Cerebral small-vessel disease : vascular risk factor profiles, clinical manifestations, and disease progression in stroke

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Cerebral small-vessel disease

Vascular risk factor profiles, clinical manifestations,
and disease progression in stroke

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Cerebral small-vessel disease: vascular risk factor profiles, clinical manifestations, and
disease progression in stroke.

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Cerebral small-vessel disease

Vascular risk factor profiles, clinical manifestations,
and disease progression in stroke

PROEFSCHRIFT

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*... the input of the science-sausage-machine is neither money nor laboratory hardware,
but human endeavour.*

Yehuda Fried and Joseph Agassi
Paranoia: a study in diagnosis (1976)

voor Maarten en mijn ouders

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General introduction

Stroke constitutes an important health care issue. Its prevalence is high, especially in the elderly: 3.5% in men older than 55 years and 1.9% in women [119]. Furthermore, stroke poses an ever increasing financial burden on society: in The Netherlands lifetime health care costs for stroke patients were estimated to be 1870 million Dutch guilders [13], and the total yearly costs of stroke (medical and productivity losses) amount to 2500 million Dutch guilders [48]. Apart from the primary morbidity of stroke, its long-term consequences may lead to substantial additional morbidity, e.g., vascular dementia [77, 83, 85, 175, 177], and vascular parkinsonism [40, 195, 196].

Up to now stroke treatment focused mainly on secondary prevention. However, the results achieved are moderate. Antiplatelet therapy results in an absolute risk reduction in non-fatal stroke of 2% (8.2% in treated patients, 10.2% in controls) in patients with a prior stroke or transient ischaemic attack at 33 months, i.e., a relative risk reduction of 23% [2]. Combination of aspirin with dipyridamole may have additional benefit [43]. The North American Carotid Surgery Trial [143] found an absolute risk reduction in ipsilateral stroke of 17% at 2 years (9% in surgical patients and 26% in controls), i.e., a relative risk reduction of 65%, in patients with a minor stroke or transient ischaemic attack with a symptomatic carotid stenosis of 70–99%. The European Carotid Surgery Trial [47] found a somewhat smaller, but still significant benefit of surgery: the absolute risk reduction was 6.6% at 3 years (10.2% in surgical patients and 16.8% in controls), i.e., a relative risk reduction of 39%. Anticoagulation-therapy in non-rheumatic atrial fibrillation in ischaemic stroke patients results in an absolute risk reduction of stroke of 8% per year (4% in treated patients and 12% in controls), i.e., a relative risk reduction of 67% per year [45]. Although these results of carotid surgery and anticoagulation-therapy in non-rheumatic atrial fibrillation are substantial, these therapies are of use in only a small proportion of patients, with a certain stroke subtype.

Stroke is not a homogeneous disease-entity. Stroke may be divided into cerebral haemorrhage and infarction. These two types can be further divided on the basis of different underlying stroke mechanisms. Cerebral haemorrhage may be secondary, e.g., to use of anticoagulants, or primary as a result of small-vessel disease. A brain infarct may result from small-vessel disease, large-vessel disease, or cardiac embolism. Risk factor profiles, symptoms and signs, pathogenesis, therapy, prognosis, and long-term sequelae differ among these stroke subtypes. The results of stroke prevention by carotid surgery and anticoagulants in non-rheumatic atrial fibrillation show that prevention in appropriate subgroups may

be highly effective. So, effective prevention of stroke depends on the pathogenesis and risk factor profiles in stroke subgroups. Knowledge of what causes a stroke in individual patients may allow intervention to be tailored more rationally.

In this study we chose to investigate several aspects of lesions presumably caused by cerebral small-vessel disease, such as small deep (lacunar) infarcts, white matter lesions (WMLs), and primary deep intracerebral haemorrhage. We aimed to investigate whether these heterogeneous lesions are homogeneous as to the type of underlying vascular disease (presumably cerebral small-vessel disease). Furthermore, possible long-term consequences of cerebral small-vessel disease were investigated, such as cerebral atrophy and vascular parkinsonism.

The specific study aims were:

1. To investigate whether primary deep intracerebral haemorrhage and small deep (lacunar) infarcts have a similar type of underlying small-vessel vasculopathy as reflected by their vascular risk factor profiles. (Chapter 2)
2. (I) To test the hypothesis that WMLs are associated with small deep (lacunar) infarcts as both are supposedly caused by small-vessel pathology, and (II) to study whether WMLs and small deep infarcts progress over time. (Chapter 3)
3. To study (I) the incidence of WMLs in first-ever ischaemic stroke patients, and (II) WMLs in relationship with vascular risk factors, symptomatic and silent infarcts, to test the hypothesis that WMLs are especially associated with multiple, usually silent small deep infarcts. (Chapter 4)
4. To test whether cerebral atrophy in stroke patients is related to presence of WMLs, stroke subtype and/or multiple brain infarcts. (Chapter 5 and 6)
5. To study (I) the prevalence of parkinsonian signs in ischaemic stroke patients, and (II) whether such signs are associated with small deep (lacunar) infarcts, WMLs, and/or territorial infarcts, to test the hypothesis that vascular parkinsonism results mainly from cerebral small-vessel disease. (Chapter 7)

