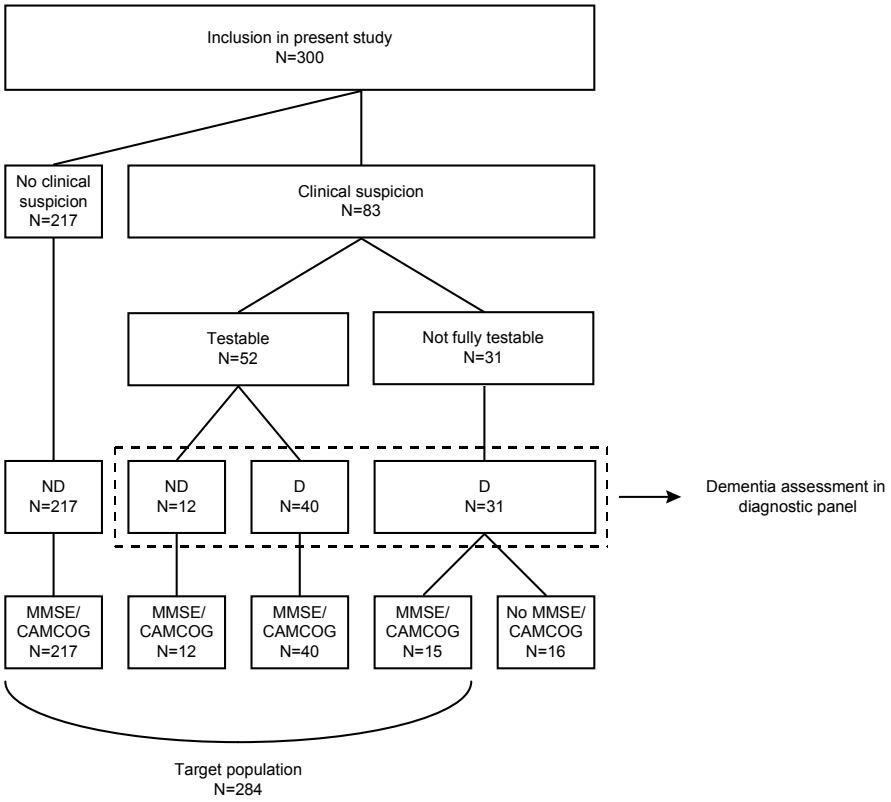
Subjects

Patients were recruited from the Rotterdam Stroke Databank, a prospective registry of patients with a transient ischemic attack (TIA), ischemic stroke or primary intracerebral hemorrhage, admitted to the Department of Neurology of the University Hospital Rotterdam. From March 1, 1993 until January 15, 1996, all consecutive patients who met the criteria for enrolment in The Dutch Vascular Factors in Dementia Study were entered.[17] Patients had to be 55 years or over, and had had a TIA with neurological signs on examination, an ischemic stroke or intracerebral hemorrhage. Patients were excluded when a reliable assessment of dementia could not be made because of aphasia (i.e. a score less than 3 on the Aphasia Severity Rating Scale from the Boston Diagnostic Aphasia Examination [BDAE]),[18] severe sensory handicaps (e.g. deafness or blindness), persistent impairment in consciousness, severe psychiatric symptoms, or insufficient command of the Dutch language. Additional exclusions were a TIA without neurological signs, concomitant primary cerebral disorder or severe comorbidity with a short life expectancy. Informed consent was obtained from all patients or from close relatives in case of impaired judgment.

Procedure

The clinical characteristics of the patients at baseline were assessed shortly after admission to the hospital. We obtained detailed information about cardiovascular risk factors, stroke characteristics, and premorbid mental and physical status. In addition to a full neurological examination, ancillary investigations consisted of standardized blood tests, chest x-ray, computed tomographic scanning and/or magnetic resonance imaging of the brain, duplex scanning of the carotid arteries, and a cardiac analysis. Premorbid cognitive functioning was established by an interview with a close relative and the score on the Blessed dementia scale. Education was categorized by the number of years of schooling completed. Between three and nine months after stroke onset cognitive functioning was assessed by a neurologist, based on clinical observation, the information of a close informant and the score on the Blessed Dementia Scale. In case of any suspicion of cognitive decline patients were invited for an extensive neuropsychological examination. We used the Aphasia Severity Rating Scale of the BDAE to assess the presence and severity of aphasia. A score of 6 indicates no aphasia, and 5,4 and 3 mild to moderate aphasia. A psychiatric examination was carried out in all demented patients to assess the presence of depression.

The "gold standard" diagnosis of dementia was based on the results of an extensive neuropsychological examination, clinical presentation, and information from a close relative. Figure 1 represents the diagnostic procedure for dementia. The extensive neuropsychological examination was carried out in all patients in whom there was any suspicion of dementia or cognitive decline. If patients were not testable due to cognitive deficits or when they refused further co-operation, the extensive neuropsychological evaluation was not performed. In some patients only a limited number of tests could be administered. The extensive neuropsychological examination consisted of an intelligence test, either the shortened version of the Groninger Intelligence Test,[19] a Dutch intelligence test, or when this was not administrable Raven's Coloured Matrices,[20] a non-verbal intelligence test. The shortened form of the Boston Naming Test (CERAD)[21] was used to examine word finding



ND = not-demented, D = demented, MMSE = Mini Mental State Examination.

Figure 1. Diagnostic procedure for dementia

difficulties. Memory was evaluated with Word List Memory (CERAD),[21] and the Rivermead Behavioural Memory Test.[22] We used Digit Span forward and backward (WAIS)[23] to assess the span of immediate verbal recall, but also as a measure for attentional capacity. Parts of the Trail Making Test,[24] and the Stroop Color Word Test[25] too were used to examine attention. Scores on verbal fluency (animals, occupations, letter B), Stroop Color Word Test part III,[25] Trail Making Test B,[24] served as indication for the level of executive functioning. Proverbs and similarities (WAIS)[23] provided a measure for abstraction and verbal concept formation. Visuo-constructive ability was examined by copying the drawing of a circle, diamond, two overlapping rectangles and a cube (CERAD).[21] Visual perception and spatial orientation were examined by Judgment of Line Orientation.[26] Based on clinical presentation, information from a close relative, the score on the Blessed dementia scale, and the neuropsychological test results, a final judgment of cognitive functioning was made by a diagnostic panel consisting of two neurologists, a neuropsychologist and a trained physician. For the assessment of dementia, the criteria of the DSM-III-R were used.[27] Further subclassification of dementia took place according to the research criteria of the NINDS-AIREN international workshop.[28]

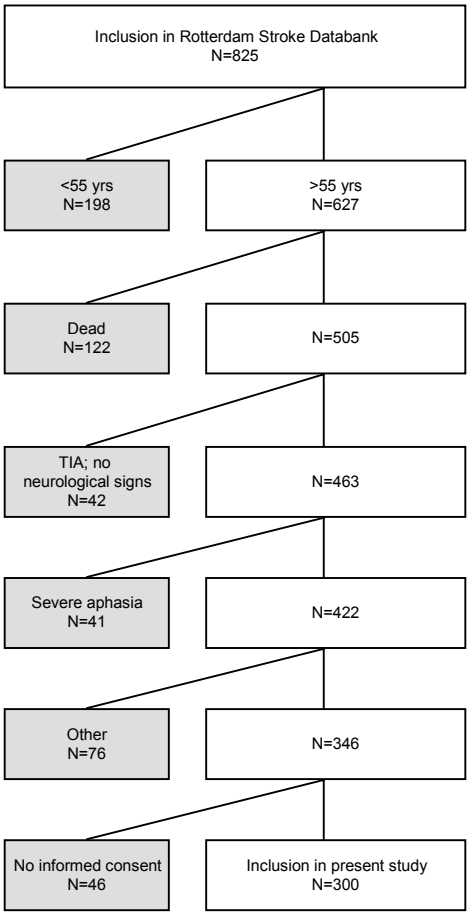


Figure 2. Selection of patients for the present study

Independently of the diagnostic procedure the MMSE and the Geriatric Mental Status (GMS),[29] and the Dutch version of the cognitive and self contained part of the CAMDEX,[30 31] the CAMCOG, was administered in all patients.

STATISTICAL ANALYSIS

For the comparison of the clinical characteristics of the demented and not-demented patients Student's t-test and a chi-square test were used when appropriate. The relation between clinical characteristics and dementia was described by means of odds ratios with a 95% confidence interval. The odds ratios for the dichotomous variables were estimated by contingency table analysis, and for the CAMCOG and MMSE by means of logistic regression. To determine the influence of other diagnostic information independently of the MMSE or CAMCOG score, multiple logistic regression was used. The diagnostic accuracy of the

CAMCOG and the MMSE, with and without adjustment for other diagnostic factors was compared by receiver operating characteristics (ROC) curves, by measuring the area under the curve. The statistical significance of the regression models was assessed by a standard likelihood ratio test, the fit was assessed by means of the Hosmer-Lemeshow chi square test, and by plotting observed and expected numbers of patients by deciles of the predicted probabilities. All statistical analyses were carried out using STATA software.[32]

RESULTS

From the 825 patients that entered the Rotterdam Stroke Databank, 198 were younger than 55 years of age, 122 died within three months after stroke onset, 42 had a TIA without any sign on neurological examination, 41 had severe aphasia, another 76 were excluded for various other reasons (e.g. moved out of the region, not speaking Dutch, short life expectancy due to other intracranial pathology), and 46 did not give informed consent (Figure 2). Of the remaining 300 patients who met the criteria for inclusion in The Dutch

Table 1. Baseline characteristics of the study population

	Total studygroup (N=284)	**Not-demented** (N=229)	**Demented** (N=55)
Age *	69.2 (8.1)	68.2 (8.0)	73.0 (7.3)‡
Years of education*	8.7 (3.1)	9.0 (3.0)	7.6 (2.9)§
Female sex†	114 (40)	84 (37)	30 (55)‖
CAMCOG*	83.3 (14.1)	88.2 (8.7)	63.2 (14.1)‡
MMSE*	25.4 (4.3)	26.7 (2.7)	19.9 (5.2) ‡
'Pre-stroke' Blessed score >0†	26 (10)	6 (3)	20 (37) ‡
Type of stroke†			
TIA	46 (16)	43 (19)	3 (5)
Ischemic infarction	203 (71)	164 (71)	39 (71)
Intracerebral hemorrhage	35 (12)	22 (10)	13 (24)§
Site of stroke†			
Right hemisphere	133 (47)	104 (45)	29 (53)
Left hemisphere	116 (41)	100 (44)	16 (29)
Infratentorial	35 (12)	25 (11)	10 (18)
Dementia type†			
Possible VaD			5 (9)
Probable VaD			35 (64)
Possible AD+CVD			15 (27)
Aphasia†	19 (7)	16 (7)	3 (5)
Apraxia†	9 (3)	3 (1)	6 (11)§
Neglect†	15 (5)	4 (2)	11 (20)‡
Hemianopia†	22 (8)	10 (4)	12 (22)‡
Facial paralysis†	54 (19)	36 (16)	18 (33)§
Any arm paresis†	69 (24)	49 (21)	20 (36) ‖
Any leg paresis†	64 (23)	44 (19)	20 (36)§

VaD = Vascular Dementia, AD+CVD = Alzheimer's disease and cerebrovascular disease
*Values are means with standard deviations in parentheses
†Values are number of patients with (column) percentages in parentheses
‡ Demented patients significantly different from not-demented patients ($p < 0.001$)
§ Demented patients significantly different from not-demented patients ($p < 0.01$)
‖ Demented patients significantly different from not-demented patients ($p < 0.05$)

Table 2. The relation between clinical characteristics and the presence of dementia

	Odds Ratio	95% CI
Univariate analysis		
CAMCOG score	0.83	0.79 – 0.87*
MMSE score	0.64	0.57 – 0.72*
Age	1.08	1.04 – 1.12*
Female sex	2.1	1.1 - 3.7
Years of education	0.83	0.73 - 0.93
TIA	0.25	0.08 - 0.77
Left hemisphere	0.5	0.3 - 1.0
Intracerebral hemorrhage	2.9	1.4 - 6.2
Aphasia	0.8	0.2 – 2.6
Apraxia	9.7	2.6 – 36.8
Neglect	11.2	3.9 – 32.4
Arm paresis	2.1	1.1 – 3.9
Leg paresis	2.4	1.3 – 4.5
Hemianopia	6.1	2.5 – 14.7
Multiple regression model		
CAMCOG score	0.83	0.79 – 0.87
Left hemispheric lesion	0.3	1.1– 0.9
Intracerebral hemorrhage	3.1	1.0 – 9.7
MMSE score	0.63	0.56 – 0.71
Left hemispheric lesion	0.3	1.1– 0.7
Intracerebral hemorrhage	2.6	1.0 – 7.4

* estimated by logistic regression; odds ratios per unit increase
CI = confidence interval, MMSE = Mini Mental State Examination

Vascular Factors in Dementia Study, sixteen were excluded from the present study because the CAMCOG was not administrable due to severe dementia. The clinical characteristics of the 284 study patients are summarized in Table 1. The mean age was about 70 years and 40% was female. One sixth of the patients had had a TIA, a little more than one tenth had had an intracerebral hemorrhage. Of the demented patients in our study population about one quarter was diagnosed as possible Alzheimer's disease with cerebrovascular disease, the other demented patients were classified as possible or probable vascular dementia. Aphasia was present in 7% of all patients. Demented patients scored significantly lower on the CAMCOG, on average 25 points (95% CI: 22.1–27.9) than not-demented patients. Demented patients were on average 4.8 years older (95% CI: 2.5–7.1) and they were more often female. They had on average 1.4 years less education than not-demented patients (95% CI: 0.5–2.3). Neurological deficits such as the presence of apraxia, neglect, hemianopia, facial paralysis and paresis of arm or leg were associated with dementia, but aphasia was not. Table 2 gives the corresponding odds ratios with 95% confidence intervals for each factor by itself. In our study, each point increase in the CAMCOG score decreased the odds of being demented by 0.83, and each point increase in the MMSE score decreased the odds of dementia by 0.64. Although the relative odds reduction per point is larger for the MMSE, the CAMCOG is by far the better test, because the range of possible scores is larger (30 vs. 107). ROC analysis shows that the CAMCOG was more accurate in screening for dementia than the MMSE (area under the ROC curve MMSE: 0.90 vs. area under the ROC curve CAMCOG: 0.95)

