Chapter 5

The silence of a brain infarct, does it matter for cognitive function? The SMART Study

Abstract

Objective

Silent brain infarcts are associated with decreased cognitive function in the general population. We examined whether this relation also exists in patients with symptomatic arterial disease. Furthermore, we compared cognitive function of patients with stroke or TIA, with cognitive function of patients with symptomatic arterial disease at other sites in the arterial tree.

Methods

An extensive screening was done in 336 consecutive patients participating in the Second Manifestations of ARTerial disease (SMART) study, including a neuropsychological test. Inclusion diagnoses were cerebrovascular disease, symptomatic coronary artery disease, peripheral arterial disease, or abdominal aortic aneurysm. MRI examination was performed to assess the presence of silent infarcts in patients without symptomatic cerebrovascular disease. The patients were assigned to one of three categories according to their patient history and inclusion diagnosis: no stroke or TIA, no silent infarcts (n = 220; mean age 57 years); no stroke or TIA, but silent infarcts present (n = 33; mean age 65 years); stroke or TIA at inclusion (n = 83; mean age 60 years). Cognitive test scores were transformed in standardized z-scores.

Results

After adjustment for age, sex, educational level and intelligence, patients with silent infarcts appeared to have slightly higher cognitive scores than patients without silent infarcts (difference in global cognitive function (95% CI): 0.11 (-0.08; 0.31)), although this was not statistically significant, while patients with stroke or TIA had lower scores on all cognitive domains except memory (difference in global cognitive function (95% CI): -0.23 (-0.35; -0.10)).

Conclusion

Silent infarcts do not influence cognitive function in patients with symptomatic coronary or peripheral artery disease, or abdominal aortic aneurysm. Patients with stroke or TIA, however, had lower scores on most tests than patients with symptoms elsewhere in the arterial tree.

Introduction

Ischemic lesions in the brain seen on imaging do not always manifest themselves as symptomatic cerebral infarcts. Silent brain infarcts are five times more common than symptomatic ones in the general population.[1] Although their name suggests that silent brain infarcts are asymptomatic, large population-based studies showed that these lesions are related to lower scores on cognitive function tests in the general population.[2-4]

Symptomatic arterial disease is related to decline in cognitive function.[5] Not only patients with cerebrovascular disease have lower cognitive function than the general population, but also patients with a manifestation of arterial disease elsewhere in the arterial tree.[6,7] Also, lower cognitive test scores predict incident myocardial infarction, stroke and cardiovascular death, implying that decreased cognitive function is an early manifestation of vascular injury to the brain.[8]

Little is known about the effect of silent brain infarcts on cognitive function within a patient group with symptomatic arterial disease. If silent brain infarcts are simply markers of arterial disease, the negative effect of these lesions on cognitive function could be absent in vascular compromised patients. We therefore examined the effect of silent brain infarcts on cognitive function in patients with coronary artery disease, peripheral arterial disease, or abdominal aortic aneurysm, and additionally compared their cognitive function with that of patients with stroke or TIA.

Methods

Subjects

Subjects were participants of the Second Manifestation of ARTerial disease study (SMART). This is an ongoing prospective cohort study at the University Medical Center Utrecht. Detailed information about the inclusion criteria and baseline measurements was published previously.[9] In short, patients, aged 18-79, newly referred with (risk factors for) arterial disease, are included. At enrolment an extensive questionnaire is filled in and baseline examinations are performed. Blood and urine are examined. Common carotid intima media thickness (IMT) is measured as a marker of the extent of atherosclerosis. Magnetic resonance imaging (MRI) of the brain and a neuropsychological examination are performed in patients with manifest arterial disease.

In the current study, the information of 390 consecutive patients with at least one manifestation of arterial disease was available. Of those patients, 83 were included with a manifestation of cerebrovascular disease, defined as stroke or transient ischemic attack (TIA) inclusion. The diagnosis was confirmed by their treating neurologists. Patients who were not independent in daily activities (modified Rankin scale >3)[10] were excluded from participating in the SMART study. The other 307 patients had manifestations of arterial disease at any localisation except for the brain: coronary artery disease, peripheral artery disease, abdominal aortic aneurysm (AAA). Their questionnaires were additionally screened for reported stroke, or symptoms suspected for TIA in history by two trained physicians. 54 patients had a probable history of TIA or stroke and were excluded. Thus, 253 patients without cerebrovascular symptoms remained in the study. In total, the study was performed in 336 patients from the SMART study.