1

Introduction

Stroke subtypes

Stroke is a general term for several types of vascular injuries to the brain. Firstly, stroke can be divided into cerebral haemorrhage ($\pm 15\%$) and cerebral infarction ($\pm 85\%$) [189]. Cerebral haemorrhage is either intracerebral or subarachnoidal. *Intracerebral haemorrhage* may be primary, or secondary, such as due to rupture of vascular malformations or use of anticoagulants. Primary intracerebral haemorrhage is predominantly located in the deep regions of the brain (69–88%), i.e., in the basal ganglia and thalamus, and furthermore in the brainstem, and less frequently in the cerebral lobes and in the cerebellum [33, 53, 146]. Hypertension is the only known risk factor for primary intracerebral haemorrhage, with a prevalence of about 60% [33, 53, 146, 189]. The deep regions of the brain are supplied by small deep penetrating arteries and arterioles, such as the lenticulostriate, thalamoperforating and anterior choroidal arteries [67] (*Figure 1.1*). These small arteries are branches of the large cerebral arteries (i.e., the anterior, middle and posterior cerebral artery). Functionally, the small deep perforating arteries are endarteries, although anastomoses may exist [69, 123, 157]. Pathologic studies showed that arteriolosclerosis is the underlying vasculopathy in primary intracerebral haemorrhage. Arteriolosclerosis probably leads to disruption of muscle and elastic elements in the arterial wall by deposition of lipid-rich hyaline material subintimal. Subsequently, this may lead to bulging of arterial walls (so-called Charcot-Bouchard microaneurysms) [33, 146].

Cerebral infarction is categorized according to involved vascular territory in posterior circulation infarcts (24%), anterior circulation infarcts (51%) and small deep (lacunar) infarcts (25%) [189]. Another classification using location, infarct size, clinical features, and underlying stroke mechanism, is in *territorial* and *small deep infarcts*. The cause of cerebral infarction is in 50% atherothromboembolism, in 20% embolism from the heart, in 25% intracranial small-vessel disease, and in 5% rarities such as arterial dissection, vasculitis, etc. [189]. *Territorial infarcts* (*Figure 1.2*) usually correspond with main stem or large branch occlusion of one of the major cerebral arteries, and extend into the cerebral cortex. Clinically they can be diagnosed by signs of cortical dysfunction, e.g., dysphasia or neglect. There is substantial necropsy and radiological support that such infarcts result from occlusion of the proximal stem of the middle or anterior cerebral artery, either by embolism or by spread of thrombus into the vessel from a more proximal occlusion. Carotid stenosis as a result of atherosclerosis may be the cause of territorial infarcts either by being a source of embolism, or by spread of thrombus into the middle or anterior cerebral artery [9, 17, 107, 142]. Another frequent source of cerebral emboli is the heart. For instance dysrhythmias, e.g., atrial fibrillation, and prosthetic heart valves, may lead to large numbers of emboli [9, 17, 62, 114, 142, 185].

Small deep (lacunar) infarcts are small infarcts in the basal ganglia, thalamus, internal capsule, or the pons (*Figure 1.2*). Compared with those with a territorial infarct, patients with a small deep infarct have a higher survival rate and less disability [19, 107].

Figure 1.1: Plastic cast (magnification 11 $\times$) showing perforating branches (black and white arrowheads) arising from the middle cerebral artery (MCA). White arrow indicates division of MCA. (From Marinkovic et al. [124].)

Hypertension is the most important vascular risk factor associated with small deep infarcts [58, 114, 127]. However, hypertension is not a stronger risk factor for small deep than for other cerebral infarcts. Just like primary intracerebral haemorrhage, small deep (lacunar) infarcts are thought to be caused by a disease of the small penetrating arteries and arterioles in the deep regions of the brain [59]. Pathological evidence points at two distinct small-vessel diseases. Arteriolosclerosis may be the cause of multiple, usually silent small deep infarcts, whereas the somewhat larger, symptomatic ones are caused by microatheromatosis [34, 58]. On clinical grounds one might argue that two distinct small deep infarct entities exist, reflecting these two types of small-vessel disease. Recently, Boiten and Lodder [20] found that multiple, usually silent small deep infarcts differed in location (more often in the anterior limb of the internal capsule and in the caudate nucleus, less often in the posterior limb of the internal capsule), involved vascular territory (more often in the lateral and medial striate arteries territory, less often in the anterior choroidal artery territory), and volume (smaller) from symptomatic lacunar infarcts. Hypertension was more frequent in patients with silent small deep infarcts (71%), than in those with a single symptomatic lacunar stroke (43%). These findings were confirmed by Mast et al. [127], who found multiple small deep infarcts, but not single ones, to be associated with

Figure 1.2: Computed tomographic scans of the two subtypes of cerebral infarction: (left) a territorial infarct in the posterior part of the area supplied by the left middle cerebral artery, (right) a small deep infarct in the anterior limb of the right internal capsule.

hypertension and diabetes mellitus. Furthermore, cerebral blood flow in the cerebral cortex was found to be significantly lower in patients with multiple small deep infarcts than in those with a single small deep infarct [133]. These studies suggest that there are indeed two distinct entities: multiple (silent) small deep infarcts probably caused by arteriolosclerosis, and the (larger) symptomatic ones due to microatheromatosis. Moreover, hypertension is probably a more important risk factor in arteriolosclerosis than in microatheromatosis.

