J Neurol (1996) 243 : 196–200

ORIGINAL COMMUNICATION

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Are white matter lesions directly associated with cognitive impairment in patients with lacunar infarcts?

Received: 11 January 1995
Recieved in revised form: 14 June 1995
Accepted: 4 July 1995

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Abstract Forty-four patients (mean age 66, SD 8 years) with either clinical evidence of a focal lacunar syndrome ($n = 36$) or with disorders of memory or gait ($n = 8$) in the presence of a lacunar infarct on CT were studied for cognitive functioning and for the presence of white matter lesions on MRI. MR images were assessed by a neurologist and a neuroradiologist blinded to the clinical data. Thirty-six patients had one or more lacunar infarcts on CT or MRI (in the thalamus in 5, in the caudate nucleus in 3 and in the internal capsule or corona radiata in the remaining patients). Twelve patients had multiple infarcts. Severe lesions of the white matter were found in 13 patients, mild to moderate lesions in 20 patients. Scores on Digit Span, Digit Symbol and delayed recall of the 15-Words test were significantly lower in the group with severe lesions, whilst there was a trend in the same direction for the Cognitive part of the Cambridge Examination of Mental Disorders in the Elderly, the Trailmaking B, Stroop colour interference test and the delayed visual reproduction of the Wechsler Memory Scale. These findings suggest that diffuse lesions of the white matter are an independent factor in the pathogenesis of intellectual dysfunction, also in patients with lacunar infarcts, but a truly independent analysis is difficult because the most severe involvement of the white matter tended to be associated with the largest number of lacunar infarcts.

Key words Lacunar infarct · White matter lesions · Computed tomography · Magnetic resonance imaging · Cognition

Introduction

Recently, the term "vascular dementia" has been re-introduced and defined by clear criteria [30]. It is meant to replace the previous notion of "multi-infarct dementia" proposed by Hachinski [16]. Dementia in stroke patients correlates with the number or volume of cortical infarcts, with the presence of multiple lacunar infarcts or a combination of cortical and lacunar infarcts [2, 5, 13, 26, 28, 38, 39].

It is well known that in patients with stroke CT may show not only distinct infarcts but also more diffuse lesions of the white matter [4, 6, 14, 15, 20, 21]. These lesions are also found, although in a smaller proportion, in patients with Alzheimer's disease [12, 29]. The presence of white matter lesions on CT correlates with cognitive impairment, in stroke patients as well as in those with Alzheimer's disease [9, 23, 24, 33, 34]. For white matter lesions seen on MRI, this association with cognitive impairment has been proved less convincingly, at least in elderly subjects without a history of stroke [17, 19].

One of the remaining issues in the understanding of dementia in stroke patients is whether this condition should be attributed only to tissue loss by infarction, to the accompanying white matter lesions, or both, or to co-existing degenerative dementia. The issue of distinguishing between focal necrosis of brain tissue and concomitant white matter disease as the cause of dementia is particularly rel-

evant in patients with lacunar infarcts, as these infarcts are small and as white matter disease more often co-exists with deep than with cortical infarcts. We have therefore studied a consecutive group of patients with small deep infarcts (not necessarily a lacunar syndrome), with respect to the number of infarcts, the extent of white matter lesions on MRI, and cognitive performance on neuropsychological examination.

Patients and methods

Forty-four native Dutch-speaking patients entered the study on the basis of the following criteria for lacunar infarction: a history of a so-called focal lacunar syndrome [22], or other neurological deficits in the presence of a lacunar infarct on CT, with or without hypodensity of the white matter on CT of the brain. We excluded patients with known non-vascular causes for lesions of the white matter, such as multiple sclerosis, acquired immune deficiency syndrome (AIDS), brain tumour, or hydrocephalus.

In all patients a complete clinical history was obtained and a neurological examination performed. The diastolic and systolic blood pressure of each patient was recorded at the time of admission or of the first outpatient visit. The mean age of the patients was 66, SD 8 years (range 41–82); 28 were men and 16 were women. Hypertension was present in 25 of the 44 patients. This condition had been diagnosed and treated before the beginning of the neurological symptoms in 18 patients. Three other patients were known to have hypertension, but did not take medication; in the 4 remaining patients hypertension was first diagnosed after the onset of neurological symptoms. Five of the 44 patients had diabetes mellitus (oral antiglycaemics in 4, insulin in 1 patient). Twenty-three of the 44 patients had a recent episode of acute neurological deficits, 13 patients had a previous history of a stroke, and the remaining 8 patients had non-localizing symptoms (memory problems or gait disturbance). Unilateral pyramidal signs were found in 30 patients, bilateral pyramidal signs in 3 patients; 3 patients had only brain stem signs. On direct questioning 11 patients admitted to behavioural or cognitive changes: slowness, impaired memory, loss of initiative, or decreased interest and concentration. We performed the following laboratory investigation: haematocrit, serum glucose, creatinine, and electrocardiography (ECG). Heart disease was defined as a history of angina pectoris, myocardial infarction or coronary bypass surgery, or ECG changes suggesting an infarct.