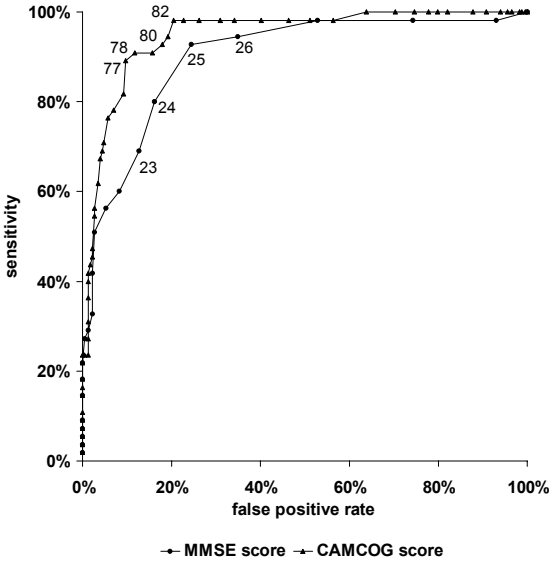


Figure 3. ROC curves to determine the diagnostic accuracy of the CAMCOG and the MMSE

(Figure 3). We could improve the predictions by adding other diagnostic factors: patients with a left hemispheric lesion had a three times lower risk of dementia, independently of the CAMCOG or MMSE score, and patients with a hemorrhage lesion had an approximately three times higher risk of dementia, independently of test score. In univariate analyses, TIA was related to a reduced risk of dementia. In the multiple regression model, however, TIA was not significantly related to a reduced risk of dementia in our study population. Age, gender and education are known to be of influence on screening test scores, but showed no significant relation with both the presence of dementia and the CAMCOG score in our study. After adjusting for site and type of stroke, the area under the curve increased with

Table 3. Observed and predicted number of demented patients, according to the four logistic regression models, by quintiles of the predicted probabilities

Hosmer-Lemeshow (χ^2)	CAMCOG[1] p=0.21		MMSE[2] P=0.02		CAMCOG adjusted[3] p=0.19		MMSE adjusted[4] p=0.05	
	observed	predicted	observed	predicted	observed	predicted	observed	predicted
	0	0.4	1	1.5	0	0.3	0	1.0
	1	1.4	2	4.7	0	0.7	0	2.3
	0	2.8	1	2.4	1	2.6	6	3.2
	12	9.2	18	10.7	13	8.7	15	11.9
	42	41.2	33	35.7	41	42.7	34	36.7

[1] $O = e^{13.2 + (-0.19 \times C)}$

[2] $O = e^{9.2 + (-0.44 \times M)}$

[3] $O = e^{13.5 + (-0.19 \times C) + (1.13 \times H) + (-1.18 \times L)}$

[4] $O = e^{9.8 + (-0.46 \times M) + (0.97 \times H) + (-1.3 \times L)}$

where O=odds of dementia, C=CAMCOG score, M=MMSE score, L=presence (1) or absence (0) of left hemispheric lesion, H=presence (1) or absence (0) of hemorrhagic stroke.

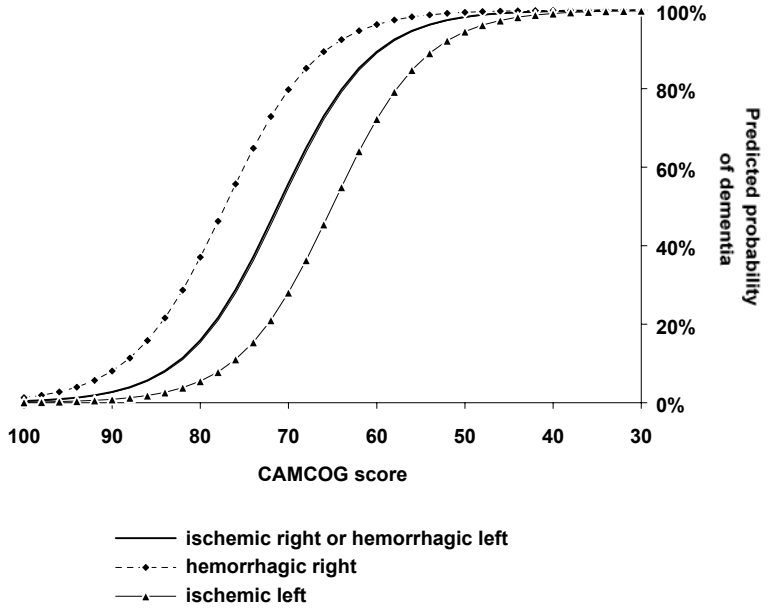


Figure 4. The relation between the risk of dementia and the CAMCOG score, with adjustment for type and site of stroke, determined by logistic regression

0.01 in both curves. The predictions based on the MMSE were always less accurate than CAMCOG based predictions, even when they were adjusted for type and site of stroke. The predictions based on the CAMCOG with adjustment for the two diagnostic factors appeared to be the best, as the area under the ROC curve was largest (0.96). The CAMCOG had the best overall fit (Table 3). Figure 4 shows the relation between the risk of dementia and the CAMCOG score in our study, adjusted for type and site of stroke. The additional diagnostic factors have a maximum effect in the middle range of the CAMCOG scores. In our study about 45% of the patients have a CAMCOG score between 55 and 87. For example, the predicted probability of dementia in a patient with a CAMCOG score of 75 would be 30% in our study. Taking into account that this patient had a left ischemic stroke would lower the probability of dementia to 10%, while a patient with a right hemorrhage stroke and the same CAMCOG score is much more likely to be demented, with a probability of 60%.

DISCUSSION

We investigated the diagnostic accuracy of the CAMCOG in patients with a recent stroke in a prospective study by comparing the CAMCOG with a final "gold standard" judgment of cognitive functioning. The CAMCOG was more sensitive and specific than the MMSE as a screening instrument for dementia in stroke patients. Despite its length and multiplicity, the CAMCOG appeared well administrable in an elderly stroke population. Of the 300 patients, the CAMCOG could be administered in 95% of the patients and the MMSE in 97%. The

experience with the CAMCOG in stroke populations is limited. Kwa et al. found that the CAMCOG was administrable in 88% of an ischemic stroke population, which also included patients younger than 55 years of age.[33] Since their main interest was in the extent to which the CAMCOG is feasible in an ischemic stroke population, they included all aphasic patients and allowed adaptations in administration like the use of gestures. We excluded patients with a severe aphasia because differentiation between dementia and severe aphasia is very difficult and sometimes impossible even for experienced neuropsychologists who use a large test battery. The CAMCOG may be administrable in such patients but the score is meaningless because it remains unclear to what extent the total score is determined by the presence of dementia or by aphasia.

The finding that the CAMCOG is a more sensitive and specific screening instrument than the MMSE in an elderly stroke population is not surprising as the CAMCOG contains more items on memory, language and construction and allows a more differentiated judgment about these functions than the MMSE. Furthermore, the CAMCOG comprises items on more cognitive domains in comparison with the MMSE, by adding subtests abstraction, fluency and perceptual tasks. It is therefore a priori quite likely that the CAMCOG is more sensitive and specific than the MMSE in a heterogeneous group such as stroke patients. On the other hand, an addition of items by itself is not enough to increase sensitivity and specificity. Grace et al. performed a study in which the original MMSE was compared with a modified version, the 3MS.[8] This modified version contains the items of the original MMSE but were given a different weight, and extra items were added, such as abstraction and fluency. In that study, the 3MS and MMSE had a similar overall classification accuracy, which was adequate for patients with left hemispheric strokes and poor for patients with right sided strokes. In our study, the CAMCOG score seemed to overestimate the risk of dementia in patients with a left hemispheric stroke compared to those with a right hemispheric stroke, which may indicate that the CAMCOG tends to overemphasize focal cognitive deficits in these patients.

Previous studies suggest that age and education are associated with dementia,[34-37] and also with the performance on the CAMCOG.[16 38] In our study, age and education had no additional diagnostic value in a multiple logistic regression model. One obvious explanation is that these factors are already accounted for in the CAMCOG score, as they are associated with dementia alone. We found that apart from the CAMCOG score, only type and site of stroke were useful in predicting the probability of dementia three months after stroke. Patients with an intracerebral hemorrhage had approximately a three times larger risk to be demented after stroke in comparison with patients with a TIA or ischemic stroke, whereas patients with a left hemispheric stroke had a three times lower risk than patients with a right hemisphere stroke. The finding that apraxia, mainly a consequence of left hemispheric lesions, was strongly associated with the presence of dementia in an univariate analysis, seems to be incongruent with this finding. The number of patients with apraxia, however, was small and therefore may have had little effect on the total group of patients with a left hemispheric stroke

Patients with a left hemispheric stroke were less likely to be demented three months after stroke, even after adjustment for other diagnostic factors, which is not in agreement with some other studies in which a left hemispheric stroke increases the risk of cognitive impairment or dementia.[39-41] There are some explanations for our finding. First, we may have overestimated the role of mild and moderate aphasia in neuropsychological test scores and

therefore underestimated the extent of general cognitive decline. The proportion of aphasic patients in our study, however, was equal for demented and not-demented patients, also when we included the demented patients in which a CAMCOG was not administrable. Second, since patients with a severe aphasia were excluded because this prevented a reliable assessment of dementia, we excluded more massive left hemispheric strokes as opposed to massive right hemispheric strokes. In our study, however, patients with left hemisphere stroke did not differ from those with a right hemispheric stroke with respect to the presence of hemianopia, facial paresis, arm or leg paresis.

In conclusion, the CAMCOG is well administrable and it is an accurate screening tool for dementia in patients with a recent stroke. Our study results suggest that the CAMCOG has additional diagnostic value compared with the MMSE, especially when type and site of stroke are taken into account. A prospective study in a different, but comparable stroke population is needed to confirm our results.

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A short screening instrument for poststroke dementia: the R-CAMCOG

Chapter 5

ABSTRACT

Background and purpose. The CAMCOG is a feasible cognitive screening instrument for dementia in patients with a recent stroke. A major disadvantage of the CAMCOG, however, is its lengthy and relatively complex administration for screening purposes. We therefore developed the Rotterdam CAMCOG (R-CAMCOG), based on the original version. Our aim was to reduce the estimated administration time to 15 minutes or less, and to retain or perhaps even improve its diagnostic accuracy.

Methods. The itemscores on the CAMCOG of 300 consecutive stroke patients, after exclusion of patients with a severe aphasia or lowered consciousness level, who were entered in the Rotterdam Stroke Databank were analyzed. The diagnosis of dementia was made independently of the (R)-CAMCOG score, based on clinical examination and the neuropsychological test results. The R-CAMCOG was constructed in three steps. First, items with floor and ceiling effects were removed. Then, subscales with no additional diagnostic value were excluded. Finally, we removed items that did not contribute to the homogeneity of the subscales. The diagnostic accuracy of the R-CAMCOG and the original CAMCOG was determined by means of the area under the ROC curve.

Results. In the three steps, the number of items was reduced from 59 to 25, divided over the subscales orientation, memory (recent, remote and learning), perception and abstraction. The subscale orientation did not reach significance in a logistic regression model, but was included in the R-CAMCOG because of its high face validity in dementia screening. Internal validation with ROC analysis suggests that the R-CAMCOG and the CAMCOG are equally accurate in screening for poststroke dementia (area under the curve is 0.95 for both tests).

Conclusions. The R-CAMCOG has overcome the disadvantages of the original CAMCOG. It is a promising, short and easy-to-administer screening instrument for poststroke dementia. It seems to be sufficiently accurate for this purpose, but the test has yet to be validated in a separate, independent study.

INTRODUCTION

Cerebrovascular disease, in particular stroke, is a major cause of dementia.[1-3] From both a clinical and research perspective it is therefore important to assess cognitive functioning after stroke. An extended neuropsychological examination, however, may not be necessary in all patients to establish a diagnosis and will be time-consuming and costly. On the other hand, brief mental status tests that have been developed to detect dementia compatible with Alzheimer's disease, are often not sensitive enough to detect the specific and heterogeneous cognitive disturbances seen in poststroke dementia. Another drawback of these tests is that they heavily rely on language, often contain constructional items, and tend to disregard subcortical disturbances.[4]

The CAMCOG is the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)[5 6] and was also primarily developed to detect cognitive disturbances compatible with Alzheimer's disease. Previous studies have nevertheless shown that the CAMCOG is a feasible test for dementia in a stroke population.[7 8] We studied its utility as a screening instrument for dementia in a stroke population and found that the CAMCOG was more accurate than the Mini Mental State Examination (MMSE). The diagnostic accuracy of the CAMCOG could even be improved when type and site of stroke were taken into account.[8]

A major disadvantage of the CAMCOG, however, is its lengthy administration time for the purpose of screening for dementia in a clinical setting, by a physician. We therefore adapted and modified the CAMCOG with two aims: to reduce its administration time from 25 minutes to approximately 15 minutes, and to retain or perhaps even improve its diagnostic accuracy. The results of the present study are based on analyses of the individual items of the CAMCOG performed in a cohort of 300 consecutive stroke patients entered in the Rotterdam Stroke Databank.

METHODS

Patients

Patients were recruited from the Rotterdam Stroke Databank, a prospective registry of patients with transient ischemic attack (TIA), ischemic stroke or primary intracerebral hemorrhage, admitted to the Department of Neurology of the University Hospital Rotterdam. From March 1, 1993 until January 15, 1996, all consecutive patients who met the criteria for enrolment in The Dutch Vascular Factors in Dementia study were included in the present study.[3] Patients had to be 55 years or over, and had had a TIA, an ischemic stroke or intracerebral hemorrhage. Patients were excluded when a reliable assessment of dementia could not be made due to aphasia (i.e. a score of <3 on the Aphasia Severity Rating Scale from the Boston Diagnostic Aphasia Examination [BDAE]),[9] severe sensory handicaps (e.g. deaf or blind), lowered consciousness level, severe psychiatric symptoms, or insufficient command of the Dutch language. Additional reasons for exclusion were a concomitant primary cerebral disorder (e.g. Parkinson's Disease) or severe comorbidity with a short life expectancy. Informed consent was obtained from all patients or from close relatives in case of impaired judgment. The local Medical Ethical Committee approved of the study.