Another presumably ischaemic type of cerebral lesion is leukoaraiosis, also termed *white matter lesions* (WMLs) (*Figure 1.3*). Hachinski et al. [78] introduced the term leukoaraiosis to describe periventricular diffuse white matter hypodensities on computed tomography (CT). WMLs were defined as focal or diffuse hypodensities in the periventricular or deep white matter (centrum semiovale), not involving the cortex, and with ill-defined margins to distinguish them from infarction [168]. WMLs were originally attributed to subcortical arteriosclerotic encephalopathy or Binswanger's disease [36, 90, 100, 117, 118, 156], but were also described in the general population [30, 49, 52, 113, 193], in patients with

hypertension [186], in stroke patients [81, 87, 91, 96, 99], and in patients with dementia [12, 31, 32, 105, 111, 154, 169]. Previous studies found WMLs to be related to various vascular risk factors: higher age [4, 30, 32, 37, 81, 87, 96, 113, 122, 171, 193], hypertension [4, 30, 32, 112, 122], use of diuretics [32], history of heart disease [30, 113], diabetes mellitus [193], and hypoxia [37]. WMLs have been associated with mental impairment and dementia [72, 94, 100, 169, 182], and with multiple neurological deficits, such as gait and balance disorders, pseudobulbar state, and incontinence [6, 8, 12, 94, 126, 149, 168, 169, 179, 196]. Although sometimes a mixture of pathologic changes are found in WMLs, many authors hold arteriolosclerosis as the primary factor in WMLs [3, 7, 28, 31, 162, 187]. However, contrary to primary intracerebral haemorrhage and small deep infarcts, WMLs are not located in the vascular territories of the small deep penetrating arteries and arterioles. The centrum semiovale, where WMLs are found, is supplied by long medullary arteries arising from the leptomeningeal plexus, which in turn arises from cerebral surface branches of the anterior, middle, and posterior cerebral arteries [64, 140]. In the white matter the capillary density is smaller than in the basal ganglia [135]. Anastomotic channels between these medullary arteries in the cortex and white matter may exist [140].

Cerebral small-vessel disease

So, cerebral small-vessel disease may express itself in different ways: (1) as primary deep intracerebral haemorrhage, (2) as small deep (lacunar) infarct, (3) as WMLs (*Table 1.1*). In primary intracerebral haemorrhage, multiple silent small deep infarcts and WMLs neuropathologic studies, which are strikingly scarce, have found arteriolosclerosis as the underlying vasculopathy [31, 53, 60, 64, 66, 187]. Arteriolosclerosis consists of patchy deposition of hyaline and lipid material, often beneath the endothelium, but sometimes more peripherally: the hyaline change gradually extends to involve the whole circumference, and when severe it replaces the normal structures of the wall apart from the endothelium, resulting in considerable narrowing of the arteriolar lumen [1]. Hyaline is a descriptive term, and is defined as any material that shows a reddish, homogenous appearance when stained with haematoxylin and eosin [194]. The nature of the arteriolosclerosis is not fully understood: initially, the hyaline material resembles fibrin in its staining properties, but later it stains like collagen [194]. Many different terms have been used in the past to describe this small-vessel disease, e.g., lipohyalinosis, fibrohyalinosis, and arteriolar hyalinosis [194]. In this thesis we chose to use "arteriolosclerosis" to describe this small-vessel disease, because it is a general term which encompasses all pathological findings in this vasculopathy, such as lipid and fibrin depositions. Arteriolosclerosis is found in hypertensive subjects and patients with diabetes mellitus, but is also seen especially in old age. Besides in the brain, it is found in the kidneys and in several other internal organs.

Apart from arteriolosclerosis, small deep infarcts may also be caused by microatheromatosis, in which a microatheroma occludes the small artery [34, 58]. The lesions of

Figure 1.3: Computed tomographic scans of different sites of white matter lesions: (left) around the frontal and occipital horns, (right) around the frontal and occipital horns and in the centrum semiovale.

atheroma consist of patches (“plaques”) of intimal thickening of the arterial walls, due mainly to deposition of lipids and formation of fibrous tissue [1]. This may result in progressive narrowing of the lumen or sudden occlusion by the formation of a thrombus on an atheromatous plaque. In sparse pathologic reports [34, 58] three possible sites of microatheromatosis have been described leading to small deep infarcts. Firstly, an atheromatous plaque in a large cerebral artery may obstruct the orifice of a deep perforating branch. Secondly, a plaque in a large cerebral artery may extend into a deep perforating branch. Furthermore, a microatheroma may originate in the orifice of a deep perforating branch. Risk factors for atheromatous changes of blood vessels are higher age, male gender, hypertension, diabetes mellitus, hyperlipidaemia, high plasma fibrinogen level and cigarette smoking [189].

Table 1.1: Affected arteries and arterioles in all types of lesions probably caused by the two types cerebral small-vessel disease.

Type of lesion	Type of small-vessel disease	Affected arteries/arterioles
Small deep infarcts:		
single symptomatic	microatheromatosis	small deep penetrating
multiple, usually silent	arteriolosclerosis	small deep penetrating
Primary intracerebral haemorrhage	arteriolosclerosis	small deep penetrating
White matter lesions	arteriolosclerosis	long medullary

Cerebral small-vessel disease and hypertension

Primary intracerebral haemorrhage, small deep (lacunar) infarcts, and WMLs are all associated with hypertension [4, 30, 32, 33, 53, 58, 112, 122, 146, 151]. However, the association between hypertension and WMLs was predominantly established in population-based studies [30, 112, 122], whereas in a stroke population this association could not be confirmed [96]. It is unclear why a substantial number of primary intracerebral haemorrhage as well as lacunar stroke patients are not hypertensive [11, 17, 33, 35, 114, 134]. So, although primary intracerebral haemorrhage, small deep infarct and WMLs all seem to result from small-vessel disease, the contribution of hypertension to the pathogenesis of each of these lesions is not clear and their vascular risk factor profiles differ.