All patients underwent CT and MRI of the brain, with a 1.5 or 0.5 T Philips Gyroscan. One neurologist and one neuroradiologist assessed the CT scans for the presence of lacunar infarcts. Infarcts were distinguished by their well-defined borders from diffuse hypodensity of the white matter. Since MRI is more sensitive for detecting small lesions, we used it in our analysis of white matter lesions. Multiple slice spin-echo (SE) sequences were performed with a repetition time (TR) of 2000 ms and an echo time (TE) of 50 and 100 ms, producing a T2-weighted image. MR images were acquired in the axial plane with a slice thickness of 7 mm and a slice increment of 1.4 in all patients. Heavily T1-weighted images were produced with a TR of 1500 ms, inversion time (TI) of 500 ms and TE of 30 ms in the axial or the coronal plane in all patients. White matter abnormalities were hyperintense on T2-weighted images and hypointense on T1-weighted images. The severity of white matter lesions for all contiguous slices was graded separately for the regions anterior and posterior to the central sulcus, according to a three-point scale: grade 0, normal or only a single lesion; grade 1 or moderate, only multiple focal lesions (punctate or patchy) in the anterior and posterior region; grade 2 or severe, multiple and confluent lesions in the anterior or posterior region or scattered throughout the entire white matter [35]. The neurologist and neuroradiologist together assessed the presence and severity of these lesions; they were blinded to clinical data.

Neuropsychological test battery

Neuropsychological assessment was carried out in all patients by the same examiner. To avoid bias by a transient impairment of cognitive function in the acute stage of the stroke, all patients were assessed at least 12 weeks later. The protocol consisted of the following tests:

1. Mini-Mental State Examination (MMSE), with a score from 0 to 30. We used a cut-off score for dementia of 26, which is the age-specific norm for subjects older than 80 years (for subjects between 60 and 80 years age the cut-off score is actually 28 [3]). The Cambridge Cognitive Examination (CAMCOG), with a maximum score of 107, which is part of the Dutch version of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX-N) [10]. The currently recommended cut-off score for dementia is 79 [31].
2. Four subtests of the Groninger Intelligence Test (GIT) to define the current intelligence quotient [27].
3. Subtests Digit Symbol and Digit Span of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), Trailmaking test part A and B, and Stroop colour word test [25]. These tests measure psychomotor speed, aspects of attention and concentration and executive control functions [8]. Results on Digit Span and Digit Symbol are expressed as age-corrected scale scores; a score more than one standard deviation below the mean was considered abnormal. The colour-interference score (decile) on the Stroop test is derived from the expected time for card III, taking into account the time needed for card II. Trailmaking part A is not included in the results; the time needed for part B was expressed on a 7-point scale, based on the percentile scores corrected for age.
4. The Dutch version of the 15-Word auditory verbal learning test; the results for immediate and delayed recall are expressed in decile scores [18]. Immediate and delayed recall of the visual reproduction subtest of the Wechsler Memory Scale (WMS); scores were corrected for age and level of education [32].

Data analysis

Differences in age between the different groups were assessed by one-way analysis of variance. CAMCOG scores, Stroop and Trailmaking scores in different groups were analysed by means of the (non-parametric) Mann-Whitney test. All P values were corrected for ties. Chi-square testing was used for analysis of differences in group characteristics (hypertension, systolic and diastolic blood pressure), and for MMSE, Digit Span, Digit Symbol, verbal and visual memory tests.

Results

One or more lacunar infarcts on CT or MRI were found in 36 of the 44 patients, including all 8 patients with non-focal symptoms. Multiple infarcts were present in 12 patients. Five patients had uni- or bilateral lacunar infarcts in the thalamus, 3 patients had an infarct in the caudate nucleus, and the remaining (28) patients had one or more lacunar infarcts in the internal capsule or corona radiata.