Procedure

During hospital admission, we obtained detailed information about cardiovascular risk factors, stroke characteristics, and premorbid mental and physical status. This procedure has been described in detail elsewhere.[8] In addition to a full neurological examination, ancillary investigations consisted of standardized bloodtests, chest X-ray, computed tomographic scanning and/or magnetic resonance imaging of the brain, duplex scanning of the carotid arteries, and a cardiac analysis. Premorbid cognitive functioning was established by an interview with a close relative and the score on the Blessed dementia scale. Between three and nine months after stroke onset general and cognitive functioning was assessed, and blood and urinary samples were taken. A neurologist who also obtained information about actual cognitive functioning performed neurological examination. Based on clinical presentation, information from a close relative and the score on the Blessed dementia scale, judgment of cognitive functioning was made by behavioral neurologists and a neuropsychologist. We used the Aphasia Severity Rating Scale of the BDAE to assess the presence and severity of aphasia. A score of 6 indicates no aphasia, and 5,4 and 3 mild to moderate aphasia. Education was categorized by years of schooling completed. An extended neuropsychological examination was carried out in all patients who presented with cognitive complaints, or when a close relative mentioned a decline in cognitive functioning. An extended neuropsychological examination was also indicated when the investigators suspected a change in cognitive functioning, even when the patient or close relative had no complaints. Therefore, in all patients in whom there was any suspicion of dementia or cognitive decline an extended neuropsychological examination was carried out. When patients were not testable due to cognitive deficits or somatic handicaps or when they refused further co-operation, extended neuropsychological evaluation was not performed. In some patients only a limited number of tests could be administered. The extensive neuropsychological examination consisted of an intelligence test, either the shortened version of the Groninger Intelligence Test,[10] a Dutch intelligence test, or when this was not administrable Raven's Coloured Matrices,[11] a non-verbal intelligence test. The shortened form of the Boston Naming Test (CERAD)[12] was used to examine word-finding difficulties. Memory was evaluated with Word List Memory (CERAD),[12] and the Rivermead Behavioural Memory Test.[13] We used Digit Span forward and backward (WAIS)[14] to assess the span of immediate verbal recall, but also as a measure for attentional capacity. Parts of the Trail Making Test,[15] and the Stroop Color Word Test[16] too were used to examine attention. Scores on verbal fluency (animals, occupations, letter B), Stroop Color Word Test part III,[16] Trail Making Test B,[15] served as indication for the level of executive functioning. Proverbs and similarities (WAIS)[14] provided a measure for abstraction and verbal concept formation. Visuo-constructive ability was examined by copying the drawing of a circle, diamond, two overlapping rectangles and a cube (CERAD).[12] Visual perception and spatial orientation were examined by Judgment of Line Orientation.[17] Furthermore, in all patients the MMSE, the Geriatric Mental Status,[18] and the Dutch version of the cognitive and self contained part of the CAMDEX, the CAMCOG, was administered.[6] These tests did not act as a screening, but were administered to standardize the procedure as much as possible with the twin population-based part of the study, The Rotterdam Study.[19] Although test behavior during the administration of the CAMCOG may have played a role in judgment of cognitive

functioning, the actual test scores were not taken in account. A psychiatric examination was performed in all demented patients to assess the presence of depression.

Based on clinical presentation, information from a close relative, the score on the Blessed dementia scale, and the neuropsychological test results, a final judgment of cognitive functioning was made by a diagnostic panel consisting of two neurologists, a neuropsychologist and a trained physician. For the assessment of dementia, the criteria of the DSM-III-R[20] were used. In short, according to these criteria there has to be a demonstrable evidence of impairment in both short term and long term memory and at least disturbances in one other cognitive domain (i.e. impairment in abstract thinking, impaired judgment, other disturbances in higher cortical functioning, such as aphasia, agnosia, apraxia, or a personality change). The disturbances should be severe enough to interfere with daily functioning and occur not exclusively during the course of delirium.

Further differentiation of dementia took place according to the research criteria of the NINDS-AIREN International Workgroup for vascular dementia.[21] Patients were diagnosed as suffering from a probable vascular dementia, possible vascular dementia, or possible Alzheimer's' Disease (AD) with cerebrovascular disease (CVD). This latter category was reserved for patients fulfilling the clinical criteria for possible AD and who also presented clinical or brain imaging evidence of relevant CVD. The severity of dementia was assessed by the Global Deterioration Scale[22] and the Clinical Dementia Rating.[23]

Construction of the R-CAMCOG

The original CAMCOG contains 67 items of which 8 items are not included in the actual CAMCOG score. Five of these 8 items are included for assessment of the MMSE score and the other three items are optional, and do not affect the total CAMCOG score. The remaining 59 items, divided over 11 subscales, make up the CAMCOG score. Thirty-nine items are scored as right or wrong. Eleven items are gradual scores in which an answer can be wrong, right to a certain degree or completely right. The remaining 9 items are made up of more questions or commands and the 'itemscore' is the sum of the number of right answers. In line with the results of a previous study we assigned zero scores to all items that could not be administered due to upper extremity paresis.[24] Items that were deemed inaccessible because of other factors, e.g. illiteracy or severe visual disturbances, were regarded as missing values, and were therefore not included in the statistical analyses.

The construction of the R-CAMCOG took place in several steps (Figure 1). The methodology and strategy was partly adapted from Van Straten et al., who adjusted the Sickness Impact Profile to a stroke population.[25]

In the first step we excluded the items which were considered to provide ceiling or floor effects. When more than 95% of the patients gave the right response to an item, we considered this a ceiling effect and when less than 5% of the patients gave the right answer to a question, this was considered a floor effect. In the second step we excluded the shortened subscales which had no additional diagnostic value. We carried out a multiple logistic regression analysis with the presence of dementia as dependent, and the shortened subscales as independent covariates. In a stepwise backward elimination procedure, the subscales with the highest diagnostic value were selected (p to enter 0.10, p to exit 0.15). In the final step we excluded items that did not contribute to the statistical coherence of a subscale. The mean inter-item correlation in each subscale, to be interpreted as internal consistency, was determined by means of Cronbach's alpha.[26]

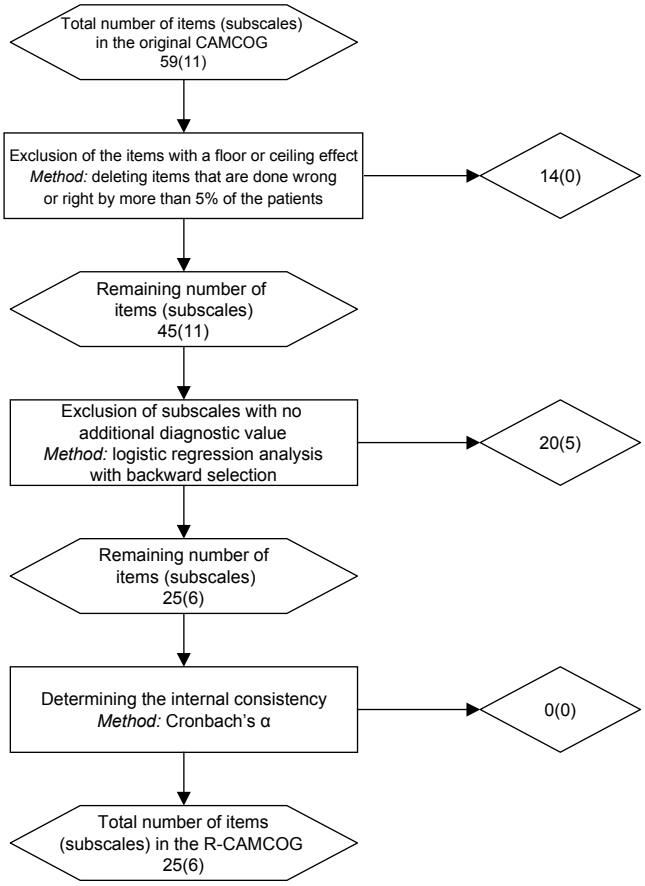


Figure 1. The steps in the construction of the R-CAMCOG

We determined the (clinical) validity of the R-CAMCOG on the original study population. In the multiple logistic regression model the total CAMCOG score was correlated to the likelihood of dementia. The dependent factor was the presence of dementia and the independent factor was the total CAMCOG score. Receiver operating characteristic (ROC) analysis was performed to assess and compare the diagnostic accuracy of the two tests, by calculating the area under the curve.

All statistical analyses were carried out using Stata Software.[27]

RESULTS

During the study period 825 patients entered the Rotterdam Stroke Databank. Of these patients, 198 were excluded because they were younger than 55 years of age, 122 had died and 42 patients had had a TIA with no neurological signs on examination. Of the remaining 463 patients, 41 had a severe aphasia (i.e. BDAE score less than 3) and 76 were

Table 1. Baseline characteristics of the study population

	Total studygroup (N=284)	**Not-demented** (N=229)	**Demented** (N=55)
Age *	69.2 (8.1)	68.2 (8.0)	73.0 (7.3)‡
Years of education*	8.7 (3.1)	9.0 (3.0)	7.6 (2.9)§
Female sex†	114 (40)	84 (37)	30 (55)‖
CAMCOG*	83.3 (14.1)	88.2 (8.7)	63.2 (14.1)‡
MMSE*	25.4 (4.3)	26.7 (2.7)	19.9 (5.2) ‡
Type of stroke†			
TIA	46 (16)	43 (19)	3 (5)
Cerebral infarction	203 (71)	164 (71)	39 (71)
Intracerebral hemorrhage	35 (12)	22 (10)	13 (24)§
Site of stroke†			
Right hemisphere	133 (47)	104 (45)	29 (53)
Left hemisphere	116 (41)	100 (44)	16 (29)
Infratentorial	35 (12)	25 (11)	10 (18)
Dementia type†			
Possible VaD			5 (9)
Probable VaD			35 (64)
Possible AD+CVD			15 (27)
Aphasia†	19 (7)	16 (7)	3 (5)
Apraxia†	9 (3)	3 (1)	6 (11)§
Any arm paresis†	69 (24)	49 (21)	20 (36) ‖

VaD = Vascular Dementia, AD+CVD = Alzheimer's disease and cerebrovascular disease
* Values are means with standard deviations between parentheses
† Values are number of patients with (column) percentages between parentheses
‡ Demented patients significantly different from not-demented patients ($p < 0.001$)
§ Demented patients significantly different from not-demented patients ($p < 0.01$)
‖ Demented patients significantly different from not-demented patients ($p < 0.05$)

excluded for several other reasons (i.e. lowered level of consciousness, severe sensory handicaps, insufficient command of the Dutch language). Furthermore, 46 patients refused to participate in the study. From the 300 patients who met the criteria for inclusion in the Dutch Vascular Factors in Dementia Study, sixteen were excluded from the present study because the CAMCOG could not be administered due to severe dementia. All 300 patients, however, had a detailed dementia assessment. The baseline and demographic characteristics of the patients of the study population are shown in Table 1. The mean age was 70 years and 40% of the patients was female. About one sixth had had a TIA and approximately 10% had had an intracerebral hemorrhage. Right hemispheric stroke was slightly more common than left hemispheric stroke (47% vs. 41%). Approximately one quarter of the patients had any arm paresis and 7% had aphasia. Demented patients were on average 5 years older than not-demented patients and had had on average 1.4 years less education. Demented patients had more often had a right hemispheric stroke or an infratentorial stroke than not-demented patients. Whether this finding is related to the exclusion of severe aphasic patients has been discussed extensively in a previous study.[8]

In the first step of the construction of the R-CAMCOG, the exclusion of items with a ceiling effect, we excluded 14 items that were failed by less than 5% of our total study population. Most of the items that were removed were part of the subscale language, in particularly comprehension (Table 2). There were no items with a floor effect in the scores. The exclusion of items with a ceiling effect did not affect the number of subscales. In the second

Table 2. Distribution of the items and subscales in the CAMCOG and the R-CAMCOG

	CAMCOG	Step 1		Step 2		Step 3	R-CAMCOG
Subscales		Exclusion of items with ceiling effect		Exclusion of least relevant subscales		Internal consistency	
Orientation	10	2	8		8		8
Language							
– *Comprehension*	9	6	3	3			
– *Expression*	8	2	6	6			
Memory							
– *Learning*	3		3		3		3
– *Recent*	4	1	3		3		3
– *Remote*	6	1	5		5		5
Concentration	2		2	2			
Praxis	8	1	7	7			
Calculation	2		2	2			
Perception	3	1	2		2		2
Abstraction	4		4		4		4
Number of items (subscales)	59 (11)	14 (0)	45 (11)	20 (5)	25 (6)	0 (0)	25 (6)

step we excluded the subscales with the lowest diagnostic value (Table 3). In the stepwise logistic regression with a backward selection on the 11 subscales, the shortened subscales orientation, language (comprehension and expression), attention, praxis, calculation were excluded, and abstraction, perception and all three memory subscales were retained.

All subscales showed a high average inter-item correlation and scale reliability coefficient, except for the subscale perception. This may be explained by the fact that this subscale is divided in two presumably distinct cognitive domains, tactile and visual perception. Therefore, the low inter-item correlation has no implications for the validity of the test and the subscale perception was included in the R-CAMCOG.

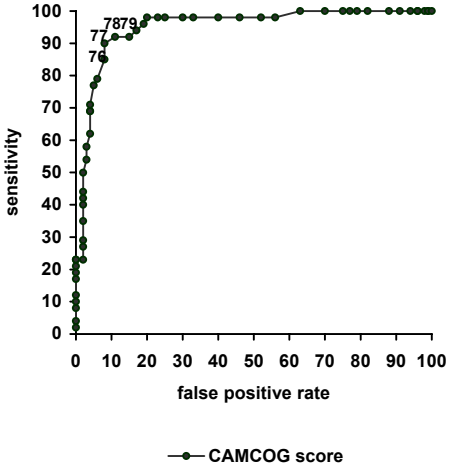
The shortened subscale orientation did not reach significance in the logistic regression model, but was included in the R-CAMCOG because it has high face validity in dementia screening.

The final version of the R-CAMCOG (appendix) contained 25 items divided over 6 subscales: orientation, memory (recent, remote and learning), perception and abstraction.

Table 3. Relationship of CAMCOG subscales to the probability of dementia in a multiple regression model after backward elimination of the subscales

	OR	**95% CI**	**P**
Orientation	.99	.63 – 1.56	.97
Memory			
– Learning	.46	.34 - .60	.00
– Recent	.57	.32 - 1.03	.06
– Remote	.77	.53 - 1.10	.15
Abstraction	.74	.58 - .93	.01
Perception	.64	.43 - .96	.03

OR: odds ratio, 95% CI: 95% confidence interval



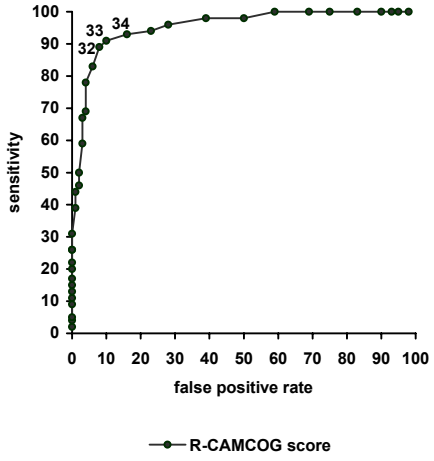


Figure 2. Receiver operating characteristic curves to determine the diagnostic accuracy of the original CAMCOG and the R-CAMCOG

Some items, like naming of objects and writing an address, were included because they were required to test recall in the memory subscale. These items, nevertheless, were not included in the R-CAMCOG score.

We compared the diagnostic accuracy of the original CAMCOG and the R-CAMCOG on the original data that were used to construct the R-CAMCOG (Figure 2). ROC analysis suggests that the R-CAMCOG is equally accurate in screening for poststroke dementia (area under the ROC curve original CAMCOG and R-CAMCOG both: 95%). The sensitivity and specificity at the optimal cut-off point is equal for the CAMCOG and the R-CAMCOG (CAMCOG cut-off point 77: sensitivity 91%, specificity 88%; R-CAMCOG cut-off point 33:

sensitivity: 91%, specificity: 90%). The diagnostic accuracy improved slightly when site and type of stroke were taken into account (area under the curve original CAMCOG and R-CAMCOG both: 96%), similarly to the results of our previous study.