Co-existence of the various clinical manifestations of small-vessel disease

Regarding their assumed common pathogenesis, co-existence of primary intracerebral haemorrhage, small deep infarct and/or WMLs might be expected in patients. Indeed, WMLs are often found in lacunar stroke [32, 87, 193] and in primary intracerebral haemorrhage patients [87]. Recurrent stroke following lacunar stroke is mostly ischaemic [19, 84], and in a minority haemorrhagic. Recently, intracerebral haemorrhage was found to be more frequent following lacunar stroke, than following territorial stroke [22]. Whether patients with a primary intracerebral haemorrhage often have multiple (silent) small deep infarcts has not been studied. If primary intracerebral haemorrhage was associated with multiple small deep infarcts, this would be yet another argument in favour of the concept that multiple, usually silent small deep infarcts are due to arteriolosclerosis.

Two distinct types of small-vessel disease

As described above, pathological evidence of two different types of vasculopathy underlying small deep infarcts (arteriolosclerosis in multiple, usually silent small deep infarcts and microatheromatosis in the larger, symptomatic ones), is scarce. Due to the low case fatality rate in patients with lacunar stroke, pathologic data are difficult to collect. Multiple small deep infarcts, WMLs, and larger symptomatic small deep infarcts may have different risk

factor profiles [20, 127]. Therefore, comparing the frequency of several vascular risk factors between patients with these different lesions may, although indirectly, point at the nature of the underlying small-vessel disease. Because more pathological studies have been done in primary intracerebral haemorrhage patients, arteriosclerosis underlying this type of stroke is well established. Therefore, comparing vascular risk factor profiles in lacunar stroke and primary intracerebral haemorrhage patients could produce indirect clues as to similarity or difference in vascular pathology. Knowledge of the pathogenesis and risk factor profiles of all lesions caused by cerebral small-vessel disease could be of benefit in the prevention of these lesions, e.g., by more diligent treatment of the risk factors, and aid in the prevention of long-term sequelae.

Long-term sequelae of cerebral small-vessel disease

Apart from immediate physical disability, stroke may have long-term consequences such as cognitive decline, psychiatric sequelae (e.g., depression), post-stroke epilepsy, and parkinsonism. Such long-term stroke consequences may relate not only to the degree of cerebral tissue loss due to the symptomatic vascular lesion, but also to generalised tissue loss manifested as cerebral atrophy. Some found cerebral atrophy related to symptomatic stroke [122, 147], and to multiple cerebral infarcts on neuroimaging [98]. Cerebral atrophy may be related to cognitive impairment [29, 71, 98, 115, 150, 176]. In stroke patients cerebral atrophy could also relate to the type of presumed vasculopathy underlying the stroke, such as small- or large-vessel disease, or cardiac embolism, but this has not been investigated so far.

Another possible long-term consequence of stroke may be the development of parkinsonian features. The concept of vascular parkinsonism is still a matter of debate. Neuroimaging studies in selected parkinsonian patients found vascular lesions, mainly small deep infarcts and WMLs, to be related to certain parkinsonian features, especially lower body parkinsonism [61], lack of resting tremor [88], marked gait difficulty [8, 126, 168], and L-dopa unresponsiveness [61]. However, in stroke patients vascular parkinsonism has hardly been investigated. If one could show that the proposed clinical signs of vascular parkinsonism would be related to (an increase of) especially small deep infarcts, WMLs, or both, this would strengthen the concept of vascular parkinsonism. Studying parkinsonism in stroke patients, e.g., the incidence of parkinsonian signs in stroke patients, and specific contributing factors to the development of these signs, could be relevant when aiming to improve functional outcome in stroke survivors. Furthermore, recognizing a vascular cause of parkinsonian features may influence the choice of therapy in parkinsonian patients.

2

Different vascular risk factor profiles in primary intracerebral haemorrhage and lacunar stroke do suggest similar type of underlying small-vessel dis

Adapted from:

Van Zagten M, Lodder J, Franke C, Heuts-Van Raak L, Claassens C, Kessels F. Di vascular risk factor profiles in primary intracerebral haemorrhage and small deep in do not suggest similar types of underlying small vessel disease. *Cerebrovasc Dis* 1994; 124.

Abstract

Objectives: To investigate vascular risk factor profiles in patients with primary intracerebral haemorrhage (PICH), lacunar, or territorial stroke, assuming that such profiles may be indicative of the nature of the underlying vasculopathy.

Design: Survey comparing vascular risk factors of prospectively registered stroke patients.

Setting: Primary and referral care centres.

Patients: Eighty-three patients with a supratentorial PICH, 241 with a lacunar, and 430 with a territorial stroke were registered.

Results: Multivariate logistic regression analysis showed that a history of ischaemic heart disease and diabetes mellitus were less strongly associated with PICH than with ischaemic stroke of either type. Hypertension did not emerge as an independent variable associated with stroke subtype.

Conclusions: These differences in vascular risk factors do not support the idea of a similar nature of the underlying small-vessel disease in PICH and the majority of lacunar strokes.