Severe lesions of the white matter on MRI were found in 13 patients. In 11 of the remaining 31 patients, such lesions were completely absent and they were mild to moderate in 20 patients. In the severe group, 4 patients had predominantly frontal lesions, in 2 patients parieto-occip-

Table 1 Demographic and clinical characteristics of three groups of patients with small-vessel disease, according to the degree of white matter disease on MRI

	Normal white matter $n = 11$	Moderate lesions $n = 20$	Severe lesions $n = 13$
Mean age	65 ± 9	70 ± 7	62 ± 8*
Male/female	10/1	11/9	7/6
Hypertension	6 (55)	12 (60)	9 (67)
Diabetes mellitus	2 (18)	2 (10)	1 (8)
Heart disease	3 (27)	4 (20)	2 (17)
Mean blood pressure	160/95	170/95	180/100
Multiple infarcts on CT	1 (9)	5 (25)	6 (52)

*$P = 0.004$, one-way analysis of variance

ital lesions were more pronounced, and in 7 patients both regions were equally involved (in 1 patient the entire white matter was affected). Six of the 13 patients with severe lesions of the white matter had multiple infarcts, against 6 of the other 31 patients.

The mean age of patients with severe lesions (62, SD 8 years) was significantly lower than that of patients with normal white matter or only moderate lesions (68, SD 7 years, $P = 0.004$). Hypertension was present in 9 (69%) of the 13 patients with severe lesions, as opposed to 55% and 60% in the other two groups (Table 1); this was not a statistically significant difference. A diastolic blood pressure of 105 mm Hg or over occurred slightly more often in the severe group (6 of 13 patients, 46%) than in the other two groups together (11 of 31 patients, 39%). A history of diabetes mellitus or heart disease and the results of laboratory investigations did not differ between the three groups.

A MMSE score of 24 or less was found in 4 of 31 patients with normal white matter or with moderate lesions, and in 5 of the 13 patients with severe lesions. This difference was not statistically significant. One of the 4 patients with an abnormal MMSE score had multiple infarcts with normal white matter, and another had a caudate infarct. The median CAMCOG score in the group with severely affected white matter (82) was lower, although not significantly, than in the combined normal and moderate group (91).

Complete neuropsychological assessment could be performed in 11 patients with normal white matter, 19 with moderate lesions, and 11 patients with severe lesions of the white matter (Table 2). The remaining 3 patients, with low scores on the MMSE and CAMCOG, were unable to complete all neuropsychological tests; 1 patient could manage only the MMSE and CAMCOG; the 2 other patients also carried out some of the other subtests. Patients with normal or moderately affected white matter had similar levels of cognitive performance, and were analysed together. Patients in the group with severe white matter lesions had significantly lower scores on the Digit Span and Digit Symbol tests. Their score on the delayed recall of the 15-Word test was also significantly worse, whereas the delayed recognition of these items was equal in both groups. There was also a trend towards lower scores on the Trailmaking B, the Stroop interference test and on the visual reproduction of the WMS. Within the severe group the patients with the most extensive lesions performed clearly worse than the patients with confluent lesions in

Table 2 Neuropsychological test results in stroke patients according to the presence or absence of severe lesions of the white matter. All test results are expressed as median scores (with range), except the Stroop test, which is in seconds (mean, range). Differences in CAMCOG, IQ and Stroop have been compared using the non-parametric Mann-Whitney test. Chi-square for MMSE, Digit Span, Digit Symbol, Trailmaking, verbal and visual memory tests; cut-off score for Digit Span and Digit Symbol 6, cut-off score for delayed recall of verbal memory 3; cut-off score for immediate and delayed recall of visual reproduction 2

	No lesions or moderate lesions $n = 30$		Severe lesions $n = 11$		P value
Level of education	4	(1–6)	3	(1–6)	
MMSE	28	(17–30)	27	(17–30)	
≤ 26	5	(20)	6	(41)	NS
CAMCOG	91	(55–103)	82	(58–100)	NS
Intelligence (IQ)	107	(72–139)	103	(65–142)	NS
Digit Span	9	(4–14)	4	(3–13)	0.05
Digit Symbol	8	(3–12)	7	(4–12)	0.02
Trailmaking B percentiles	4	(1–6)	4	(1–6)	0.07
Stroop III interference score	59	(20–159)	84	(6–192)	NS
Verbal memory (15-WT)					
direct recall	5	(1–10)	2	(1–6)	NS
delayed recall	3	(1–10)	1	(1–6)	0.02
delayed recognition	27	(13–30)	27	(12–29)	NS
Visual memory					
direct recall	1.5	(0–4.5)	2	(0–6)	NS
delayed recall	1.5	(0–5)	2	(0–6)	NS

one region only, but these patients also had the highest number of lacunar infarcts.

