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Cognitive disorders in patients with occlusive disease of the carotid artery: a systematic review of the literature

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INTRODUCTION

Patients with occlusive disease of the internal carotid artery (ICA) are at risk of future transient or permanent neurological deficits. The major cause of cerebral ischemia in patients with occlusive disease of the ICA is intracranial arterial obstruction by thrombo-embolism. In addition, a compromised cerebral blood flow may play an important role in the recurrence of ischemic episodes in a sizeable proportion of patients, in particular in those with carotid occlusion.⁶⁵

Although the detrimental influence of major ischemic stroke on cognition is well known,^{92,115} the consequences of minor ischemic stroke or transient ischemic attacks (TIAs) are less well described.^{31,47} Even less is known about the influence of chronic cerebral hypoperfusion on cognitive functioning.^{65,85} The aim of this systematic literature review is to establish the current state of knowledge about prevalence, nature, severity, course and cause(s) of cognitive deficits in patients with stenosis or occlusion of the carotid artery that has not (yet) been surgically treated.

METHODS

Literature searches were carried out on Medline and Psychlit between 1980 and 1999 using a combination of neurovascular and neuropsychological key words. Neurovascular key words were atherosclerosis, carotid artery disease, embolism, hemodynamics, cerebral ischemia, amaurosis fugax, TIA, RIND, cerebral infarction, endarterectomy, cerebral revascularization or alternatives presented in the thesaurus of Medline and Psychlit. Neuropsychological key words were cognition, cognitive disorders, dementia, psychometrics, neuropsychology or alternatives presented in the thesaurus. Furthermore, relevant papers and books were checked for references. Studies published since 1980 written in English, German, French or Dutch and describing neuropsychological assessment of groups of patients ($n > 1$) with carotid stenosis or occlusion were included. Papers focusing on cognitive changes after revascularization without description of pre-operative findings, and papers using cognitive dysfunction as an inclusion criterion were excluded. Twenty papers, all written in the English language, satisfied the inclusion criteria.^{6,8,14,17,37,45,47,48,54,60,61,85,87,88,90,91,107,118,132,135} By consensus, two of these were dismissed^{8,90}

because of overlap of patient groups and findings reported by the same authors.^{6,91} We selected the papers with stronger emphasis on the neuropsychological findings,⁶ and larger size of the patient sample and longer follow-up.⁹¹

Data on design (retrospective, prospective, cross-sectional, longitudinal, exclusion criteria), demographic characteristics of patients (age, gender), clinical diagnosis (no symptoms, TIA, stroke), carotid lesions (stenosis, occlusion, side), cerebral imaging (presence of infarct, location and size of infarct, presence of atrophy), psychological tasks and test batteries used, integration of test performances (specified according to number and nature of parameters of cognitive deficit [various separate parameters, general index of impairment]), interpretation of test results (ipsative, normative, controlled) and conclusions of authors (presence, nature and severity of cognitive deficits) were extracted from the papers and tabulated. Inventoried but not tabulated were criteria for inclusion of patients, education of patients, presence of pre-existing dementia, diagnostic criteria for ischemic symptoms, severity of stroke, location of symptoms (cerebral, ocular), number of ischemic episodes in patients, degree of stenosis, presence of white matter lesions, cerebral perfusion, time interval between latest ischemic episode and neuropsychological assessment, bandwidth of assessment procedures, and course of cognitive dysfunctioning.

RESULTS

In fourteen papers (78%) the authors concluded that cognitive dysfunction was present (Tables 1-3 A), whereas in four studies (22%) no cognitive dysfunction was found (Tables 1-3 B). (To promote readability, we referenced in the text only those issues not tabulated.) The only study investigating the course of cognitive deficits in patients with TIA or stroke who did not undergo surgical intervention (n=14) did not find improvement or deterioration during a two-year follow-up.⁹¹ Study design and characteristics of patient groups are summarised in Table 1.