Introduction

Small deep, often called "lacunar" infarcts usually result from local obstruction of a small penetrating artery [11]. At autopsy on a limited number of cases Fisher found small-vessel atheromatosis in symptomatic small deep infarcts, and arteriolosclerosis in cases with multiple, mostly silent small deep infarcts [58]. A stroke subtype that also occurs as a result of small penetrating artery pathology is primary intracerebral haemorrhage (PICH), in which arteriolosclerosis is the most prevalent vasculopathy [53, 60]. Differences in type of underlying small-vessel pathology between PICH, and lacunar stroke may be reflected by differences in vascular risk factor profile. Knowledge about the nature of the small-vessel affliction in small deep infarcts is limited. Therefore, comparing the frequency of several vascular risk factors between patients with these different stroke subtypes may, although indirectly, provide information about the nature of the small-vessel disease in lacunar stroke; if vascular risk factor profiles in patients with lacunar stroke and PICH would be similar, arteriolosclerosis might be the most prevalent vasculopathy in lacunar stroke as it is in PICH.

Patients and methods

Patients with a supratentorially located PICH in the region of the basal ganglia were prospectively registered at the De Wever Hospital Heerlen and the University Hospital Utrecht. All patients, admitted or visiting the out-patient clinic, with a first-ever supratentorial brain infarct with symptoms lasting longer than 24 hours were registered in a prospective registry at the University Hospital Maastricht. Routine investigations included standard blood tests, electrocardiogram, chest X-ray (in 60% of PICH), CT scan of the brain, and noninvasive carotid studies in the infarct patients. Echocardiography, 24-hour ECG monitoring, and cerebral angiography were done in selected cases.

Definitions

The following *vascular risk factors* were recorded: age, gender, hypertension (known hypertension, or at least 2 separate blood pressure recordings of higher than 160/90 mmHg before or at least 1 week after stroke), diabetes mellitus (known diabetes mellitus, or fasting serumglucose higher than 7 mmol/l, or a postprandial serumglucose higher than 11 mmol/l, both on at least 2 separate occasions), hypercholesterolemia (known hypercholesterolemia, or serumcholesterol higher than 6.4 mmol/l), history of ischaemic heart disease (myocardial infarction, angina pectoris), cardiac source of embolism (atrial fibrillation, mitral stenosis, prosthetic aortic or mitral valve, recent myocardial infarction (within 6 weeks preceding stroke), endocarditis, cardiomyopathy, left ventricular aneurysm, intra-ventricular thrombus), and significant (more than 50%) carotid stenosis ipsilateral to the

symptomatic stroke.

Primary intracerebral haemorrhage was defined as a primary supratentorially located haemorrhage in the region of the basal ganglia. Patients with secondary intracerebral haemorrhage, such as those using anticoagulants, those in whom subarachnoid haemorrhage was suspected to be the primary underlying cause, and those with lobar haematoma involving the cortex most likely to be associated with amyloid angiopathy or vascular malformation, were excluded.

Lacunar stroke was defined (1) as an acute stroke syndrome with a CT lesion compatible with occlusion of a single perforating artery, i.e., a small, subcortical, sharply margined hypodense lesion with a diameter smaller than 20 mm (small deep infarct), or (2) as a specific lacunar syndrome (i.e., unilateral motor and/or sensory symptoms and signs that completely involve at least 2 of 3 body parts (face, arm, and leg) without disturbance of consciousness or language, visual field defect, or other signs of cortical dysfunction) when the CT scan showed no specific lesion.

Territorial stroke was defined (1) as an acute stroke syndrome with CT findings compatible with infarction involving the cortex, or (2) when no specific lesion was visible on CT, as a clinically identified cortical syndrome consisting of unilateral motor and/or sensory symptoms and signs in combination with signs of cortical dysfunction with or without visual field defect, or as isolated monoparesis [16], or as isolated cortical dysfunction (usually dysphasia). Patients with a large subcortical infarct were included in the territorial stroke group because of similar pathogenesis [18, 21].

Patient population

Eighty-three patients with a PICH were registered. PICH was confirmed by CT in 82 patients, and by autopsy in 1. Furthermore, we registered 247 lacunar and 457 territorial stroke patients, of whom 241 and 430, respectively, had CT and entered the study.

Statistical analysis

Bivariate statistical analysis with crude odds ratios ((c)OR) with 95% confidence intervals (CI) and subsequent multivariate logistic regression analysis with adjusted odds ratios ((a)OR) with 95% CI determined the association of vascular risk factors with stroke subtype as dependent variable. The patients were categorized into 3 age groups: 65 years or younger, between 66 and 75 years, and older than 75 years.

Results

Table 2.1 shows the baseline characteristics of the three stroke groups. Median age was 69 (range: 42–89) years in PICH-patients, 68 (range: 26–93) years in lacunar stroke patients, and 73 (range: 24–96) years in territorial stroke patients. Patients with territorial stroke

were significantly older than the other stroke patients (χ^2 -test: vs. lacunar stroke $p=0.0001$; vs. PICH $p=0.02$).

Table 2.1: Baseline characteristics of patients with primary intracerebral haemorrhage, lacunar stroke, and territorial stroke.

Baseline characteristics	PICH N=83	Lacunar stroke N=241	Territorial stroke N=430
Male gender	44 (53)	131 (54)	220 (51)
Age (years) ≤ 65	34 (41)	89 (37)	110 (26)
66–75	21 (25)	91 (38)	144 (33)
> 75	28 (34)	61 (25)	176 (41)
Hypertension	36 (43)	110 (46)	184 (43)
Diabetes mellitus	6 (7)	47 (20)	72 (17)
Ischaemic heart disease	2 (2)	46 (19)	122 (28)
Cardiac source of embolism	8 (10)	32 (13)	156 (36)

PICH = Primary intracerebral haemorrhage.