The study was approved by the ethics committee of our institution and written informed consent was obtained from all participants.

Silent brain infarcts

In the 253 patients without signs of (previous) TIA or stroke, the presence of silent cerebral infarcts was assessed on MRI scans.

The MR investigations were performed on a 1.5-T whole-body system (Gyroscan ACS-NT, Philips Medical Systems, the Netherlands). The scanning protocol included a fluid-attenuated inversion recovery (FLAIR) sequence (repetition time 6000 ms, echo time 100 ms, inversion time 2000 ms) and a turbo spin-echo T2-weighted sequence (repetition time 2200 ms, echo time 100 ms). Images were obtained of 19 transaxial slices per scan. Slice thickness was 4 mm, with no interslice gap. The MRIs were read on hard copies.

The whole brain, including cortex, brain stem, and cerebellum, was searched for silent infarcts. Infarcts were defined as focal lesions of at least 3 mm in diameter, with signal intensity corresponding to liquor (hyperintense on T2-weighted images and low signal on the FLAIR image). The infarcts were often surrounded by a hyperintense gliotic rim on the FLAIR sequence. They were distinguished from white matter lesions on FLAIR, as the latter were of high signal intensity. Dilated perivascular spaces were also differentiated, based on their localisation (along perforating or medullary arteries, often present bilaterally, usually in the lower third of the basal ganglia or in the centrum semiovale), shape (round/oval), and the absence of gliosis. The infarcts were scored in consensus by an investigator and a neuroradiologist, who were blinded for the history, diagnosis, and neuropsychological test results of the patients.[11]

Table 1. Baseline characteristics, according to the presence of manifest cerebrovascular disease and the presence of silent cerebral infarcts (n (%) or mean ± sd)

Cognitive domain	Unadjusted ß (95% CI*)	Adjusted† ß (95% CI*)	Adjusted‡ ß (95% CI*)
	No stroke or TIA (n = 253)		
	No silent infarcts (n = 220)	Silent infarcts (n = 33)	Stroke or TIA (n = 83)
Age	57 ± 9	65 ± 8	60 ± 9
Sex (male)	189 (86)	27 (82)	60 (72)
Educational level (0-7)	3.3 ± 1.8	2.9 ± 1.9	3.2 ± 1.9
NART*	75.8 ± 17.9	72.9 ± 20.1	76.7 ± 16.9
systolic blood pressure	137 ± 18	159 ± 27	151 ± 22
diastolic blood pressure	82 ± 11	90 ± 15	87 ± 11
Body Mass Index	27.2 ± 4.1	27.1 ± 2.4	26.9 ± 4.0
diabetes	38 (20)	12 (38)	17 (22)
Intima Media Thickness	0.9 ± 0.2	1.1 ± 0.4	1.1 ± 0.3
ICA-stenosis ≥ 70%	8 (4)	1 (3)	30 (38)
cardiovascular disease†	170 (77)	24 (73)	17 (21)
peripheral arterial disease†	45 (21)	8 (24)	2 (2)
abdominal aortic aneurysm†	24 (11)	3 (9)	3 (4)

* NART = National Adult Reading Test
† Patients were classified into more than one category when they had more than one localisation of manifest arterial disease

Cognitive function

Educational level was defined in 7 categories, graded from primary school to academic degree, according to the Dutch educational system. Premorbid intellectual functioning was assessed with the National Adult Reading Test (NART).[12] Dutch version. This test is widely used for estimating intelligence in neuropsychological research.[13]

A set of standardized neuropsychological tests was selected, sensitive to mild impairments. The four cognitive domains and the accompanying tests were as follows: Memory : Rey Auditory Verbal Learning Task (immediate and delayed recall) and Rey-Osterrieth Complex Figure delayed recall test;[14] Attention: accuracy and timing score of the Visual Elevator Test (subtest of the Test of Everyday Attention);[15] Executive function: Brixton Spatial Anticipation Test[16] and the Verbal Fluency Test;[17] Visuoperception and construction: Rey-Osterrieth Complex Figure copy test.[14]

Table 2. Crude results on neuropsychological tests, and z-score of global cognitive function, according to the presence of silent brain infarcts and manifest cerebrovascular disease (score ± sd)