Patient characteristics

The demographic features of the patient groups were roughly equal in the eighteen studies. On average, 75% of patients were male. The mean age varied between 50 and 65 years. Average number of years of education, reported in nine papers (50%), varied

Nielsen ^{88k}	P	pre/post bypass ^d	?	52	7/26	0	33 ^c	13	17	23/10/1?	30 ^e	?
Parker ^{89l}	P	0-6-24 months ^l	-	60	?, ?	33	13	46	0	11/11/10 ^l	?	?
			psychosis, organic brain syndrome, communicative disorders, alcohol abuse									
Benke ⁴⁴	P	no	?	64 (32)	8/12	0	0	20	0	8/6/6	?	?
Yamauchi ³²	R	no	cortical infarctions, major head injury, alcohol abuse	64 (5)	3/9	1	8	1	11	4/8/0	9 ^{lm}	?
B.												
Kelly ⁶⁰	P	pre/post CE	psychiatric, other neurological disease, acute physical distress	62 (8)	12/23	35	0	35	?	12/13/10 ^l	?	?
Boeke ⁷	P	pre/post CE	?	61	2/13	15	0	15	?	?/7/6	?	?
Van den Burg ⁸⁸	P	pre/post CE	psychiatric, other neurological disease	59	7/13	12	8	20	?	10/10/1?	?	?
Iddon ⁸⁴	P	pre/post CE	stenosis <70%, dementia, depression	65 (9)	?, ?	30	0	30	?	?/7/?	?	?

CE= carotid endarterectomy CAS= carotid arterial system VAS= vertebral arterial system
a number of patients
b based on examination of arteries unless otherwise specified, l= left side, r= right side, b= both sides, query as entry: either no information or no information on asymptomatic side
c stroke or RIND
d extracranial-intracranial bypass
e according to CT-scan
f minor infarction

g one patient without any carotid lesion
h as derived from reported side of symptoms
i territorial or watershed infarction
j as derived from reported side of surgery
k three patients without any carotid lesion
l 32 patients with CE between 1st and evaluation according to MRI

between 7 and 13 years.^{6,14,60,61,85,91,107,118,132} In seven studies, patients with concomitant psychiatric and/or neurological diseases were excluded.^{54,60,61,85,91,118,132} Risk factors for carotid occlusive disease, such as diabetes mellitus and atherosclerotic cardiovascular disease, were reported to exist in the patient group of five studies.^{14,60,91,107,132} In the other papers no information was given on concomitant disorders or diseases. Only four papers (22%) mentioned diagnostic criteria for ischemic symptoms.^{45,48,54,118} In one study, ischemic episodes were labelled as TIAs, whereas the neurological deficits were reported to continue for 4 weeks and longer.³⁷ For the current survey, we considered these episodes as strokes. Five of the nine studies describing stroke patients included patients with minor strokes.^{45,47,88,132,135} One study described both minor (25%) and major (15%) stroke patients,¹¹⁸ and three papers did not provide information on the severity of stroke.^{6,37,91} In two studies (11%) only patients with cerebral symptoms were included,^{88,135} four studies (22%) included both patients with cerebral and ocular symptoms,^{6,37,48,132} and in ten papers (56%) no information regarding the location of symptoms was presented.^{17,45,47,54,60,61,87,91,107,118} The number of ischemic episodes and the time interval between the latest ischemic episode and the psychological assessment were mentioned in a minority of papers (22% and 33%, respectively); the number of episodes varied between 1 and at least 50,^{47,48,87,135} and the interval varied between 3 days and at least 4 months.^{47,48,87,88,132,135} In one study the mean degree of stenosis was 59%,¹⁴ in five studies the degree of stenosis was at least 70%,^{6,54,60,85,132} in one at least 60%,⁶¹ and in another at least 50%.⁴⁵ The remaining papers (56%) did not mention the degree of stenosis.^{17,37,47,48,87,88,91,107,118,135} Nine studies (50%) included patients with bilateral carotid obstruction. Eight studies (44%) did not provide information on uni- or bilaterality of carotid obstruction. The five studies that reported cerebral imaging found ischemic lesions and cerebral atrophy in varying proportions of stroke and TIA patients. Only one study assessed white matter lesions, and reported high intensity areas in all patients.¹³²

No interpretable differences in patient characteristics were found between studies confirming and those denying cognitive deficits. As only a minority of papers provided information on neurovascular characteristics, such as the degree of carotid stenosis or the number and location of ischemic brain lesions, no conclusions can be drawn regarding the concordance in neurological features of the patient groups in the eighteen studies.