DISCUSSION

In this study, we have developed a short and feasible screening instrument for poststroke dementia, the R-CAMCOG, based on the original CAMCOG. We analyzed the individual itemscores of the CAMCOG of 300 consecutive stroke patient of the Rotterdam Stroke Databank, aged 55 or over, without severe aphasia or sensory handicaps, and with a normal consciousness level. In three steps, the number of items was reduced from 59 to 25, divided over the subscales orientation, memory (recent, remote, learning), perception and abstraction. The administration time was reduced to approximately 10 minutes. Analyses in our original study population showed that the sensitivity and specificity were high and generally equal for the original CAMCOG and the R-CAMCOG.

To our knowledge, there are no dementia screening instruments that have been developed especially to screen for poststroke dementia. Some existing mental status tests, however, have been used and studied for this purpose. The MMSE is still a frequently used test in patients with a recent stroke, but has several disadvantages due to its emphasis on language and constructional items. We compared the MMSE to the CAMCOG in the Dutch Vascular Factors in Dementia Study and found that it was a less accurate screening instrument than the CAMCOG.[8] Tatemichi et al. used the MMSE as a screening instrument and found that it can be of use when adjustments are made for the high rate of false positive scores, but an independent, prospective evaluation has not been carried out.[28] Grace et al. performed a study in a geriatric stroke population, in which the original MMSE was compared with a modified version, the 3MS.[29] In this study the 3MS was not better than the MMSE in diagnosing dementia. Thus, with its longer administration time, the 3MS had no clear advantage in clinical use in a geriatric stroke population.

Two other neuropsychological instruments that have been used in a stroke population, the Neurobehavioral Cognitive Status Examination[30] and the Mattis Dementia Rating Scale,[31] are also classified as screening instruments. Considering the structure of these tests and the administration time, however, these tests are in fact microbatteries, and in our opinion do not serve the purpose of a dementia screening instrument

Previously, we found that the CAMCOG is a feasible screening instrument in a stroke population,[8] which confirmed an earlier study.[7] Nevertheless, the CAMCOG still has drawbacks, when it is applied in patients with a recent stroke. The CAMCOG contains items that seem inassessable in some stroke patients due to upper extremity paresis or aphasia; this will lead to missing values. Recently, we studied the significance of missing values due to upper extremity paresis and concluded that this does not affect the discriminatory ability of the constructional items of the CAMCOG.[24] Another major drawback of the CAMCOG is its lengthy and relatively complex administration. In the R-CAMCOG these disadvantages have been overcome.

The domains and items of the R-CAMCOG overlap with other dementia screening instruments, such as the MMSE,[32] 3MS,[33] and the short Blessed Test.[34] All mental status tests contain orientation and memory questions. In our study, the subscale orientation

did not reach significance in a stepwise logistic regression analysis, but we included the orientation items because of their high face validity in clinical settings.[4 35] Memory items are also represented in virtually all dementia screening instruments, but the extent to which memory is measured varies distinctively between the different tests. An advantage of the R-CAMCOG is that it emphasizes memory, by definition the most important feature of dementia. The R-CAMCOG, however, examines different aspects of memory and is therefore better able to detect subcortical features of memory disturbances as can be seen in poststroke dementia. In the R-CAMCOG, visual and verbal memory are tested, with a recall measure and a recognition condition to distinguish learning from retrieval deficits. Memory for remote and recent facts is also included in the R-CAMCOG.

Decreased abstraction is recognized as a possible feature of dementia, yet most mental status tests tend to neglect this ability. In the R-CAMCOG, the level of abstraction is measured by means of similarities.

The subscale perception of the R-CAMCOG includes tactile perception of coins and recognition of objects from an unusual view. Even though (visual)agnosia is a well-known feature of dementia, often included in diagnostic criteria, most mental screening tests do not test the presence of visual perceptual deficits other than in an object-naming task. In our experience, however, the item 'unusual views' (where objects to be named are photographed from an unusual angle), is generally more difficult and complex than merely naming objects, and may be better in screening for more subtle visual disturbances.

The subscales praxis and language were not included in the logistic regression model, even though these items seem by itself useful in screening for dementia. A possible explanation for this may be the redundancy of the items. A substantial number of items of the extensive subscale language was removed because of a floor effect in the first step of the construction of the R-CAMCOG. The low complexity of the language comprehension questions may be an explanation for this finding.

Executive functioning is assumed to play an important role in dementia, but is not tested in the R-CAMCOG. This may be largely inherent to the original CAMCOG, which contains hardly tasks that measure executive functioning. As yet, it is unknown whether the absence of executive tasks is a limitation of the R-CAMCOG. It seems plausible, however, that many of the tasks that measure executive functioning are too demanding for stroke patients in view of the somatic handicaps.

The final version of the R-CAMCOG shows overlap with other mental status tests with measures of orientation and memory, but lacks specific language items and constructional commands like drawing. Consequently, the R-CAMCOG can be used to screen for dementia without the disadvantage of confounding by the direct consequences of a stroke, like upper extremity paresis or mild aphasia. Clinical validation of the R-CAMCOG on the original data that were used to construct the R-CAMCOG showed a high sensitivity and specificity. External validation and assessment of reliability in a different series of stroke patients will be necessary to determine the value of the R-CAMCOG as a dementia screening instrument in patients with a recent stroke.

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APPENDIX. THE ITEMS OF THE R-CAMCOG

Naming
Shoe Typewriter Scales Suitcase Barometer Lamp

Orientation
What day of the week is it? /1
What is the date today? Date Month Year /3
Can you tell me where we are now?
For instance in what province we are in. /1
What is the name of this town (city)? /1
What floor of the building are we on? /1
What is the name of this place? /1

Remote memory
Can you tell me when the First World War began? /1
Can you tell me when the Second World War began? /1
Who was the leader of the Russians in the Second World War? /1
What was Mae West famous for? /1
Who was the famous flyer whose son was kidnapped? /1

Recent memory
What is the name of the present Queen?
Who will follow her? /1
What is the name of the prime minister? /1
What has been in the news in the past week or two? /1

Recall
Can you tell me what were the objects in het coloured pictures I showed you a little while ago?
Shoe Typewriter Scales Suitcase Barometer Lamp /6

Recognition
Which of these did I show you before?
Shoe Typewriter Scales Suitcase Barometer Lamp /6

Writing an address
Write this name and address on the envelope
Mr. John Brown 42 West Street Bedford

Perception
I am going to place a coin into your hand and I want you to tell me what is is without looking at it.
Nickel Dime /2

These are pictures of objects taken from unusual angles. Can you tell me what they are?

Spectacles Shoe Purse/Suitcase Cup&Saucer Telephone Pipe /6

Abstraction

In what way are an apple and a banana alike? /2
In what way are a shirt and a dress alike? /2
In what way are a table and a chair alike? /2
In what way are a plant and an animal alike? /2

Recall address

What was the name and address you wrote on the envelope a short time ago?

Mr. John Brown 42 West Street Bedford /5

Orientation	/8
Memory (recall and recognition)	/17
Remote memory	/5
Recent memory	/3
Abstraction	/8
Perception	/8
R-CAMCOG score	/49

The diagnostic value of the R-CAMCOG in poststroke dementia

Chapter 6

ABSTRACT

Objectives. Specific screening-tests to detect poststroke dementia are lacking. We recently showed that an adaptation of the CAMCOG, the R-CAMCOG, had an excellent sensitivity and specificity in the detection of poststroke dementia. In this study, we externally validated the diagnostic accuracy of the R-CAMCOG in a new, representative cohort of stroke patients.
Methods. The R-CAMCOG and an extensive neuropsychological examination were administered, independently of each other, in 121 patients aged 55 and over with a stroke in the preceding 3 to 9 months. The gold standard for the diagnosis of dementia was based on the results of the extensive neuropsychological examination, clinical presentation, and information from a close relative, as well as on the DSM-IV criteria.
Results. Of the 121 patients, 35 were demented (29%) The diagnostic accuracy at the pre-specified cut-off point of 33/34 was established through Receiver Operating Characteristics (ROC) analyses (sensitivity: 66%, specificity: 94%). At a cut-off point of 36/37 sensitivity would be 83% and specificity 78%.
Conclusion. The R-CAMCOG is a useful screening tool for poststroke dementia in a clinical setting.

INTRODUCTION

Until recently, no specific screening tests to detect poststroke dementia were available. This will lead to an increased risk of misclassification in screening procedures, as most screening tests are aimed at cortical disturbances, compatible with Alzheimer's disease. We recently reported that the CAMCOG is suitable for screening in poststroke dementia,[1] but that it has a major drawback, namely the relatively lengthy administration time of approximately 25 minutes. We therefore made an adaptation of the CAMCOG, the Rotterdam CAMCOG, which is easy to administer and takes approximately 10 minutes.[2] These aspects are important in stroke management, because of the high caseload: approximately one quarter of all hospitalized stroke patients will be demented.[3-5] A first analysis of the diagnostic value of the R-CAMCOG on the same dataset that was used to develop the test suggested that the high sensitivity and specificity were preserved after adaptation.[2] External validation and assessment of reliability in a different series of stroke patients is necessary to determine the value of the R-CAMCOG as a dementia-screening instrument in patients with a recent stroke. In this study, we prospectively assessed the diagnostic accuracy of the R-CAMCOG in a new, representative cohort of 121 stroke patients.

METHODS

Patients

From October 2000 to July 2002 stroke patients from various centres in the region were included in the present study. Patients had to be 55 years or over, and had a transient ischemic attack (TIA) with neurological signs on examination, ischemic stroke or intracerebral hemorrhage, within the preceding 3 to 9 months. The stroke had to be confirmed by a neurologist and neuro-imaging had to be available. Patients were excluded when a reliable assessment of dementia could not be made because of aphasia (i.e. a score less than 3 on the Aphasia Severity Rating Scale from the Boston Diagnostic Aphasia Examination),[6] severe sensory handicaps (e.g. deafness or blindness), persistent impairment in consciousness, severe psychiatric symptoms, or insufficient command of the Dutch language. Additional exclusions were a TIA without neurological signs on examination, concomitant primary cerebral disorder or severe comorbidity with a short life expectancy. Informed consent was obtained from all patients or from close relatives in case of impaired judgment. The local Medical Ethics Committee approved the study.

Procedure

In each centre, consecutive eligible patients or their family were asked to participate in the study. At inclusion, detailed information about cardiovascular risk factors, stroke characteristics, and premorbid status was obtained from the patient files. Premorbid cognitive functioning was assessed by means of an interview with a close relative and the score on the Blessed dementia scale[7] to establish prestroke cognitive decline or dementia. Education was categorized by level: 1 indicates less than 6 years of primary education, 7 indicates academic schooling.[8] Between three and nine months after stroke onset two trained research assistants administered either the R-CAMCOG or an extended neuropsychological

examination, independently of each other. We used the same neuropsychological testbattery as in our previous study.[1] The research assistant who administered the R-CAMCOG was unaware of the neuropsychological test results, and vice versa. The "gold standard" diagnosis of dementia was based on the results of the extensive neuropsychological examination, clinical presentation, and information from a close relative. When a patient was not able to perform a test due to a motor handicap, we used the results of the non-motor counterpart(s).

In some patients not all tests could be administered due to cognitive disturbances and these patients were only included when a reliable judgment of cognitive functioning could be made. A final judgment of cognitive functioning was made by a diagnostic panel (neurologist and neuropsychologist). For the assessment of dementia, the criteria of the DSM-IV were used.[9] Further subclassification of dementia was made according to the research criteria of the NINDS-AIREN international workshop,[10] with possible Alzheimer's disease (AD) with cerebrovascular disease as a possible diagnosis next to probable and possible vascular dementia (VAD).

STATISTICS

For the comparison of the clinical characteristics of the demented and not-demented patients, Student's t test and a chi-square test were used when appropriate. The diagnostic accuracy (sensitivity and specificity) of the R-CAMCOG was estimated with receiver operating characteristic (ROC) analyses at a pre-specified cut-off point of 33/34.[2] All statistical analyses were carried out with Stata software.[11]

We estimated that a sample size of 150, with a prevalence of dementia of 20% would provide sufficiently accurate estimates of sensitivity and specificity (standard error of the mean: resp. 0.05 and 0.03). For logistic reasons, the total number of included patients was lower (121 vs. 150). Before analyzing the data we noted that, the standard error of our estimates would not be affected, because we had a higher frequency of patients with dementia than previously expected (29% vs. 20%). We could therefore expect that the precision of our estimates would not be affected by the smaller sample size.

RESULTS

Of 130 patients considered eligible by the treating physician, nine had to be excluded: two patients were younger than 55, two patients had a history of psychiatric illness, in two (nursing-home) patients the diagnosis of stroke could not be confirmed, and in three patients informed consent was withdrawn after initial consent.

The baseline characteristics of the study-population are shown in Table 1. Mean age was 70 years and approximately 40% was female. Demented patients were 7 years older than non-demented patients ($p<0.001$). There was no significant difference in level of education. None of the patients who suffered a TIA were demented. Six patients were demented before their most recent stroke (Alzheimer's disease: 2, Vascular Dementia: 4). The total score, and subtestscores on the R-CAMCOG were significantly lower in the demented group.

Table 1. Demographic and clinical characteristics of the study population

	Demented (N=35)	**Not-demented** (N=86)	**Total** (N=121)	**P**
Age * (SD)	74.9 (8.8)	68.1 (8.3)	70 (9.0)	<0.001
Years of education* (SD)	8.9 (4.1)	9.6 (3.1)	9.4 (3.4)	0.17
Level of education				
Primary school	17 (48%)	27 (31%)	44 (37%)	
Vocational education	10 (29%)	28 (33%)	38 (31%)	0.18
Secondary education	8 (23%)	31 (36%)	39 (32%)	
Female sex	13 (37%)	33 (38%)	46 (38%)	0.9
Type of stroke				
TIA	0 (0%)	25 (29%)	25 (21%)	
Infarction	28 (77%)	50 (58%)	77 (63%)	0.001
Intracerebral hemorrhage	8 (23%)	11 (13%)	19 (16%)	
Site of stroke				
Infratentorial	1 (3%)	9 (11%)	10 (8%)	
Right hemisphere	23 (66%)	39 (46%)	62 (52%)	0.11
Left hemisphere	11 (31%)	36 (43%)	47 (40%)	
CT variables				
Main findings (N=120)				
Normal CT	3 (9%)	29 (34%)	32 (27%)	0.05
Recent infarct only	15 (43%)	27 (32%)	42 (35%)	
Old infarct only	4 (11%)	10 (12%)	14 (12%)	
Single intracerebral hemorrhage	7 (20%)	7 (8%)	14 (11%)	
Multiple lesions	6 (17%)	12 (14%)	18 (15%)	
Recent infarct type (N=58)				
Large (endzone and/or large deep)	17 (81%)	21 (57%)	38 (66%)	
Lacune	4 (19%)	16 (43%)	20 (34%)	0.06
Leukoaraiosis (N=120)	19 (54%)	23 (27%)	42 (35%)	0.004
Cerebral atrophy (N=120)	9 (26%)	14 (16%)	23 (19%)	0.24
R-CAMCOG subscores (SD)				
Orientation (max.=8)	5.5 (2.1)	7.6 (0.6)	7.0 (1.6)	<0.001
Memory (max.=25)	14.1 (4.5)	20.1 (2.7)	18.4 (4.3)	<0.001
Abstraction (max.=8)	4.7 (2.2)	6.3 (1.5)	5.8 (1.9)	<0.001
Perception (max=8)	4.5 (1.3)	6.1 (1.3)	5.7 (1.5)	<0.001
Total (max=49)	28.8 (8.2)	40.1 (4.1)	36.8 (7.6.)	<0.001

The diagnostic accuracy and test characteristics of the R-CAMCOG were determined at the pre-specified cut-off value of 33/34, which suggested the highest diagnostic accuracy in a previous study (Figure 1). The sensitivity at this cut-off value was 66% (95% CI: 50%–82%), the specificity was 94% (95% CI: 89%–99%), with a positive predictive value of 82%.