Tasks	Test	Stroke or TIA absent (n = 253)		Stroke or TIA present (n = 83)
		Silent infarcts absent (n=220)	Silent infarcts present (n=33)	
Memory				
- RAVLT*	highest	9.4 ± 2.6	8.8 ± 2.3	9.3 ± 3.1
	mean	7.1 ± 2.0	6.6 ± 1.9	6.9 ± 2.3
	delayed	7.0 ± 3.4	6.3 ± 2.5	6.7 ± 3.3
- Rey-O-CF†	delayed	20.1 ± 7.0	19.2 ± 6.6	18.6 ± 6.7
Attention				
- Visual elevator test	accuracy	8.3 ± 2.0	7.9 ± 2.5	7.4 ± 2.7
	timing score	5.0 ± 2.3	6.6 ± 4.7	6.1 ± 3.2
Executive function				
- Brixton SAT‡ (number of errors)		18.3 ± 6.1	19.8 ± 5.5	22.0 ± 7.2
- Verbal Fluency test		10.6 ± 4.3	9.9 ± 4.4	9.4 ± 4.3
Visuoperception and construction				
- Rey-O-CF†	copy	34.6 ± 3.8	34.1 ± 3.4	33.5 ± 4.2
Global cognitive function				
- standardized z-score		0.09 ± 0.57	-0.16 ± 0.71	-0.27 ± 0.74

* RAVLT = Rey Auditory Verbal Learning Task
† Rey-O-CF = Rey-Osterrieth Complex Figure
‡ Brixton SAT = Brixton Spatial Anticipation Test

Statistical analysis

The raw scores of the neuropsychological tasks were transformed into z-scores (individual score minus the average score, divided by the standard deviation of that score). Compound z-scores for the cognitive domains were made, and a sum score for global cognitive function was derived from the mean of the domain scores.
Analysis of variance (ANOVA; SPSS 12.0.1; SPSS, Chicago, Ill) was used to calculate the difference between z-scores of cognitive function in patients with silent brain infarcts and in patients with symptomatic cerebrovascular disease, compared to the reference group (no silent infarcts and no symptomatic cerebrovascular disease). The results were adjusted for age, sex, educational level, and intelligence.

Table 3. Age, sex, education and intelligence-adjusted difference in z-score for the domains of cognitive function.*

	Stroke or TIA absent		Stroke or TIA present
	Silent infarcts absent n=220 reference	Silent infarcts present n=33	n=83
Domain	Z-score (95% CI†)	Difference (95% CI†)	Difference (95% CI†)
Memory	0.00 (-0.09; 0.10)	0.24 (-0.04; 0.52)	-0.03 (-0.22; 0.15)
Attention	0.08 (-0.02; 0.18)	0.09 (-0.23; 0.40)	-0.33 (-0.54; -0.13)
Executive function	0.08 (-0.01; 0.17)	0.10 (-0.18; 0.37)	-0.33 (-0.52; -0.15)
Visuoperception and construction	0.02 (-0.11; 0.15)	0.12 (-0.27; 0.50)	-0.17 (-0.42; 0.10)
Global cognitive function	0.04 (-0.02; 0.11)	0.11 (-0.08; 0.31)	-0.23 (-0.35; -0.10)

* Values are the adjusted mean differences in z-score between patients with silent infarcts and the reference group, and with stroke or TIA and the reference group. A positive value indicates a better score than the reference group in the cognitive domain.
† 95% CI = 95% confidence interval

Results

Two hundred and fifty three patients without symptomatic cerebrovascular disease were included in this study (86% male; mean age 58 ± 9 years), and 83 patients with stroke or TIA at inclusion (72% male, mean age 60 ± 9 years). Of the patients without stroke or TIA, 33 patients (13%) had silent brain infarcts: 24 patients had one infarct, six patients had two, one patient had three, and two patients had five. The lesions were mostly small vessel lesions, located in the white matter (59%), basal ganglia (16%), and thalamus (6%); only few were large vessel lesions, located in the cerebellum (12%), and the frontal and parietal cortex (6%). Table 1 shows the main characteristics of all patients. Among patients without symptomatic cerebrovascular disease, patients with silent infarcts were older, had higher blood pressure, and more often had diabetes than those without silent infarcts. Patients with stroke or TIA were only slightly older, more often were females, had higher systolic blood pressure, and more often had ICA-stenosis ≥ 70%.

In table 2, the raw scores on all neuropsychological tests and the z-score for global cognitive function are given for the three groups. This shows an unadjusted overall lower cognitive function in patients with silent infarcts, and an even lower score for patients with stroke or TIA.