Percentages between parentheses.

Table 2.2 and Figure 2.1 show the crude and adjusted odds ratios with 95% confidence intervals of clinical variables comparing patients with PICH with those with lacunar or territorial stroke. Ischaemic heart disease was less strongly associated with PICH than with ischaemic stroke of either type (PICH vs. lacunar stroke: (a)OR 0.1, 95% CI 0.03–0.5; PICH vs. territorial stroke: (a)OR 0.1, 95% CI 0.02–0.3). The probability of having diabetes mellitus was significantly smaller in patients with PICH than with both types of ischaemic stroke (PICH vs. lacunar stroke: (a)OR 0.3, 95% CI 0.1–0.9; PICH vs. territorial stroke: (a)OR 0.4, 95% CI 0.2–1.0). A cardiac source of embolism was equally present in patients with PICH and with lacunar stroke, but significantly less frequent when PICH patients were compared with territorial stroke patients ((a)OR 0.2, 95% CI 0.1–0.4). Increasing age did not emerge as an independent variable associated with a specific stroke subtype. This was also the case with hypertension, the most frequent vascular risk factor in all three subgroups.

Discussion

Our study is not population-based, and may therefore suffer bias. Patients with deeply located brain haemorrhage may be the least liable to admission bias, whereas especially patients with a lacunar stroke may have been under-represented in our study because of lesser deficit in such patients. However, the Maastricht University Hospital, also serving as primary care facility, is the only hospital in our referral area. Furthermore, ambulant

Table 2.2: Crude and adjusted odds ratios with 95% confidence intervals of clinical variables comparing patients with primary intracerebral haemorrhage with those with lacunar or territorial stroke.

Vascular risk factors		PICH vs. Lacunar stroke				PICH vs. Territorial stroke			
		(c)OR	95% CI	(a)OR	95% CI	(c)OR	95% CI	(a)OR	95% CI
Age (yrs)	66–75 vs. ≤ 65	0.6	0.3–1.1	0.6	0.3–1.2	0.5	0.3–0.9	0.6	0.3–1.2
	> 75 vs. ≤ 65	1.2	0.7–2.2	1.3	0.7–2.4	0.5	0.3–0.9	0.8	0.4–1.5
Male gender		1.0	0.2–5.8	0.9	0.5–1.5	1.1	0.5–2.3	0.8	0.5–1.4
Hypertension		0.9	0.4–2.1	0.9	0.5–1.5	1.1	0.5–2.5	1.1	0.7–1.8
Diabetes mellitus		0.3	0.1–0.8	0.3	0.1–0.9	0.4	0.2–1.0	0.4	0.2–1.0
Ischaemic heart disease		0.1	0.03–0.4	0.1	0.03–0.5	0.1	0.02–0.2	0.1	0.02–0.3
Cardiac source of embolism		0.7	0.2–2.0	1.0	0.4–2.6	0.2	0.1–0.4	0.2	0.1–0.4

PICH = Primary intracerebral haemorrhage. CI = Confidence interval.

(c)OR = Crude odds ratio. (a)OR = Adjusted odds ratio.

patients visiting the out-patient clinic were also included, whereas the relative frequency of different infarct subgroups and the distribution of vascular risk factors among these subgroups were similar when compared with a population-based series [114]. Therefore, any referral bias in our study is likely to be small.

Because post-stroke-detected hypertension was included as vascular risk factor, higher initial case fatality in PICH might have biased towards a lower detection of this feature in this subgroup compared with infarct cases. However, the lower proportion of hypertensive PICH patients who died within the first week compared with those surviving, respectively 11/31 versus 25/52 (OR 0.59, 95% CI 0.19–1.87), and the fact that in less than 4% of infarct patients hypertension was detected after stroke does not argue in favour of such bias.

Earlier we found no difference in the frequency of hypertension between lacunar, and territorial stroke patients without a potential cardio-embolic stroke source [17, 114]. Now we found a similar frequency in patients with a deeply located PICH. Hypertension may be an equally important risk factor in lacunar stroke as in PICH. From pathological, clinical, and epidemiological studies hypertension emerged as the most strongly PICH-related risk factor [33, 53, 146]. In the Hisayama epidemiological study hypertension appeared to be the only risk factor associated with PICH in a multiple regression analysis [173]. Mohr et al. [134] found hypertension, defined as a blood pressure $\geq 160/100$ mmHg, equally often in PICH as in lacunar stroke, but less frequently in patients with “large artery thrombosis”. The higher diastolic blood pressure cut-off point in that study may explain the difference with our findings. The similar frequency of hypertension in PICH and lacunar stroke patients suggests that the underlying small-vessel disease may also be similar. However, we

Figure 2.1: Crude and adjusted odds ratios with 95% confidence intervals of clinical variables comparing patients with primary intracerebral haemorrhage (PICH) with those with lacunar or territorial stroke.

cannot rule out the possibility that PICH is related to higher blood pressure levels, hypertension of longer duration, or both. More severe hypertension may lead to arteriolosclerosis rather than atheromatosis of the small vessels [20].

It is unclear why a substantial number of PICH as well as lacunar stroke patients are not hypertensive [11, 17, 33, 35, 114, 134]. Diabetes may be involved in the development of the small-vessel disease that leads to PICH. However, we found diabetes significantly less frequent in PICH than in the lacunar and territorial stroke patients. Gross et al. [74] also found only 1 diabetic patient among 21 with PICH, whereas several stroke registries found diabetes mellitus also less prevalent in PICH than in brain infarction [14, 62, 134, 164]. Therefore, our data and those of others do not suggest that diabetes mellitus is an essential factor in the small-vessel vasculopathy underlying PICH. The similar frequency of diabetes in lacunar and territorial stroke may reflect similar type of vasculopathy, which is most likely atheromatosis [17, 114]. Similar reasoning may apply to a history of ischaemic heart disease.