Table 2 Psychological tasks and test batteries used in 14 studies finding cognitive deficits (A) and 4 studies denying cognitive deficits (B)

PSYCHOLOGICAL TASKS OR TEST BATTERIES ^a	
AUTHORS ordered according to year of publication	
A.	
Hemmingsen ¹⁷	Digit span, similarities, block design (WAIS), word pairs, story recall, visual gestalts, facial recognition, trailmaking, word fluency
Baird ⁶	WAIS, Wechsler Memory Scale, Halstead-Reitan Battery, Wisconsin card sorting test
Drinkwater ²⁷	WAIS, Russell-Wechsler Memory Battery, Halstead-Reitan Battery
Hamster ⁴⁵	Digit symbol (WAIS), multiple choice vocabulary test, culture fair intelligence test, visual retention, attention set test, revision test, attention stress test, Vienna reaction timer, Freiburg personality inventory, scales for psychosomatic complaints
Nielsen ⁸⁷	information, arithmetic, similarities, digit span, block design, picture arrangement (WAIS), trailmaking, symbol digit modalities, 15 words learning, story recall, face recall, visual gestalts
Seidenberg ²⁰⁷	WAIS, Wechsler Memory Scale (Russell), Halstead-Reitan Battery
Younkin ¹³⁵	Wechsler Memory Scale, trailmaking B, finger tapping, temporal orientation
Hemmingsen ¹⁸	Digit span, digit symbol (WAIS), visual gestalts, word pairs, story recall, trailmaking
Kelly ⁶⁶	Wechsler Memory Scale, object memory, sentence production, picture vocabulary, picture absurdities, stereognosis, praxis, finger tapping, right-left discrimination
Naugle ⁸⁵	WAIS, Wechsler Memory Scale (Russell), grooved pegboard, trailmaking, category test, written word fluency
Nielsen ⁸⁸	information, arithmetic, similarities, digit span, block design, picture arrangement (WAIS), trailmaking, symbol digit modalities, 15 words learning, story recall, face recall, visual gestalts
Parker ⁹¹	WAIS, Wechsler Memory Scale (Russell), Halstead-Reitan Battery, profile of mood states, Tennessee self-concept scale
Benke ⁴⁴	Block design (WAIS), verbal analogies, word list memory, lexical decision, word fluency
Yamauchi ¹³²	Digit span, arithmetic, picture arrangement, object assembly, block design, digit symbol (WAIS)
B.	
Kelly ⁶⁶	Wechsler Memory Scale, object memory, sentence production, word association, picture vocabulary, stereognosis, praxis, right-left discrimination, picture absurdities, hidden patterns, arithmetical reasoning, proverbs, state-trait anxiety, mini-mult
Boeke ⁷	15 words, recurring faces, word fluency, reaction time, finger tapping, list of complaints, questionnaire on well-being
Van den Burg ¹¹⁸	Groningen Intelligence Test, Raven Progressive Matrices, 15 words, recurring faces, word fluency, four choice reaction time, finger tapping, Minnesota rate of manipulation
Iddon ¹⁴	National Adult Reading Test, pattern recognition, spatial recognition, spatial span, spatial working memory, attentional set shifting, paired associates learning, matching to sample, word fluency, mini mental state examination, depression inventory
<p>WAIS= Wechsler Adult Intelligence Scale a detailed description can be found in the respective papers or in neuropsychological handbooks⁷⁰</p>	

Study design

In fourteen studies (78%) the design was prospective. Two papers (11%) mentioned that patients were included consecutively.^{48,61} In fifteen studies (83%), patients were referred to the surgical department of a hospital for (evaluation of) treatment of the carotid occlusive disease.^{6,17,37,45,47,48,54,60,61,87,88,91,107,118,135} In three studies (17%), patients were seen in the neurological department, because of ischemic symptoms,¹³² carotid bruits,⁸⁵ or unspecific complaints as headache and dizziness.¹⁴ Twelve studies (67%) primarily addressed the outcome after surgery. The pre-operative findings of these studies were assessed in this review. In eight studies (44%) the number of patients was less than 30. No interpretable differences in study design were found between studies confirming and those denying cognitive deficits. The four studies denying cognitive deficits were prospective and longitudinal, and assessed mainly TIA patients. However, five other prospective and longitudinal studies did find cognitive deficits in TIA patients.^{45,47,48,87,135}