DISCUSSION

In this study, we confirmed the diagnostic accuracy of the R-CAMCOG in a representative stroke population. The findings of this study are different from our previous study in which the R-CAMCOG was developed. Not surprisingly, the sensitivity and specificity of the R-CAMCOG was higher in the previous study that provided the data used to construct the test. This is attributable to several types of optimism bias, that work during selection and evaluation of predictors.[12] This in fact provided the rationale for carrying out this study.

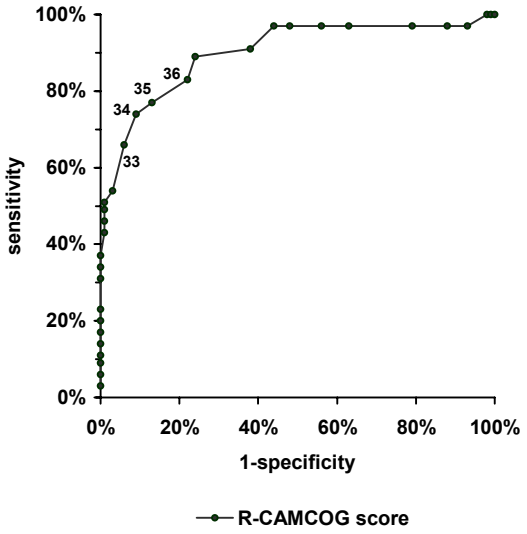

Figure 1. Receiver operating characteristic curve to determine the diagnostic accuracy of the R-CAMCOG in a prospective study

The clinical validity and usefulness of the R-CAMCOG depends on its accuracy and ease of use. In this respect, it is a limitation of this study that we could not directly compare the R-CAMCOG with the MMSE or other tests. At the pre-specified cut-off point, the sensitivity of the R-CAMCOG was estimated at 66% (95% CI: 50%–82%). The MMSE's sensitivity was 69% (95% CI: 57%–81%) at the accepted cut-off value of 23/24 in our previous study on vascular factors in dementia in a very similar stroke population. The R-CAMCOG, however, has a higher specificity (94% vs. 84%).[1]

A high specificity is of great importance, because the diagnostic work-up that follows in screen-positive patients will be time consuming for the patient and is expensive. The moderate sensitivity at the cut-off point of 33/34 may be a disadvantage in view of the recent developments of new and experimental treatments for poststroke dementia. For these purposes it may be a useful suggestion to set the cut-off value higher, as is frequently done with screening instruments in other studies. With a cut-off point of 36/37 the sensitivity increases considerably to 83% (95% CI: 71%–95%), while the specificity still is acceptable (78%; 95% CI: 70%–86%). Further testing of R-CAMCOG positive patients would yield a diagnosis of dementia in every second patient, while among R-CAMCOG negative patients 1 in every 20 patients would be demented and "missed" initially.

For the present study, patients with a moderate or severe aphasia were excluded, because the R-CAMCOG was not considered suitable as a screening instrument in this subgroup. A screening tool for patients with moderate to severe aphasia would have additional value, but may not be easily realized.

Furthermore, a recent study of Graham et al.[13] showed that executive functioning plays an important role in a particular subgroup of vascular dementia, e.g. subcortical vascular dementia. It remains unclear whether the lack of executive items in the R-CAMCOG is a drawback in screening for poststroke dementia. The clinical picture of stroke patients as

well as the restraints due to the direct consequences of a stroke, like a hemi-paresis or mild aphasia may lay other demands on a screening instrument.

The impetus for developing a feasible and valid instrument to screen for poststroke dementia stems from the relative incompetence of the existing screening instruments for this purpose. Our study results suggest that the R-CAMCOG may be of limited use as a screening instrument in a large population, but is a useful instrument in screening for poststroke dementia in a clinical setting.

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Screening for poststroke dementia: clinical usefulness of the MMSE and the R-CAMCOG

Chapter 7

ABSTRACT

Background. The results of cognitive screening tests for poststroke dementia are usually interpreted dichotomously by means of a single cutpoint. This may lead either to redundant neuropsychological testing in subjects with obvious dementia and in false positive cases, or to unjustified reassurance of patients and relatives, all depending on the choice of the cutpoint. This calls for the use of two cutpoints. We examined whether the clinical usefulness of two cognitive screening tests, the MMSE and R-CAMCOG, could be enhanced by this approach.

Methods. We used data from two separate studies of poststroke dementia, with identical in- and exclusion criteria and procedure. We estimated the result-specific likelihood ratios from the MMSE and the R-CAMCOG from ROC curves, fitted with the Dorfman-Alf algorithm. We then defined cutpoints below and above which an additional neuropsychological examination would not contribute to the diagnosis, because the test result indicates a low, or high probability of poststroke dementia. These posterior probabilities were called threshold probabilities. Furthermore, we computed the proportion of patients in which an extended neuropsychological testing is necessary, because of diagnostic uncertainty.

Results. The area under the fitted ROC curve did not differ (MMSE: 0.895, R-CAMCOG: 0.895). However, with a threshold probability of poststroke dementia of 5% and 95% the number of additional neuropsychological evaluations necessary for the diagnosis of poststroke dementia in a series of 1000 patients would be considerably lower when the R-CAMCOG is used instead of the MMSE (624 vs. 778). Threshold probabilities of 10% and 90% would lead to a larger difference in number of neuropsychological examinations: 419 vs. 592.

Conclusions. We provided a rational, probabilistic way to interpret screening test scores for poststroke dementia. The use of more than one cutpoint, depending on the intended level of diagnostic certainty, could lead to a reduction of redundant neuropsychological examinations.

INTRODUCTION

Cognitive screening tests can be useful in the diagnosis of dementia after stroke, but their accuracy and clinical value may be limited if the conclusion and subsequent diagnostic procedure are based on a single cutpoint. In that case, subjects with a score below a certain cutpoint are diagnosed as probably demented and are subjected to further testing, while subjects with a score above the chosen cutpoint are considered cognitively normal. This dichotomous interpretation of test results may lead either to redundant neuropsychological testing in subjects with obvious dementia and in false positive cases, or to unjustified reassurance of patients and relatives, all depending on the choice of the cutpoint.

In two earlier studies, we validated screening tests for poststroke dementia. In the hospital-based part of the Dutch Vascular Factors in Dementia Study (DVFDS) we evaluated the diagnostic accuracy of the MMSE and the CAMCOG and found that both tests are feasible in a stroke population, with an advantage for the CAMCOG.[1] Since an important drawback of the CAMCOG is its lengthy and relatively complex administration for screening purposes, we adapted and modified the CAMCOG to a shorter and easier-to-administer screening test, the R-CAMCOG.[2] We recently assessed the accuracy of the R-CAMCOG.[3] Although both the MMSE and the R-CAMCOG are feasible screening tests for poststroke dementia, their diagnostic accuracy is not optimal.

In the present study we analyzed the data on the MMSE and R-CAMCOG from two prospective, hospital-based studies on poststroke dementia. Instead of exclusively using sensitivity and specificity to determine a single cutpoint as a measure for the diagnostic accuracy, we determined two cutpoints, a lower below which a neuropsychological assessment is not informative because patients are evidently demented, and an upper above which additional testing is not required because patients are almost certainly cognitively normal. We used these parameters to compare the diagnostic accuracy and clinical usefulness of the MMSE and R-CAMCOG in a typical clinical setting.

PATIENTS AND METHODS

Patients

The present study is based on the results from two prospective studies on poststroke dementia. In the first study, the hospital based part of the Dutch Vascular Factors in Dementia Study (DVFDS), consecutive eligible patients were recruited from a prospective registry of patients with a TIA, ischemic stroke or primary intracerebral hemorrhage, admitted to the Department of Neurology of a University Hospital. From March 1, 1993 until January 15, 1996, 284 patients were included.[4]

In the second study, in which the R-CAMCOG was externally validated, 121 consecutive eligible patients with a TIA, ischemic stroke or an intracerebral hemorrhage were included.[3] The distribution of patients per institution was matched to the distribution of discharge destination from a large regional stroke service in order to ensure the recruitment of patients in different settings with a wide range of stroke severity.

The in- and exclusion criteria were similar in both studies. Patients had to be 55 years or over, and had a TIA with neurological signs on examination, an ischemic stroke or

intracerebral hemorrhage. Patients were excluded when a reliable assessment of dementia could not be made due to aphasia (i.e. a score of <3 on the Aphasia Severity Rating Scale from the Boston Diagnostic Aphasia Examination [BDAE]),[5] severe sensory handicaps (e.g. deaf or blind), lowered consciousness level, severe psychiatric symptoms, or insufficient command of the Dutch language. Additional reasons for exclusion were a concomitant primary cerebral disorder (e.g. Parkinson's Disease) or severe comorbidity with a short life expectancy. Informed consent was obtained from all patients or from close relatives in case of impaired judgment. The local Medical Ethical Committee approved of both studies.

Procedure

For all patients, detailed information about cardiovascular risk factors, stroke characteristics, premorbid mental and physical status, and data on neuro-imaging were available, in identical format. The study procedures have been described in detail elsewhere.[1 3]

Premorbid cognitive functioning was established by an interview with a close relative and the score on the Blessed dementia scale. Between three and nine months after stroke onset cognitive functioning was assessed. We used the Aphasia Severity Rating Scale of the BDAE to assess the presence and severity of aphasia. A score of 6 indicates no aphasia, and 5, 4 and 3 mild to moderate aphasia. Education was categorized by years of schooling completed.

In the DVDFS, a judgment of present cognitive functioning was made by a neurologist, based on clinical presentation, information from a close relative and the score on the Blessed dementia scale.[6] An extended neuropsychological examination was carried out in all patients who presented with cognitive complaints or when a close relative mentioned a decline in cognitive functioning. An extended neuropsychological examination was also indicated when the investigator suspected a change in cognitive functioning, even when the patient or close relative had no complaints. Therefore, in all patients in whom there was any suspicion of dementia or cognitive decline an extended neuropsychological examination was performed.

In the R-CAMCOG validation study, all patients underwent an extended neuropsychological examination. Two trained research assistants administered either the R-CAMCOG or a neuropsychological examination, independently of each other, between three and nine months after stroke onset. The research assistant who administered the R-CAMCOG was unaware of the neuropsychological test results, and vice versa.

The extensive neuropsychological examination consisted of an intelligence test, either the shortened version of the Groninger Intelligence Test,[7] or when this was not administrable Raven's Coloured Matrices[8] a non-verbal intelligence test. The shortened form of the Boston Naming Test (CERAD)[9] was used to examine word-finding difficulties. Memory was evaluated with Word List Memory (CERAD),[9] and the Rivermead Behavioural Memory Test.[10] We used Digit Span forward and backward (WAIS)[11] to assess the span of immediate verbal recall, but also as a measure for attentional capacity. Parts of the Trail Making Test,[12] and the Stroop Color Word Test[13] too were used to examine attention. Scores on verbal fluency (animals, occupations, letter B), Stroop Color Word Test part III,[13] Trail Making Test B,[12] served as indication for the level of executive functioning. Proverbs and similarities (WAIS)[11] provided a measure for abstraction and verbal concept formation. Visuo-constructive ability was examined by copying the drawing of a circle, diamond, two

overlapping rectangles and a cube (CERAD).[9] Visual perception and spatial orientation were examined by Judgment of Line Orientation.[14] In some patients only a limited number of tests could be administered due to cognitive disturbances, and these patients were only included when a reliable judgment of cognitive functioning could be made.

Furthermore, in both study groups, the MMSE or R-CAMCOG was administered independently of the validating neuropsychological examination.

Based on clinical presentation, information from a close relative, the score on the Blessed dementia scale, and the neuropsychological test results, a final judgment of cognitive functioning was made by a diagnostic panel consisting either of two neurologists, a neuropsychologist and a trained physician (DVFDS) or a vascular neurologist and a neuropsychologist. For the assessment of dementia, the criteria of the DSM-IV[15] were used. Further differentiation of dementia took place according to the research criteria of the NINDS-AIREN International Workgroup for vascular dementia, with three possible diagnoses: probable vascular dementia, possible vascular dementia, and possible Alzheimer's disease (AD) with cerebrovascular disease (CVD).[16] The latter category was reserved for patients fulfilling the clinical criteria for possible AD and also presenting clinical or brain imaging evidence of relevant CVD. The severity of dementia was assessed by the Global Deterioration Scale[17] and the Clinical Dementia Rating.[18]

STATISTICAL ANALYSIS

For a comparison of the clinical characteristics of the demented and not-demented patients, Student's t-test and a chi square test were used when appropriate.

The cumulative distribution of the two test scores was displayed as a receiver operating characteristic (ROC) curve, and the area under the curve was estimated using the method suggested by Hanley and McNeil.[19] Next the ROC curves were fitted and parameterized, according to the method suggested by Dorfman and Alf,[20] based upon the binormal model. This allowed us to obtain consistent estimates of the result-specific likelihood ratio. The result-specific likelihood ratio represents the likelihood of a certain (categorical) test result given the disease in question, divided by the likelihood of the test result given absence of the disease. On a smooth ROC curve it is equal to the tangent of the curve.[21] This likelihood ratio for a single test value is considered the most appropriate parameter for evaluating diagnostic tests.[22]

For each test we defined cutpoints below and above which an additional neuropsychological examination would not be contributory to the diagnosis, because patients either have a very high, or a very low probability on dementia, e.g. are either obviously demented or can be considered cognitively normal. The lower cutpoint was chosen at 1%, 5%, or 10% of the intended threshold probability of poststroke dementia, and the upper cutpoint at 99%, 95%, and 90% of the intended threshold probability. These posterior probabilities correspond to result-specific likelihood ratios of 0.03, 0.16, 0.33, 27, 54 and 273, assuming a prior probability of poststroke dementia of 25%. We computed the proportion of patients in the grey area, e.g. the proportion of patients in which an extended neuropsychological testing is necessary, because of diagnostic uncertainty.