The results of the adjusted differences in z-scores of cognitive function are shown in table 3. After adjustment for age, sex, education and intelligence, patients with silent infarcts had slightly higher, i.e. better, scores on all domains, although this was not significant. Patients with stroke or TIA had lower scores than patients with symptomatic atherosclerosis at other sites of the arterial tree on all domains except for memory. The strongest confounder in the model was age: differences in z-score were about 0.10 lower after adjustment for age.

Discussion

Our study was conducted in patients with symptomatic arterial disease. We compared patients with silent brain infarcts, and patients with stroke or TIA, with a group of patients with non-cerebral localisations of manifest arterial disease. We found that silent brain infarcts do not independently influence cognitive function in this vascular high-risk population. However, patients with stroke or TIA did have lower cognitive function than patients with non-cerebral localisations of manifest arterial disease.
Several studies have been conducted on the determinants of silent brain infarcts. In the SMART study, again in patients with non-cerebrovascular symptomatic arterial disease, we found that age, hypertension, elevated creatinine, elevated homocysteine, abdominal aortic aneurysm and increased IMT were related to the presence of silent brain infarcts.[11] In the population-based Cardiovascular Health Study, conducted in 3660 elderly participants aged 65 years or older, silent brain infarcts occurred in 20%, and were related to age, male sex, diastolic blood pressure, creatinine, smoking, ICA-stenosis, and diabetes.[3] In another population-based study, the Rotterdam Scan Study, 20% of the 1077 participants, aged 60-90 years, had silent brain infarcts, and these were related to age, female sex, and hypertension.[18] Patients in the SMART study were relatively young (mean age 58 years), but the high prevalence of cardiovascular risk factors increased their risk for silent brain infarcts at a younger age. We expected to find these lesions in a similar or higher percentage of patients compared with population-based studies. Nevertheless, the prevalence was only 13%. A possible explanation is that we had a strict definition for silent brain infarcts and that we have differentiated them from perivascular spaces.[11] We believe this was a proper study population to conclude that silent infarcts are only a marker for arterial disease, comparable to the presence of coronary artery disease, peripheral artery disease or AAA with regard to cognitive function.

To our knowledge, our study is the first investigating cognitive function within three patient groups with symptomatic arterial disease. Many studies have been conducted in population-based studies. Cross-sectional studies showed a relation

between silent brain infarcts and cognitive function [19,20]. Large longitudinal studies also showed a higher risk of cognitive decline or dementia in patients with silent brain infarcts.[2,4,21,22] Absent relations between silent brain infarcts and cognitive function were not reported. The fact that we did not find a difference in cognitive function between patients with silent infarcts and the patients without silent infarcts, does not contradict previous literature. The patients without silent infarcts in our study were not free of symptomatic arterial disease and thus also had lower scores on cognitive tests than healthy subjects. In a prospective study in 599 subjects, those with generalized atherosclerosis had lower baseline scores on cognitive tests than those without, and also had accelerated cognitive decline during follow-up.[5]

The relation between symptomatic stroke or TIA and lower cognitive function is not surprising. Similar results have been described in previous literature.[5] A probable explanation for the difference with silent infarcts, is the size of the lesions and the fact that stroke and TIA patients often suffered from large vessel disease, and not mostly small vessel disease, as in silent infarcts. In our study, patients in the stroke or TIA group had much higher prevalences of severe ICA-stenosis (38%) than the group with silent infarcts (3%).

We did not find a relation between stroke or TIA and lower scores on memory tasks. In contrast, in the previously mentioned population-based study in 599 subjects, patients with a history of stroke had lower scores on immediate and delayed recall memory, compared with elderly participants without stroke or symptomatic cardiovascular pathology.[5] An important difference is that that study concerned subjects aged 85 years and older, whereas our study population was much younger. Perhaps therefore, memory impairment was not yet discernible in our patients. Furthermore, selection bias could have occurred, since patients with a modified Rankin scale > 3 were excluded from this study.

Because in the SMART study previous stroke or TIA was based on self-report, misclassification could have occurred. To reduce misclassification, we have reviewed all the questionnaires, and we have excluded all patients reporting stroke or TIA, or symptoms of TIA, in history. Thus, for the patient group with stroke or TIA, we only included patients in which the diagnosis was confirmed by the treating neurologist at inclusion. Patients with possible stroke or TIA in history were not included in any of the patient categories for this particular study.

From this study we conclude that the silence of brain infarcts does matter for cognitive function. Patients with silent brain infarcts do not have lower scores on cognitive function than patients with non-cerebral symptomatic arterial disease, while patients with stroke or TIA clearly do have lower cognitive function.

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