Psychological assessment

We counted 79 different psychological assessment procedures in the eighteen studies (Table 2). Some of the procedures belong to a standard neuropsychological battery (e.g. Halstead-Reitan Battery) or a psychometric scale (e.g. Wechsler Adult Intelligence Scale). Thirty-seven procedures (47%) were used in only one study, whereas 13 (16%) were used in two studies, 19 (24%) in four to six studies and 10 (13%) in seven to fourteen studies. The bandwidth of psychological assessment varied between the studies, but did not discriminate between the studies finding and those denying cognitive deficits.

Integration and interpretation of test performances (Table 3)

Test performances can be quantified in separate test parameters or in a general index of impairment, which is based on performances on various tests. Interpretation of test performances can be ipsative, i.e. by comparison with premorbid level of functioning, or normative, i.e. by comparison with norms or control data.

Six studies (33%) employed a general impairment index, according to the scoring method of Russell et al.^{100,101} In the studies using separate test parameters for statistics, the number of parameters varied between 1 and 30. Three studies^{14,61,91} adjusted for multiple statistical comparisons by using a conservative level of statistical significance (0.002 or 0.01 instead of 0.05). No paper stated the percentage of patients with cognitive deficits. Instead, the means or medians of performances of the patient group were compared with

those of control persons or with norms. No interpretable differences appeared between the studies finding and those denying cognitive deficits in methods for integration and interpretation of test performances.

Type and severity of cognitive deficits (Table 3)

Six of the studies finding cognitive deficits (43%) did not specify the nature of cognitive impairment. Two studies (14%) concluded there was general impairment of cognitive functioning. In six studies (43%) specific domains of functioning were reported to be implicated, among which impairment of reasoning, memory and (psycho)motor skills were reported in more than two studies.

Seven of the studies finding cognitive deficits (50%) concluded mild impairment, three (21%) moderate or severe impairment, and in four (29%) the severity of impairment was not estimated. None of the studies mentioned criteria for severity.

Risk factors for cognitive deficits

Ten papers (56%) searched for determinants of cognitive deficits, such as side of carotid lesion, degree of carotid stenosis, vascular disease in other parts of the brain or body, type of ischemic event (ischemic stroke or TIA), recency of the ischemic event, presence of cerebral atrophy, and presence of white matter lesions. Patients with left, right or bilateral carotid stenosis did not differ in severity of cognitive impairment.^{17,45,47,48,61,88} The only study assessing the influence of degree of carotid stenosis on cognitive functioning considered both as continuous variables and did not find significant correlations.¹⁴ Degree of carotid occlusive disease was diagnosed by means of angiography,^{47,48,61,88} Doppler sonography and angiography,⁴⁵ or Duplex sonography.¹⁴ One study did not specify how the degree of stenosis was determined.¹⁷ In one paper, interactive effects of atherosclerotic heart disease and cerebrovascular disease on cognitive functioning were mentioned.¹⁰⁷ Another study reported more severe cognitive impairment for stroke compared to TIA patients,¹³⁵ whereas two studies found a similar degree of cognitive impairment for TIA and stroke patients.^{45,47} Time interval between stroke and neuropsychological assessment did not correlate with degree of cognitive impairment.¹³⁵ The two studies that assessed CBF by means of ¹³³Xenon-SPECT⁴⁸ or ¹³³Xenon-inhalation¹³⁵ did not correlate CBF and cognitive functioning prior to surgical intervention. Yamauchi et al.¹³² found atrophy of the corpus callosum to be associated with cognitive impairment and with changes in hemodynamic parameters measured by ¹⁵O-PET. The callosal atrophy