Within the normal group, 1 patient with a relatively large subcortical infarct (still less than 1.5 cm) involving the caudate nucleus and 1 patient with a lacunar infarct in the thalamus had impaired performance on cognitive tests. Cognitive testing was normal in the other patients with very small lacunar infarcts in the caudate nucleus (2 patients) and with a lacunar infarct in the thalamus (2 patients).

Discussion

We found that severe lesions of the white matter on MRI were present in 13 of the 44 patients with lacunar stroke (30%), that these patients were younger than the other patients with lacunar stroke, and that they performed worse on some neuropsychological subtests than patients with normal white matter and those with only moderate lesions. The heterogeneous distribution of the severe lesions is interesting with regard to pathogenesis as well as to the effect on cognitive function, but the group was too small for meaningful subdivisions to be made.

A drawback of our study is that it is cross-sectional and that we have no information about a temporal association of changes in cognitive performance and the occurrence of lacunar infarction. Such information may help to distinguish between vascular dementia and Alzheimer's disease in patients with cognitive impairment.

Nine of the 13 patients with severe lesions of the white matter in this series had hypertension, versus 18 of the 31 patients with normal white matter or moderate lesions. In a previous case-control study, we found that patients with hypertension frequently had confluent lesions of the white matter [36]; that case-control study also showed a trend towards higher diastolic blood pressures for patients with such lesions. In other studies, lesions of the cerebral white matter were also associated with hypertension, and with a history of stroke [1].

The presence of confluent lesions of the white matter is associated with a non-significant trend towards lower scores for the MMSE and CAMCOG, and with significantly lower scores on some tests measuring attention, concentration and verbal memory. There was a remarkable dissociation between impairment of delayed recall of verbal memory and good performance on recognition of verbal items. This feature of verbal memory performance together with a trend towards lower scores in the Trail-making B and Stroop colour interference test fits a subcortical type of cognitive impairment. Within the group with severe lesions, some patients performed in the normal range, whereas others showed cognitive impairment. The confluent lesions were classified according to a simple scale and still encompassed a wide range of white matter involvement, from confluent lesions in only a single region of the brain to involvement of the entire white matter. This might explain why the patients with the most extensive lesions performed worse than patients with lesions limited to the frontal or parieto-occipital region. The extent of white matter lesions might also explain studies of elderly persons without a history of stroke, in which no significant correlation between white matter lesions and cognitive impairment was found [17, 19]. It proved difficult to separate the effects on cognitive functioning of multiple infarcts and severe lesions of the white matter, as multiple infarcts were found more often in the group with severe lesions. Other studies showed that patients with multiple lacunar infarcts had a pattern of cognitive impairment consistent with frontal lobe dysfunction, although true dementia scores were found in only 27% [2, 39]. Babikian et al. [2] introduced the term "cognitive impairment without dementia" for borderline performances in patients with multiple infarcts, but did not determine the role of chronic lesions of the white matter. Two other studies of patients with lacunar infarcts showed that the presence of dementia correlated with the presence of white matter lesions [11, 37], in addition to other factors such as enlarged ventricles and brain atrophy.

Most patients with a single infarct and normal white matter or only moderate lesions had normal neuropsychological test results, that is a MMSE and CAMCOG score in the normal range and scores above the norm on the other tests from the neuropsychological test battery. A lacunar infarct in the right caudate nucleus, found in one of our patients with poor cognitive performance, may lead to abulia, reduced activity and slowness, in keeping with the borderline performance on testing [7]. The poor test results in one patient with severe cortical atrophy might be attributed to a possible co-existing dementia of the Alzheimer type. Two other patients with normal white matter also performed in the impaired range on neuropsychological examination. Their test results could be explained by other factors, such as a possible co-existent dementia of the Alzheimer type or a low level of education.

The fundamental issue addressed by our study is whether cognitive impairment in stroke patients can be caused by diffuse lesions of the white matter, independently of the presence of multiple infarcts. Our study tends to confirm this, but we cannot be sure, since the most severe lesions of the white matter were associated with multiple infarcts and our series was too small to disentangle these two factors in a conclusive fashion. Hachinski [16] proposed in the 1970s that in patients with dementia there are two chief pathological processes: Alzheimer changes and multiple infarcts. Thanks to the increasing sensitivity of brain imaging in the last decade a third major factor in the pathogenesis of dementia has emerged in the form of diffuse lesions of the white matter [12. 14]. Future studies should have a longitudinal design to differentiate between cognitive impairment due to a co-existing degenerative process and that due to lacunar infarcts and diffuse white matter lesions.

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