The number of patients in this latter category depends on the discriminatory ability of the test, and on the closeness of the actual, result-specific likelihood ratios to the desired values:

the better the test, the smaller the number of patients requiring further neuropsychological testing. All statistical analyses were carried out with Stata statistical software.[23]

RESULTS

The baseline characteristics of the patients from the two studies are shown in Table 1. Mean age was 70 years and approximately 40% was female. The mean number of years of education was similar in both studies. The proportion of demented patients was higher in the R-CAMCOG validation study (28.9% vs 19.4%), but patient groups did not differ in distribution of type and site of stroke. Demented patients were older and had less years of education than not-demented patients in both studies.

Table 1. Clinical characteristics of both study populations.

	DVFDS (N=284)	R-CAMCOG (N=121)	P
Age *	69.2.(8.1)	70.0 (9.0)	0.84
Poststroke dementia	55 (19.4%)	35 (28.9%)	<0.05
Female sex	114 (40%)	46 (38%)	0.69
Years of education*	8.7 (3.1)	9.4 (3.4)	0.97
Type of stroke			
TIA	46 (16.2%)	25 (20.7%)	
Ischemic stroke	203 (71.5%)	77 (63.6%)	0.29
Intracerebral hemorrhage	35 (12.3%)	19 (15.7%)	
Site of stroke			
Infratentorial	35 (12.3%)	10 (8.4%)	
Right hemisphere	133 (46.8%)	62 (52.1%)	0.43
Left hemisphere	116 (40.9%)	47 (39.5%)	

DVDFS: Dutch Vascular Factors in Dementia Study, R-CAMCOG: external validation study of the R-CAMCOG, TIA: transient ischemic attack
* mean with standard deviation between parentheses

Figure 1 shows the ROC curves, fitted and parameterized with the Dorfman-Alf algorithm for both the MMSE and the R-CAMCOG. The areas under the curve were almost identical in size, estimated either from original data (MMSE: 0.900, SE 0.026; R-CAMCOG: 0.900, SE 0.034), or from the fitted curves (MMSE: 0.895, SE: 0.024; R-CAMCOG: 0.895, SE: 0.034). The result-specific likelihood ratios were estimated from the ROC curve, and nearest cutpoints were chosen for the MMSE and the R-CAMCOG. Tabel 2 shows lower and upper cutpoints for the MMSE and the R-CAMCOG to realize a certain diagnostic probability of poststroke dementia, assuming a prior odds for poststroke dementia of 1:3, e.g. a prior probability of 25%.

In an example with symmetrical threshold probabilities (5% and 95%) the nearest MMSE scores on the ROC curve are 28 and 13 (Table 2). The proportion of patients with an MMSE score at or above 28 is 0.198 and at or below 13 is 0.025. The nearest R-CAMCOG scores on the ROC curve for the cutpoints corresponding with threshold probabilities of 5% and 95% are 42 and 24, which leaves a proportion of patients with an R-CAMCOG score at or above 42 of 0.288 and at or below 24 of 0.088.

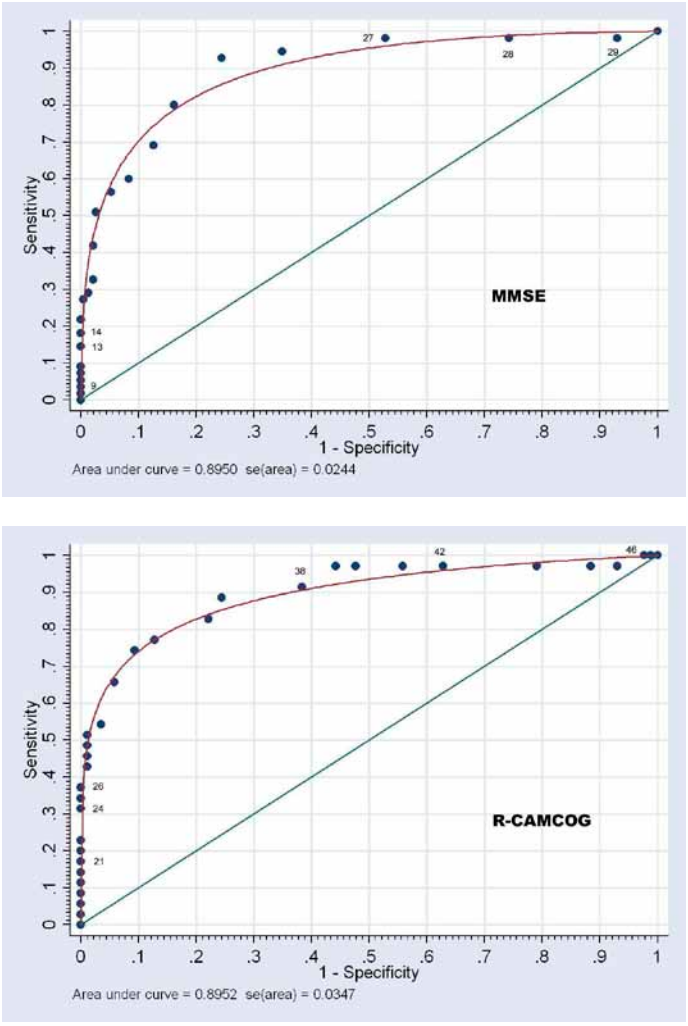

Figure 1. The ROC curves for the MMSE and the R-CAMCOG, parameterized and fitted with the Dorfman-Alf algorithm

The number of patients who need an extended neuropsychological examination can be calculated by subtracting the number of patients with scores below the lower cutpoint and scores exceeding the upper cutpoint from the total population. In a hypothetical cohort of 1000 patients the number of patients tested with the MMSE that are considered cognitively normal at a threshold probability of 5% is 198 (0.198 x 1000) and the number of patients that is obviously demented at a threshold probability of 95% is 25 (0.025 x 1000). The number of patients in the grey area, e.g. the number of patients in which the diagnosis is not certain, that needs an additional neuropsychological examination is 777 (1000 minus 198+25).

Table 2. Choice of cutpoints for R-CAMCOG and MMSE to realize a certain diagnostic probability of poststroke dementia, assuming a prior odds for poststroke dementia of 1:3. Next, nearest cutpoints are chosen, based on result-specific likelihood ratios estimated from the fitted ROC curves.

Threshold probability	Post odds	rs-LR	MMSE score	P(MMSE≥y)	R-CAMCOG score	P(RC≥y)
1%	1:99	.03	29	0.053	46	0.015
5%	1:19	.16	28	0.198	42	0.288
10%	1:9	.33	27	0.362	38	0.489
Threshold probability	**Post odds**	**rs-LR**	**MMSE**	**P(MMSE≤z)**	**R-CAMCOG score**	**P(RC≤z)**
90%	9:1	27	14	0.046	26	0.092
95%	19:1	57	13	0.025	24	0.088
99%	99:1	297	9	0.015	21	0.046

Rs-LR: result-specific likelihood ratio,
P(RC≥y): probability of an R-CAMCOG score at or above a certain value (y), P(MMSE ≥y): probability of an MMSE score at or above a certain value (y), P(RC≤z): probability of an R-CAMCOG score at or below a certain value (z), P(MMSE ≤z): probability of an MMSE score at or below a certain value (z)

A very high threshold probability (1% and 99%) results in large, almost equal numbers of additional neuropsychological examinations for both the MMSE (932) and the R-CAMCOG (939). When a lower diagnostic certainty is acceptable, e.g. 10% and 90% for the lower and upper cutpoint, 592 patients need an additional neuropsychological examination when screened with the MMSE and 419 patients when screened with the R-CAMCOG.

DISCUSSION

In this study, we evaluated the diagnostic value of the MMSE and R-CAMCOG as screening instruments for poststroke dementia. Areas under the ROC curve were high, and identical indicating acceptable diagnostic accuracy. Instead of exclusively using sensitivity and specificity of a single cutpoint as measures for diagnostic accuracy, we determined the usefulness of more than one cutpoint, based on result-specific likelihood ratios, which were related to threshold probabilities of poststroke dementia above and below which further neuropsychological testing is not necessary. The first, the lower cutpoint that indicates the score below which a neuropsychological assessment is not informative, because patients are evidently demented, and the second, an upper cutpoint above which additional testing is not required because patients are likely to be cognitively normal. We found that depending on the intended level of threshold probability, a choice can be made between the R-CAMCOG and MMSE. The choice for a certain cutpoint need not only be determined by the result-specific likelihood ratios, but also by the ratio of losses incurred by making a false positive or a false negative diagnosis. Here, we implicitly assumed that these losses were equal.

A limitation of this study is that it is based on data of two cohorts of patients. We tried to overcome this drawback by estimating accuracy in the source populations, and transposing our estimates to a hypothetical population, thus ensuring that prior probability was identical for both tests. Furthermore, both studies were carried out by the same investigators, who applied a similar procedure and used the same definitions and variables. Small differences

in patient selection between both studies, however, are inevitable. In the DVFDS, for instance, the number of prestroke dementia was considerably higher and more in line with the results of other studies in poststroke dementia than in the R-CAMCOG study (33% vs. 17%). Furthermore, only two patients in the R-CAMCOG study were diagnosed with AD+CVD, while 15 patients were diagnosed as such in the DVFDS study (6% vs. 27%). An explanation for the underrepresentation of prestroke cognitive decline and the small number of AD patients may be inherent to the selection of the patients. In the DVFDS, we included consecutive patients admitted to the department of neurology of our hospital, whereas the cohort in the R-CAMCOG study consisted of patients discharged from different hospitals. Although we tried to construct a representative cohort, we may have included a larger group with a relatively good outcome, and thus have disregarded patients with a pre-existent dementia or Alzheimer's disease.

The MMSE clearly has some general advantages in screening for cognitive deterioration. It is widely used and internationally accepted, and has been evaluated in different patient groups, and different diseases. Furthermore, the MMSE is brief, and easy to administer. The strength of the R-CAMCOG in screening for poststroke dementia is that -although the overall diagnostic accuracy, as estimated from the area under the ROC curve, is similar- the distributions of scores are more finely categorized, thus allowing the clinician to use more precise cutpoints. This results in less overlap in scores between demented and not-demented patients than in the MMSE, with a smaller chance of misclassification. Furthermore, the R-CAMCOG has no floor- or ceiling effects, in contrast to the MMSE that has a known ceiling effect, especially in higher educated patients.

Our results suggest that in clinical settings, e.g. in smaller hospital based studies, the R-CAMCOG is more able to identify patients with or without poststroke dementia than the MMSE. This can be explained by the differences in test contents between the MMSE and the R-CAMCOG. The MMSE consists of 30 items with simple questions on several domains. The R-CAMCOG contains more items and emphasis lies on memory and these items account for almost half of the score. Moreover, memory is tested more comprehensively in the R-CAMCOG, with a retrieval and a recognition condition. As memory disturbances are still a core feature in dementia diagnosis, both in widely used diagnostic criteria as well as in our own clinical experience, the focus on memory items is an evident strength of the R-CAMCOG compared with the MMSE.

Furthermore, the MMSE contains tasks that require motor involvement, like drawing, writing and praxis. Such skills are frequently disturbed in stroke patients, due to pareses or neglect. The R-CAMCOG does not contain instructions with motor involvement that influence the score.

The MMSE has another drawback when it comes to screening for poststroke dementia. It contains questions regarding verbal expression or comprehension, that may cause problems for patients with aphasia, a common consequence of a stroke. In the R-CAMCOG, verbal responses are needed, but are not judged on linguistic aspects.

In our study, we used the NINDS/AIREN diagnostic criteria for vascular dementia. Over the years many studies have criticized these criteria, for instance for their lack of empirical evidence.[24-26] Moreover, criticism was aimed at the diagnostic criteria for dementia for their emphasis on memory disturbances. Recent studies, though, found that disturbances in executive control functions are prominent and more severe in vascular dementia, while memory disturbances are relatively mild.[27 28] Surprisingly, in the development of the

R-CAMCOG, executive function items did not contribute to its discriminatory ability, and a more prominent factor was memory. An explanation could be that most tests for executive function require a motor action (e.g. Trail Making Test part B, clock drawing) or need language involvement (e.g. verbal fluency, Stroop part III). Impairments in these two domains are frequently a direct consequence of a stroke.

Until now there is no perfect screening instrument for poststroke dementia. In this study, we provide an alternative way to interpret screening test scores, and a procedure that allows a more balanced diagnostic judgment. Due to its short and easy administration the MMSE may be more suitable in larger epidemiological studies, whereas the R-CAMCOG may be useful in smaller hospital-based studies and in clinical practice, where adequate selection of patients is of utmost importance.

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General discussion

Chapter 8

The aim of this thesis was to gain further insight in the diagnosis of dementia after a stroke. In the prospective hospital based part of the Dutch Vascular Factors in Dementia study (DVFDS),[1] we investigated which clinical variables in the acute phase of stroke predicted poststroke dementia. The central topic of this thesis was to determine the usefulness of cognitive screening instruments in the diagnosis of poststroke dementia. We established the feasibility and diagnostic accuracy of existing screening instruments, the MMSE and the CAMCOG, and of a newly developed screening instrument, the R-CAMCOG.

In this chapter, I will summarize the main findings, followed by some methodological considerations. The value and use of screening instruments in the diagnosis of poststroke dementia and the diagnosis of dementia after a stroke itself will be discussed. I will end with conclusions and suggestions for future research.

MAIN FINDINGS

In line with the findings of other hospital based studies in stroke patients, we found that approximately one quarter of the stroke patients were demented three to nine months after the stroke, and about one fifth when patients with a moderate or severe pre-existent dementia were excluded.

Easily obtainable clinical variables in the acute phase that were included in a prediction model for poststroke dementia were age, level of education, female sex, mean arterial blood pressure, presence of white matter lesions, neglect, hemorrhagic stroke and atrial fibrillation.

The MMSE and the CAMCOG both proved feasible screening instruments for dementia in a stroke population. We encountered no severe problems in the administration of the two tests and there were relatively few missing values. The CAMCOG, however, came out as the better test, with a higher diagnostic accuracy. The diagnostic accuracy of both tests could be improved by taking type and site of stroke into account. Patients with a hemorrhagic stroke had a threefold higher risk of dementia compared with patients with a TIA or ischemic stroke, whereas the risk of dementia was lower in patients with a left hemispheric stroke.

The relatively lengthy and complex administration makes the CAMCOG less suitable for screening purposes. We therefore developed the R-CAMCOG, based on the original CAMCOG. Internal validation suggested that the R-CAMCOG and the CAMCOG were equally accurate in screening for poststroke dementia in the target population, with an excellent diagnostic accuracy.