Table 3 Integration and interpretation of test results in 14 studies finding cognitive deficits (A) and 4 studies denying cognitive deficits (B)

AUTHORS	INTEGRATION OF TEST PERFORMANCES			INTERPRETATION OF TEST RESULTS			CONCLUSIONS OF AUTHORS	
	single test parameters (nr)	general index of impairment	ipsative	norms	control group	nature of deficits	severity of deficits	
ordered according to year of publication								
A.								
Hemmingsen ⁷	13	no	no	yes	no	general	subnormal	
Baird ⁶	30	yes ^a	yes ^b	yes	no	no statement	mild	
Drinkwater ⁷	15	yes ^c	no	yes	no	problem solving, motor skills, memory	severe	
Hamster ⁶	10	no	no	yes	no	memory, attention, psychomotor	considerable	
Nielsen ⁸	15	no	no	yes	non-cerebral outpatients ^d	tempo, general knowledge, arithmetic, memory, learning	slight	
Seidenberg ³⁹⁷	17	yes ^a	no	yes	no	no statement	mild to moderate	
Younkin ³⁵	0	yes ^c	no	yes	no	no statement	no statement	
Hemmingsen ⁸	10	no	no	yes	patients with PVD ^e	no statement	slight	
Kelly ⁶⁶	22	no	no	yes	patients with PVD ^f	memory	mild	
Naugle ⁶⁵	13	yes ^c	no	yes	healthy persons, non-cerebral patients ^f	memory, manual dexterity, visual-spatial reasoning	no statement	
Nielsen ⁸	15	no	no	yes	non-cerebral patients ^f	sequential thinking, verbal repetition and learning, arithmetic	slight	
Parker ⁹¹	21	yes ^a	no	yes	non-cerebral patients ^f	no statement	no statement	

Author	5	no	no	no	no	no	no	no	relatives, non-cerebral patients ^f	multimodal, non-focal	substantial
Benke ⁴	5	no	no	no	no	no	no	no	relatives, non-cerebral patients ^f	multimodal, non-focal	substantial
Yamauchi ³²	1 ^g	no	no	no	no	no	yes	no	no	no statement	varied
B.											
Kelly ⁶⁰	15	no	no	no	no	yes	yes	patients with PVD ^f	patients with PVD ^f	no deficits	no deficits
Boeke ²⁷	8	no	no	no	no	yes	yes	non-cerebral patients ^f	non-cerebral patients ^f	no deficits	no deficits
Van den Burg ¹¹⁸	18	no	no	no	no	yes	yes	healthy persons ^g , patients with PVD ^f	healthy persons ^g , patients with PVD ^f	no deficits	no deficits
Iddon ³⁴	11	no	no	no	no	yes	yes	healthy persons ^h	healthy persons ^h	no deficits	no deficits

PVD= peripheral vascular disease

a average impairment rating^{60,61,66}

b present versus estimated premonbid IQ

c impairment index^{60,61,66}

d sex-, age-, education-matched

e age-matched
f age-, education-matched
g sum of six subtest scores
h age-, intelligence-matched

was hypothesised to reflect the severity of disconnection of cortical regions as caused by white matter lesions and cerebral atrophy due to ICA occlusive disease. According to these authors, cortical disconnection may be an important factor in the development of cognitive impairment in ICA occlusive disease without large cortical lesions.

DISCUSSION

Neuropsychological audit of TIA and stroke sequelae offers a framework for interpreting complaints on cognition and, hence, for adequate counselling and care. This review addresses cognitive functioning of patients with carotid occlusive disease who did not (yet) undergo surgery.

We found eighteen studies about cognitive functioning of asymptomatic, TIA or stroke patients with occlusive disease of the carotid artery. As almost no follow-up studies were performed in the population of patients who did not undergo surgery, information on the natural course of cognitive functioning is too scarce for conclusions.

Transversal results on cognitive functioning of patients varied from no deficits to obvious cognitive impairment. Patient characteristics, study design, neuropsychological assessment procedures and interpretation varied widely between the eighteen studies. However, when comparing the fourteen studies reporting cognitive deficits and the four studies reporting uncompromised cognition, we could not detect systematic biases explaining the difference in study results. As the majority of studies did not report on relevant neurovascular variables, such as cerebral infarction or hypoperfusion, it remains uncertain whether heterogeneity in the neurological condition of patients caused the difference in study results.