Comparison of risk factor profiles in our study lends support to the assumption that, although both PICH and symptomatic lacunar infarcts result from a cerebral small-vessel vasculopathy, the nature of this vasculopathy may differ between these stroke subtypes. In

PICH arteriolosclerosis is the most prevalent vasculopathy [53, 60]. However, pathological evidence, although scarce, points at atheromatosis as the cause of symptomatic small deep infarcts, whereas multiple, mostly silent small deep infarcts are caused by arteriolosclerosis [34, 58].

Of course one should realize that these inferences from our indirect clinical approach may not necessarily be true, and that definite confirmation awaits neuropathological data. It would be interesting to see how often stroke recurrences after lacunar stroke are PICH. If the number is low, this would support the notion of different types of underlying small-vessel pathology. Recurrent stroke following lacunar stroke is mostly ischaemic [19, 84], and in a minority haemorrhagic. However, intracerebral haemorrhage was found to be more frequent following lacunar stroke, than following territorial stroke [22].

Measuring the mere presence or absence of hypertension may be insufficient to detect all different stroke-related phenomena caused by hypertension. Duration and severity of hypertension, blood pressure variations, effects of treatment, concomitant hypertensive end-organ damage, etc. may be relevant in this respect. Prospective studies in hypertensive patients could provide more insight into the question whether different types of hypertension eventually result in different stroke subtypes related to different types of cerebral small-vessel disease.

3

Significant progression of white matter lesions and small deep (lacunar) infarcts in stroke patients

Adapted from:

Van Zagten M, Boiten J, Kessels F, Lodder J. Significant progression of white matter lesions and small deep (lacunar) infarcts in patients with stroke. *Arch Neurol* 1996;53:650-655.

Abstract

Objectives: To investigate whether the extent of white matter lesions (WMLs) and the number of small deep and territorial infarcts progress over time in stroke patients and to test the hypothesis that WMLs are associated with small deep infarcts.

Design: Computed tomographic (CT) follow-up study in a cohort of 107 ischaemic stroke patients (median follow-up 3.0 years).

Setting: Primary and referral care centre.

Patients: Sixty-three of 144 registered patients with a first-ever symptomatic lacunar stroke and 44 of 155 with a territorial stroke entered this study. Forty-seven (33%) of the non-participating patients with a lacunar stroke and 54 (35%) of those with a territorial stroke died, and 34 (24%) and 57 (37%), respectively, refused CT follow-up.

Main outcome measures: The extent of the WMLs and the number of small deep and territorial infarcts on CT scans at study entry and at follow-up.

Results: Progression of WMLs occurred in 26 patients (26%), and multivariate regression analysis showed that it was associated with symptomatic lacunar stroke at study entry, silent small deep infarcts at study entry, old age and longer follow-up. We found progression of small deep infarcts in 41 patients (38%). The progression was associated with symptomatic lacunar stroke at study entry and longer follow-up. Progression of both WMLs and small deep infarcts, which occurred in 16 patients (16%), was related to symptomatic lacunar stroke at study entry, silent small deep infarcts at study entry and longer follow-up. The number of territorial infarcts increased in 14 patients (13%). The increase was associated with symptomatic territorial stroke at study entry and a history of ischaemic heart disease.

Conclusions: The marked progression of WMLs and small deep infarcts that occurred mainly in lacunar stroke patients suggests that both WMLs and small deep (lacunar) infarcts are caused by a similar vasculopathy that affects small vessels, which is progressive despite standard stroke treatment.

Introduction

Since the introduction of computed tomography (CT), periventricular white matter lesions (WMLs), often called leukoaraiosis [78] have attracted much attention. They are commonly found in patients with dementia, both in those with vascular dementia and in those with Alzheimer disease, but also in normal subjects and in patients with other risk factors [4, 15, 26, 30, 31, 36, 50, 63, 66, 87, 90, 100, 154, 160]. WMLs are associated with small deep (lacunar) infarcts, especially with deep intracerebral haemorrhage [15, 20, 32, 87], and it is thought that small deep infarcts are caused by a similar vasculopathy.

Whether the extent of WMLs and the number of small deep infarcts progress over time is unknown, because brain imaging follow-up studies have not been performed. We report the results of a prospective CT follow-up study in patients with a first-ever brain infarct. The aim of this study was to answer the question whether WMLs and the number of small deep and territorial infarcts are associated. There is an association between either of these infarct subtypes and progression of WMLs. Do they progress more markedly in lacunar rather than in territorial infarcts? Can vascular risk factors predict progression of WMLs?

Patients and methods

Patients were registered at the University Hospital of Maastricht from June 1992 in a prospective registry of all patients, admitted to the neurology clinic, with a first-ever supratentorial brain infarct within 24 hours. Routine investigations included standard blood tests, chest X-ray, CT scan of the brain, and noninvasive carotid studies. ECG monitoring, and cerebral angiography were done in selected patients.