External validation in a new comparable stroke population was performed in the R-CAMCOG study. In this study, the R-CAMCOG had a moderate sensitivity and an excellent specificity at a prespecified cut-off point of 33/34. Finally, we compared the clinical usefulness of the R-CAMCOG and the MMSE in screening for poststroke dementia, by determining cutpoints at different threshold probabilities below and above which an extended neuropsychological examination is presumed to have little or no additional value in the diagnosis of poststroke dementia. Based on these data we were able to calculate the proportion of patients in whom diagnostic uncertainty requires extended neuropsychological testing. Although the overall diagnostic accuracy, as estimated from the area under the ROC curve, was similar for both the MMSE and the R-CAMCOG, the distributions of scores of

the R-CAMCOG were more finely categorized, thus allowing the clinician to use more precise cutpoints. Furthermore, in the R-CAMCOG the distribution of scores in demented and not-demented patients showed less overlap than in the MMSE, with a smaller chance of misclassification. Therefore, the R-CAMCOG seems to be the better screening test in smaller, hospital based studies, where adequate selection of patients is most important. Due to its short and easy administration the MMSE seems to have an advantage over the R-CAMCOG in large epidemiological studies, where different requirements on diagnostic accuracy apply.

METHODOLOGICAL CONSIDERATIONS

Methodological issues specific for each study have been described extensively in the separate chapters. Here, I will elaborate on some general specific methodological aspects of our studies.

Selection bias

Selection bias results from the selective exclusion of patients with the same disease in whom a different association may exist between a determinant and an outcome variable in comparison with those who participate in the study. The in- and exclusion criteria in our studies may have caused selection bias, especially the exclusion of patients with a moderate or severe aphasia. We excluded patients with a moderate or severe aphasia because this could confound neuropsychological test results, which may not only be a factor of influence in verbal tests, but also in tests with an instruction that rely on verbal support or tests that make use of symbols. Most other hospital-based studies of poststroke dementia have also excluded patients with moderate to severe aphasia and it was also an exclusion criterion in the research criteria for vascular dementia of the NINDS-AIREN International Workshop.[2-4] Consequently, cognitive decline after left hemispheric stroke may be underestimated.

Recruitment bias

In the hospital-based part of the DVFDS we followed another inclusion strategy than in the R-CAMCOG study. In the former, we included all consecutive patients who were admitted to a single university hospital and fulfilled the in- and exclusion criteria. In the R-CAMCOG study, we attempted to construct a representative stroke population, based on the discharge location of the participating hospitals in a regional stroke service. The reason for this was that we wanted to ensure the recruitment of patients with a wide range of stroke severity in order to establish the discriminatory value of the R-CAMCOG. In the R-CAMCOG study, the prevalence of dementia was somewhat higher than in the study in which we evaluated the CAMCOG (29% vs 19%), and comparable to other hospital based studies with the same design.[3 5-7] On the other hand, the proportion of demented patients with a pre-existent dementia was lower in the R-CAMCOG study (17% vs. 33%). The low prevalence of pre-existent dementia and Alzheimer's disease probably results from a recruitment bias. The differences in dementia prevalence between the study populations was not considered a methodological problem in the external validation of the R-CAMCOG, because we wanted to establish the discriminatory ability of the test. In the study in which we compared the clinical usefulness of the R-CAMCOG and the MMSE, however, we needed to address this

problem. As I describe in chapter 7 we tried to overcome this drawback by estimating accuracy in the source population, and transposing our estimates to a hypothetical population, thus ensuring that prior probability was identical for both tests. Furthermore, both studies were performed by the same investigators, followed a similar procedure and used the same definitions and variables. Small differences in patient selection between both studies however, are inevitable.

Confounding factors in neuropsychological testing

The "gold standard" diagnosis of dementia in our studies was based on clinical presentation, information from a close relative, and for the major part on the results of an extensive neuropsychological examination.

Confounding is a frequent and inevitable phenomenon in neuropsychological practice. Statistical confounding can occur when an extraneous factor is associated both with the studied determinant and the outcome variable, which may obscure a relation. Age, sex, level of education or intelligence are potential confounders in studies of cognitive functioning. In neuropsychological practice the effect of these general confounders can be minimized by the use of adjusted norms. Neuropsychological performance can also be influenced by other factors that confound the test results. Some general confounding factors are common in all patients, like motivational problems, fear of failure, aggravation, fatigue, pain, emotional preoccupations, stress, mood disturbances, distractibility, and cultural background. These factors may influence neuropsychological test performance, and the neuropsychologist has to weigh the contribution of the confounders to the neuropsychological test results. Other confounding variables are found in specific diseases or patient groups. In stroke patients, specific confounding factors have to be taken into account in neuropsychological testing. Unlike primary degenerative dementia syndromes like Alzheimer's disease or frontotemporal dementia, performance in stroke patients may be hampered by the direct consequences of a stroke, such as hemiparesis, aphasia or neglect.

A common consequence of a stroke is a hemiparesis. Obviously, a paretic arm, especially the dominant, influences performance on constructional tasks such as drawing, but also on paper-and-pencil tasks with a timed condition, as for instance the Trail Making Test. This may cause invalid test results or missing values. In our studies, there were relatively few missing values in the screening tests, but we found that missing values due to an arm paresis did not occur randomly in stroke patients. Items were more frequently scored as inassessable in demented than in not-demented patients. The presence or absence of an arm paresis, however, did not affect the relationship between dementia and constructional items, nor did it influence the discriminatory ability of the constructional items. We conclude that missing values in constructive items due to an arm paresis can be discarded and safely replaced by zero scores. An explanation for this may be that not-demented patients in general are better able to compensate for their paresis than demented patients.

Previously, I discussed the possible selection bias due to the exclusion of patients with a moderate or severe aphasia. The inclusion of patients with a mild or moderate aphasia, however, may also have influenced the neuropsychological test results. We may have overestimated the role of mild and moderate aphasia in neuropsychological test performance and hence underestimated the extent of general cognitive decline. The proportion of patients with a mild aphasia in the DVFDS, however, was equal among demented and not-demented patients, and thus confounding, if any, is probably minimal.

Patients with hemi-inattention or -neglect were entered in our studies if they met the in- and exclusion criteria. Similar to aphasia, neglect may both directly and indirectly influence the neuropsychological test results. In neglect, visual and attentional problems may be expected and take a prominent place, but the impact of neglect is often more general and can be reflected in the performance on any task. Furthermore, neglect is often a consequence of right hemispheric stroke that is frequently accompanied by diminished insight in one's own performance, often reflected by an overestimation of cognitive functioning and denying or minimizing cognitive deficits. This may lead to a biased judgment of the investigator. Finally, neglect may be less manifest in a clinical setting than (even mild) aphasia. Aphasia is a well-known consequence of a stroke and easier recognized during an interview than neglect, either sensory or visual.

To minimize the effect of confounding factors in neuropsychological testing, we administered more than one test for a cognitive domain, e.g. a verbal and a predominantly non-verbal memory test, or tests for executive functioning in timed and not-timed conditions. Furthermore, all neuropsychological tests were either administered by a clinical neuropsychologist or by trained test assistants under strict supervision of a clinical neuropsychologist.

SCREENING INSTRUMENTS IN POSTSTROKE DEMENTIA

At the time we started our studies there were no dementia screening instruments specifically designed for vascular dementia or poststroke dementia. Systematic research of the clinical determinants of dementia after stroke had only just started, and was focused on the diagnosis and features of poststroke dementia, and not on the instrument by which the diagnosis was made. In the previous chapters, I have described the advantages and drawbacks of screening instruments. Due to the heterogeneity of the cognitive profile in dementia after stroke and possible confounding factors, we expected that the MMSE would not meet the requirements of a useful screening test for dementia after a stroke. We therefore decided to study the feasibility and diagnostic accuracy of the CAMCOG in screening for poststroke dementia. Despite the fact that the CAMCOG was also originally designed to diagnose primary degenerative dementia, we hypothesized that it would provide a more differentiated picture of cognitive functioning, and hence be a more accurate screening instrument in a stroke population. We confirmed this hypothesis in the DVFDS, but should have foreseen that the CAMCOG would not become a useful screening test in a clinical setting, simply because the CAMCOG does not fulfill a major demand of a cognitive screening instrument, namely a brief and easy administration.

Next to a high diagnostic accuracy, a short and easy administration was one of the main requirements for the R-CAMCOG. In line with the concepts of vascular dementia at the time, we envisaged a prominent role for tasks that measure executive functioning in the R-CAMCOG. The R-CAMCOG, however, does not contain executive tasks, which reflects the fact that the original CAMCOG contains only a few tasks that measure executive functioning to some extent, such as clock drawing and wordfluency. These subtests, however, had no discriminatory ability in our analyses. One explanation may be that these tasks require either a motor action or language involvement, two domains that are frequently affected by a stroke, and therefore have minimal discriminatory ability. Another explanation may be

that disturbances in executive functioning play a less prominent role in poststroke dementia than previously assumed. Several studies have tried to determine a unitary cognitive profile of vascular dementia, and have frequently concluded that executive functioning deficits are more prominent and memory deficits are relatively mild in vascular dementia.[8-10] There are, however, several potential limitations of these comparative studies.[10] The uncertainty regarding the validity of the vascular dementia concept, the use of different diagnostic criteria, and possible circular reasoning owing to the dementia criteria used may obscure or emphasize differences. Furthermore, methodological shortcomings in the design of many studies, such as a selection bias regarding patients with relative mild cognitive decline and different severity of cognitive decline among patient groups, obscures the separate cognitive profiles. As I will discuss in the next section, the diagnostic criteria for vascular dementia are subject to considerable debate. Perhaps executive functioning deficits play a dominant role in some distinct forms of dementia after a stroke but not in others. Patients with dementia and lacunar infarcts and/or white matter lesions, recently coined as subcortical vascular dementia, predominantly have executive function deficits,[11 12] analogous to other subcortical dementia syndromes. In contrast, the clinical picture of patients with large cortical infarcts may be dominated by cortical deficits and neurological disturbances.

The central cognitive function tested in the R-CAMCOG is memory. An advantage of the R-CAMCOG is that memory is tested more comprehensively than in most brief screening instruments, with both a recall and a recognition condition. A differentiation between an attentional problem, which is often the underlying cause of a low or subnormal score on the memory items of the MMSE, and a memory problem can easier be made. Furthermore, the larger number of items in the R-CAMCOG prevents ceiling effects, which can be important in poststroke dementia, because memory disturbances may vary from mild to severe.

A major advantage of the R-CAMCOG in screening for dementia in stroke patients, however, is that it minimizes confounding effects from the direct consequences of a stroke. Although the R-CAMCOG contains questions that need a verbal or motor response, they are not judged on linguistic or constructional aspects.

THE DIAGNOSIS OF DEMENTIA IN STROKE PATIENTS

Stroke has been recognized as a cause of dementia since Hachinski proposed the concept of multi-infarct dementia. On the basis of a correlation between the presence of dementia with volume of brain tissue lost to infarction,[13] Hachinski introduced the first set of diagnostic criteria for vascular dementia: the Hachinski Ischemic Score.[14]

In the early nineties the research criteria for vascular dementia have been designed by the NINDS-AIREN International Workshop.[4] These criteria have been applied in several hospital based studies of dementia after a stroke and were also used in our studies. [6 15-18] Over the years many researchers have criticized these and other research criteria, for instance for their lack of empirical evidence. Criticism was also directed at the general diagnostic criteria for dementia that are based on the concept of Alzheimer's disease with emphasis on memory disturbances. Another target for criticism was the fact that the criteria relied heavily on the multi-infarct model with stroke as the cause for dementia.

The results of studies in stroke populations increased the awareness that several mechanisms may underlie dementia after a stroke.[19] Dementia may be a direct consequence

of the vascular lesions in the brain, but may also be due to sofar asymptomatic Alzheimer pathology or white matter lesions. Furthermore, a summation of infarcts in the brain, white matter lesions and Alzheimer pathology may lead to dementia, even when each type of lesion in itself is not severe enough to induce dementia. The term poststroke dementia is purely descriptive, has no inherent pathophysiological meaning and includes all possible mechanisms of dementia.

An advantage of this term and its implied multifactorial approach is that it enables research in the vascular factors that play a role in different forms of dementia, which may provide insight in pathophysiological mechanisms. A drawback is that it includes dementia with different cognitive profiles, which may obscure the clinical picture.

A recent published consensus statement proposes to replace the term vascular dementia by vascular cognitive impairment.[20] This new clinical entity comprises hereditary vascular dementia's, multi-infarct dementia, poststroke dementia, subcortical ischemic vascular dementia, mild cognitive impairment, but also degenerative dementia syndromes. The common feature is that vascular pathology either causes or substantially contributes to the cognitive impairment. Despite the progress made on the field of vascular dementia, the developments are evolutionary rather than revolutionary. From a clinical point of view, a useful recommendation in the consensus statement is the urge to distinguish homogeneous subtypes of vascular cognitive impairment, and to develop new diagnostic criteria for vascular cognitive impairment.

CONCLUSIONS AND FUTURE DIRECTIONS

We performed our studies at a time of changing ideas and concepts regarding vascular dementia and dementia after stroke. Despite the progress made on possible mechanisms, the redefinition of diagnostic criteria and attempts on subtyping vascular dementia syndromes, the diagnosis of poststroke dementia is complex and time consuming. This is largely due to the heterogeneous nature of its clinical picture and the many confounding factors that may hamper a judgment of cognitive functioning. In this thesis, I have provided clues for identifying patients at risk for dementia in the acute phase of stroke by means of easily obtainable clinical variables. Furthermore, the R-CAMCOG proved a feasible and useful screening instrument in the diagnosis of dementia three to nine months after a stroke. Especially its excellent specificity makes the R-CAMCOG suitable for smaller clinical studies or therapeutic trials in which adequate selection of potential candidates is desired.

In view of the high incidence of dementia after a stroke and the advances in the development of therapeutic strategies, it is important to early select stroke patients with a high risk of dementia for further diagnostic work up, in order to optimize management and care of both patients and relatives. For this purpose, a cognitive screening instrument developed for administration in the acute phase of a stroke with a high predictive value for poststroke dementia would be a valuable contribution. However, the feasibility, and reliability of evaluation of cognition in the acute phase of stroke may raise problems. Fluctuating level of consciousness, general malaise, stress, and fatigue are common features within the first days after stroke that likely influence performance on neuropsychological tests. Moreover, a substantial proportion of the stroke patients in the acute phase may be too ill to be tested. The clinical heterogeneity of the 'umbrella' concept of poststroke

dementia hampers the quality of patient selection, in the acute as well as the chronic phase after a stroke. Future research should therefore be aimed at gaining further insight in more homogeneous subtypes of cognitive impairment related to stroke. Recently, diagnostic criteria for subcortical vascular ischemic dementia have been proposed.[12] Other potential subgroups may be cognitive impairment due to multiple cortical infarcts or the specific cognitive profiles after a strategic infarct. The value of screening instruments, including the MMSE and the R-CAMCOG, needs to be re-evaluated in these specific subgroups of stroke patients.