Seven of the eleven studies (64%) analysing the performances of TIA patients concluded that cognitive deficits were present.^{6,45,47,48,61,87,135} Furthermore, all three studies assessing asymptomatic patients with carotid obstruction found cognitive deficits.^{14,45,85} Hence, the absence or disappearance of neurological signs does not guarantee undisturbed cognitive functioning in patients with carotid obstruction.

None of the studies distinguished patients with cognitive deficits from those without by individual estimation of dysfunctioning. Therefore, the literature offers no information on the prevalence of cognitive impairment in the patient population with carotid occlusive disease.

Of the eight studies specifying the nature of cognitive deficits, two concluded global impairment and six specific deficits in, for example, memory, reasoning or (psycho)motor skills. However, in neuropsychology one should beware of deriving the nature of impairment from the measurement pretension of the test, based on psychometric research in a healthy population.²⁵ None of the studies addressed this topic.

The majority of papers estimating severity of cognitive impairment concluded mild impairment (70%), presumably based on clinical impression as none of them mentioned the criteria for severity of impairment. To avoid subjective evaluation, a principled estimation should be made.

Another point of interest concerns the vascular risk factors of cognitive dysfunctioning. Subgroups of patients at risk of cognitive impairment may exist. Although some papers searched for risk factors, various clinical subgroups and possible causative factors are not examined yet. Some relevant variables concerning the existence of structural brain pathology are the nature and location of the symptoms (TIA or stroke, cerebral or ocular), and the size and location of infarcts. Besides structural brain pathology, chronic cerebral hypoperfusion may be a risk factor for cognitive deficits. Degree of the carotid obstruction, uni- or bilaterality of the carotid obstruction, presence of atherosclerotic disease in other brain arteries (e.g. in the vertebrobasilar arterial system), and presence of collateral circulation do affect the vascular supply of the brain. A comprehensive assessment of risk factors, by means of a multiple regression analysis including various neurological and demographic factors or by delineating well defined clinical subgroups, has yet to be accomplished.

Most likely, a nonrepresentative portion of the patient population with occlusive disease of the carotid artery has been sampled so far. Twelve studies (67%) were designed to address the outcome after surgery and, hence, included only patients suitable for surgery. As the indications and contra-indications for operation were mentioned in only two of these papers,^{60,118} the nature of the selection bias remains unknown. Furthermore, although the design of most studies was prospective, only two papers mentioned that patients were included consecutively. Only a principled and consecutive inclusion can prevent biases in the patient sample.

To get a clear picture of the influence of carotid occlusive disease on cognition, patients should be screened for concomitant disorders, e.g. depression or anxiety, that might affect cognitive functioning. Disentangling causes of demonstrated cognitive deficits is hampered by the co-existence of other neurological diseases affecting cognitive func-

tioning. As only a minority of the studies discussed in this review (39%) stated that patients with concomitant psychiatric and/or neurological diseases were excluded, we can not be sure that the cognitive deficits described are caused by the carotid occlusive disease.

We conclude that the majority of the current papers indicate a detrimental influence of carotid occlusive disease on cognition, but unbiased evidence has yet to be assembled. Apparently, the cognitive impairment is of a global, diffuse nature and mild to moderate in severity. Further research is needed to describe cognitive functioning in a representative sample of the patient population with carotid occlusive disease. We propose a prospective study with consecutive and principled inclusion of patients to prevent biases in sample selection. To assess natural course of cognitive functioning, a follow-up study is necessary. Since there are no indications that cognitive impairment is confined to a specific cognitive domain, a broad range of cognitive skills should be assessed. A consensus on the methods for neuropsychological assessment, such as recently was accomplished for the assessment of neurobehavioral outcomes after cardiac surgery,⁸⁴ would promote adequate assessment. To ascertain the causative factors of cognitive deficits, clinical subgroups of patients should be delineated and both structural and hemodynamic components of brain functioning should be assessed.