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Summary / Samenvatting

Chapter 9

SUMMARY

A stroke often results not only in physical disability, but also in cognitive impairment or even dementia. Between 10 and 40% of patients with a recent stroke becomes demented. The diagnosis of dementia after a stroke is difficult because of very heterogeneous cognitive disturbances, that may be characterized as cortical or subcortical, or a combination of the two. Furthermore, judgment of cognitive functioning may be hampered by the somatic symptoms that often accompany a stroke.

In clinical practice, cognitive screening instruments are important, both to select patients who need further neuropsychological testing and as a diagnostic tool in patients with obvious dementia. Most existing screening instruments used in a clinical setting, however, are developed to detect dementia compatible with Alzheimer's disease and their value in detecting dementia after stroke is less well known. In this thesis, I describe and discuss the diagnosis of dementia after stroke, with emphasis on the value of screening instruments in the diagnosis of poststroke dementia.

In ***chapter 2***, we described which easily obtainable clinical information after acute stroke is useful in predicting poststroke dementia. In the Dutch Vascular Factors in Dementia Study (DVFDS), a prospective and consecutive hospital-based cohort of acute stroke patients, the diagnosis of dementia at 3 to 9 months after the onset of stroke was based on the results of an extensive neuropsychological examination, clinical presentation, information from a close relative and the score on the Blessed dementia scale. Of the 291 patients, 62 (21%) were demented. The final model for early prediction of poststroke dementia included age, sex, years of education, previous stroke, white matter lesions on CT scan, neglect, hemorrhage on CT scan, mean arterial blood pressure, and atrial fibrillation. ROC analysis showed that the area under the curve for this model was 0.82, with a high specificity and a moderate sensitivity (resp. 95% and 37%).

Chapter 3 provides an overview of the strengths and weaknesses of existing mental status tests in dementia screening in general, and describes the additional considerations for dementia screening in patients after a stroke. Although adaptations of existing tests may increase their diagnostic value in stroke patients, I end this chapter with the recommendation that a screening instrument especially aimed at poststroke dementia should be developed.

We compared the diagnostic accuracy of the CAMCOG and the MMSE in patients with a recent stroke in ***chapter 4***. Of 300 consecutive patients aged 55 or over, who were included in the DVFDS, 71 (23.7%) were demented 3 to 9 months after their stroke. Sixteen severely demented patients were not testable and excluded. The CAMCOG and MMSE score were significantly related to dementia (both $p<.0001$). The CAMCOG was the more accurate screening instrument (area under the curve CAMCOG: 0.95 vs. area under the curve MMSE: 0.90). Two other clinical variables independently improved the diagnostic accuracy of the MMSE and CAMCOG: patients with a left hemispheric lesion had a lower, and patients with hemorrhagic stroke a higher chance of being demented. The effect of left hemispheric lesion as an independent diagnostic factor could not be explained by selection or its association with aphasia alone.

Chapter 5 describes the development of the Rotterdam CAMCOG (R-CAMCOG), based on the original CAMCOG. We analyzed the itemscores on the CAMCOG of the patients included in the DVDFS. In three steps, the number of items was reduced from 59 to 25,

divided over the subscales orientation, memory (recent, remote and learning), perception and abstraction. The subscale orientation did not reach statistical significance in a logistic regression model, but was included in the R-CAMCOG because of its high face validity in dementia screening. Internal validation suggested that the R-CAMCOG and the CAMCOG are equally accurate in screening for poststroke dementia (area under the curve is 0.95 for both tests). A major advantage of the R-CAMCOG, however, is its shorter and easier administration.

In ***chapter 6***, we describe the study in which we externally validated the diagnostic accuracy of the R-CAMCOG in a new, representative cohort of stroke patients. Of the 121 patients, 35 (29%) were demented. The diagnostic accuracy at the pre-specified cut-off point of 33/34 was established through ROC analyses (sensitivity: 66%, specificity: 94%). At a cut-off point of 36/37 sensitivity would be 83% and specificity 78%.

We examined whether the clinical usefulness of the MMSE and the R-CAMCOG could be enhanced by an alternative approach in ***chapter 7***. Usually, the results of cognitive screening tests for poststroke dementia are interpreted dichotomously by means of a single cutpoint, which may lead either to redundant neuropsychological testing, or to unjustified reassurance of patients and relatives, all depending on the choice of the cutpoint. This calls for the use of two cutpoints. We defined cutpoints below and above which an additional neuropsychological examination would not contribute to the diagnosis, because the test result indicates a low, or high probability of poststroke dementia. Furthermore, we computed the proportion of patients in whom extended neuropsychological testing is necessary because of diagnostic uncertainty. The area under the fitted ROC curve did not differ between the MMSE and the R-CAMCOG (both tests: 0.895). However, the number of additional neuropsychological evaluations necessary for the diagnosis of poststroke dementia in a series of 1000 patients would be different for the R-CAMCOG and the MMSE, for cutpoints at different levels of diagnostic certainty.

In ***chapter 8***, I discuss some general methodological considerations concerning the studies described in this thesis. Furthermore, the role of screening instruments in the diagnosis of poststroke dementia is reviewed. Finally, I reflect on the changing diagnostic and mechanistic concepts of poststroke dementia. Despite the progress made on the redefinition of diagnostic criteria and the differentiation between several subtypes of vascular dementia, the diagnosis of poststroke dementia is still a complex one and its pathogenesis poorly understood.

SAMENVATTING

Een beroerte leidt vaak niet alleen tot lichamelijke handicaps, maar ook tot cognitieve stoornissen of een dementiesyndroom. Ongeveer 10 tot 40% van de patiënten met een recente beroerte ontwikkelt een dementie. De diagnose dementie na een beroerte is niet eenvoudig te stellen. Eén van de oorzaken daarvan is o.a. het heterogene karakter van de cognitieve stoornissen, die als corticaal of subcorticaal geclassificeerd kunnen worden. Ook is een combinatie van de twee mogelijk. Bovendien kan een oordeel over het cognitieve functioneren gecompliceerd worden door de somatische symptomen die vaak gepaard gaan met een beroerte.

In de klinische praktijk nemen cognitieve screening instrumenten een belangrijke plaats in; enerzijds om patiënten te selecteren die in aanmerking komen voor aanvullend neuropsychologisch onderzoek, anderzijds als een diagnostisch instrument bij patiënten met een duidelijke dementie. De meeste bestaande screening instrumenten die in de praktijk worden gebruikt zijn echter ontwikkeld om stoornissen op te sporen die passen bij een dementie van het Alzheimer type en hun waarde bij het opsporen van een dementie na een beroerte is minder bekend. In dit proefschrift beschrijf ik de diagnose van dementie na een beroerte, met nadruk op de waarde van screening instrumenten.

In ***hoofdstuk 2*** beschrijven we welke gemakkelijk verkrijgbare klinische informatie in de acute fase na een beroerte bruikbaar is voor het voorspellen van dementie na een beroerte. In de Dutch Vascular Factors in Dementia Study (DVFDS), een prospectief cohort waarin opeenvolgende patiënten met een acute beroerte werden geïncludeerd, werd de diagnose dementie 3 tot 9 maanden na de beroerte gesteld. De diagnose was gebaseerd op de resultaten van een uitgebreid neuropsychologisch onderzoek, klinische indruk, heteroanamnestische informatie, en de score op de Blessed dementie schaal. Van de 291 patiënten waren er 62 (21%) dement. Het uiteindelijke model voor vroege voorspelling van dementie na een beroerte bevatte leeftijd, geslacht, opleidingsjaren, eerder doorgemaakte beroerte, witte stof afwijkingen op CT scan, halfzijdige verwaarlozing, bloeding op CT scan, gemiddelde arteriële bloeddruk, en atriumfibrilleren. ROC analyse toonde een gebied onder de curve voor dit model van 0.82, met een hoge specificiteit en een matige sensitiviteit (resp. 95% en 37%).

Hoofdstuk 3 geeft een overzicht van de sterke en zwakke punten van bestaande cognitieve tests in dementie screening in het algemeen. Daarna worden de extra overwegingen bij de dementie screening bij patiënten met een beroerte beschreven. Aanpassingen in een test kunnen zinvol zijn en de diagnostische waarde verhogen, maar ik besluit dit hoofdstuk met de aanbeveling om een screening instrument speciaal voor dementie na een beroerte te ontwikkelen.

We vergeleken de diagnostische nauwkeurigheid van de CAMCOG en de MMSE in patiënten met een recente beroerte in ***hoofdstuk 4***. Van de 300 opeenvolgende patiënten van 55 jaar of ouder die waren geïncludeerd in de DVFDS, waren er 71 (23,7%) dement 3 tot 9 maanden na de beroerte. Zestien ernstig demente patiënten waren niet testbaar en werden geëxcludeerd. De CAMCOG en MMSE scores hadden een significante relatie met de aanwezigheid van dementie (beide $p<.0001$). De CAMCOG was een nauwkeuriger screening instrument (gebied onder de curve CAMCOG: 0.95 vs. gebied onder de curve MMSE: 0.90). Twee andere klinische variabelen verbeterden de diagnostische nauwkeurigheid van de

MMSE en de CAMCOG; patiënten met een linker hemisfeer lesie hadden een kleinere kans en patiënten met bloeding hadden een grotere kans om dement te worden. Wat de linker hemisfeer lesie als een onafhankelijke diagnostische factor betreft kon dit niet verklaard worden door een selectie of de associatie met afasie alleen.

In ***hoofdstuk 5*** beschrijf ik de ontwikkeling van de Rotterdam CAMCOG (R-CAMCOG), gebaseerd op de originele CAMCOG. We analyseerden de itemscores op de CAMCOG van de patiënten die waren geïncludeerd in de DVFDS. In drie stappen werd het aantal items gereduceerd van 59 tot 25, verdeeld over de subschalen oriëntatie, geheugen (recent, ver verleden, en leren), perceptie en abstractie. De subschaal oriëntatie bleek geen statistisch significante factor in een logistisch regressie model, maar werd toch opgenomen in de R-CAMCOG vanwege de hoge klinische waarde bij dementie screening. Interne validatie wees er op dat de R-CAMCOG en de CAMCOG een gelijke nauwkeurigheid hebben in screening voor dementie na een beroerte (gebied onder de curve is 0.95 voor beide tests). Een belangrijk voordeel van de R-CAMCOG is de kortere en eenvoudigere afname. ***Hoofdstuk 6*** bevat de studie waarin we de diagnostische nauwkeurigheid van de R-CAMCOG extern gevalideerd hebben in een nieuw, representatief cohort patiënten met een beroerte. Van de 121 patienten waren er 35 (29%) dement. De diagnostische nauwkeurigheid op het vooraf bepaalde afkappunt van 33/34 werd bepaald middels ROC analyses (sensitiviteit: 66%, specificiteit: 94%). Bij een afkappunt van 36/37 zou de sensitiviteit 83% zijn en de specificiteit 78%.

We onderzochten of de klinische bruikbaarheid van de MMSE en de R-CAMCOG verbeterd kon worden door een alternatieve benadering in ***hoofdstuk 7***. Meestal worden de resultaten van cognitieve screening tests dichotoom geïnterpreteerd middels één afkappunt. Dit kan leiden tot overbodig neuropsychologisch onderzoek bij patiënten die evident dement zijn of tot onterechte geruststelling van patiënten en hun familie, afhankelijk van het gekozen afkappunt. Dit geeft aanleiding tot het gebruik van twee afkappunten. We definieerden afkappunten waaronder en -boven een aanvullend neuropsychologisch onderzoek niet zou bijdragen tot de diagnose, omdat de testresultaten een kleine of grote kans op dementie aangeven. Daarnaast berekenden we het percentage patiënten bij wie een neuropsychologisch onderzoek nodig is vanwege de diagnostisch onzekerheid. Het gebied onder de ROC curve verschilde niet tussen de MMSE en de R-CAMCOG (beide tests 0.895). Het aantal aanvullende neuropsychologische onderzoeken dat nodig is voor de diagnose dementie na een beroerte in een serie van 1000 patiënten was echter verschillend voor de MMSE of de R-CAMCOG, afhankelijk van het gekozen niveau van diagnostische zekerheid. In ***hoofdstuk 8*** worden algemene methodologische overwegingen besproken die betrekking hebben op de studies uit dit proefschrift. Daarna bespreek ik de rol van screening instrumenten in de diagnose dementie na een beroerte. Tot slot ga ik in op de veranderende diagnostische en pathogenetische concepten van dementie na een beroerte. Ondanks de voortgang die gemaakt is, bijvoorbeeld bij het herdefiniëren van de diagnostische criteria en het maken van onderscheid tussen verschillende vormen van vasculaire dementie, is dementie na een beroerte nog altijd moeilijk te diagnosticeren en de onderliggende pathogenese grotendeels onbegrepen.

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Ook mijn paranimfen Nel van Amerongen en Harriët Smeding waren eens collega's op de afdeling neuropsychologie. Harriët, onze levens vertonen veel parallellen, en we hebben daarom gespreksonderwerpen genoeg, zowel positief als negatief. Wat is het heerlijk om ongebreideld te kunnen snoeven of somberen, zonder schuldgevoel achteraf. Nel, ook nu onze levens minder verweven zijn en misschien minder zichtbare parallellen vertonen, verwonder ik mij nog altijd over de bijna vanzelfsprekende herkenning in elkaar. Onze verbondenheid is mij dierbaar en waarschijnlijk het belangrijkste wat ik van mijn studie meegekregen heb. Dank Harriët en Nel, dat jullie erbij zijn.

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Zonder de jongens thuis verliep het leven misschien ordelijker, georganiseerder en met meer regelmaat, maar met jullie is er chaos, rumoer, en vooral veel liefde. Lieve Fop, Jens en Sten, laten we het nog lang goed hebben samen.

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CURRICULUM VITAE

Inge de Koning werd op 5 augustus 1963 geboren in Zaltbommel. Na het behalen van het VWO diploma aan de Rijksscholengemeenschap in Amersfoort begon zij in 1983 haar studie Psychologie aan de Rijksuniversiteit te Utrecht. Zij studeerde in 1989 af als neuro- en revalidatiepsycholoog aan de Katholieke Universiteit in Nijmegen. Sinds 1991 is zij werkzaam als neuropsycholoog in het Erasmus Medisch Centrum Rotterdam (voorheen Academisch Ziekenhuis Rotterdam/Dijkzigt). In 1993 werd begonnen met het onderzoek beschreven in dit proefschrift. Daaruit voortvloeiend deed zij een subsidieaanvraag voor de externe validering van de R-CAMCOG. In 1994 trad zij als staflid toe tot de Geheugenpoli, een samenwerkingsverband tussen de afdelingen geriatrie, psychiatrie en neurologie. Vanaf 1999 is zij hoofd van de sector neuropsychologie op de afdeling neurologie. In 1999 werd zij als GZ psycholoog ingeschreven in het BIG register.

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