Definitions

The following *vascular risk factors* were recorded: age, gender, hypertension (systolic blood pressure ≥ 160 mmHg, or diastolic blood pressure ≥ 95 mmHg, or at least 2 separate blood pressure recordings of $\geq 160/95$ mmHg, or at least 1 week after stroke), diabetes mellitus (known diabetes, or serumglucose higher than 7 mmol/l, or a postprandial serumglucose higher than 11 mmol/l, or both on at least 2 separate occasions), hypercholesterolemia (known hypercholesterolemia, or serumcholesterol higher than 6.4 mmol/l), history of ischaemic heart disease (myocardial infarction, angina pectoris), history of chronic obstructive pulmonary disease (smoking, cardiac source of embolism (atrial fibrillation, mitral valve disease), recent myocardial infarction (within 6 weeks), cardiomyopathy, left ventricular aneurysm, intraventricular haemorrhage).

(more than 50%) carotid stenosis ipsilateral to the symptomatic stroke.

Lacunar stroke was defined (1) as an acute stroke syndrome with a CT lesion compatible with occlusion of a single perforating artery, i.e., a small, subcortical, sharply margined hypodense lesion with a diameter smaller than 20 mm (small deep infarct), or (2) as a specific lacunar syndrome (i.e., unilateral motor and/or sensory symptoms and signs that completely involve at least 2 of 3 body parts (face, arm, and leg) without disturbance of consciousness or language, visual field defect, or other signs of cortical dysfunction) when the CT scan showed no specific lesion.

Territorial stroke was defined (1) as an acute stroke syndrome with CT findings compatible with infarction involving the cortex, or (2) when no specific lesion was visible on CT, as a clinically identified cortical syndrome consisting of unilateral motor and/or sensory symptoms and signs in combination with signs of cortical dysfunction with or without visual field defect, or as incomplete involvement of 2 body parts, or as isolated monoparesis [16], or as isolated cortical dysfunction (usually dysphasia). Patients with a large subcortical infarct were included in the territorial stroke group because of similar pathogenesis [18, 21]. In the study, we included patients with lacunar stroke, presumably due to small-vessel occlusion, and patients with territorial stroke, presumably due to large-vessel atherosclerosis. Patients with a cardiac source of embolism or a specific stroke cause such as vasculitis or arterial dissection were not included.

Silent brain infarct was defined as a low-density area on CT compatible with infarction but without a history of stroke, as taken from the patient's history, from family, or any other accessible information. Also, the stroke symptoms at study entry had to be anatomically incompatible with this infarct. Old infarcts can usually be distinguished from new ones because they are more hypodense, and there may be signs of surrounding tissue loss, like retraction of brain structures towards the infarct. Silent infarcts were also categorized as small deep or territorial.

Progression of small deep or territorial infarcts was defined as new symptomatic or silent infarcts visible on the CT at follow-up, which were not visible on the CT at study entry.

White matter lesions were defined as focal or diffuse hypodensities in the periventricular or deep white matter, not involving the cortex, and with ill-defined margins to distinguish them from infarction [168]. The presence of WMLs around frontal or occipital horns or in the centrum semiovale was noted separately. No effort was made to quantify the degree of white matter density in these different sites, as this might depend on the tuning of the CT scan. Patients were said to have *WML progression* when the CT at study entry showed no WMLs, whereas the CT at follow-up did show WMLs, or when patients who had WMLs at study entry had new WMLs in other areas on the CT at follow-up.

Patient population

Sixty-three of 144 consecutively registered patients with a symptomatic lacunar and 44 of 155 with a symptomatic territorial stroke entered this follow-up study. Of the remaining patients, 47 (33%) with a lacunar stroke and 54 (35%) with a territorial stroke had died, and 34 (24%) and 57 (37%), respectively, refused follow-up CT, mainly because they were unable to visit the out-patient clinic owing to severe disablement. *Table 3.1* shows baseline characteristics of those registered patients who did not enter this follow-up study and were still alive at time of follow-up. The patients who did not participate were older and had a higher Rankin (handicap) score than patients participating in the follow-up study. The median follow-up for all study patients was 3.0 (range: 1.2–4.7) years: 2.8 (range: 1.2–4.3) years for those with a lacunar stroke and 3.2 (range: 1.7–4.7) years for those with a territorial stroke. All patients underwent CT at study entry and at follow-up. The median time between CT at study entry and at follow-up was 2.9 (range: 1.1–4.7) years: 2.8 (range: 1.2–4.3) years for patients with a lacunar stroke and 2.9 (range: 1.1–4.7) years for patients with a territorial stroke. The CT scans obtained at study entry and at follow-up were mixed together and then reviewed for the presence and extensiveness of WMLs and for the number of small deep and territorial infarcts by 2 neurologists who were blind to the patients' identity and the timing of the CT. Only those WMLs and infarcts on which both investigators agreed were registered. A third investigator analyzed whether the extensiveness of WMLs and/or the number of infarcts had changed during follow-up.

Table 3.1: Baseline characteristics of lacunar and territorial stroke patients, not entering this follow-up study and alive at time of follow-up.

Baseline characteristics	Lacunar stroke N=34	Territorial stroke N=57
Male gender	13 (38)	34 (60)
Age (years) ≤ 60	4 (12)	18 (32)
61–67	7 (21)	7 (12)
> 67	23 (68)	32 (56)
Hypertension	17 (50)	27 (47)
Diabetes mellitus	5 (15)	7 (12)
Hypercholesterolemia	3 (9)	16 (28)
Ischaemic heart disease	5 (15)	16 (28)
COPD	3 (9)	3 (5)
Smoking	8 (24)	28 (49)
Carotid stenosis	2 (6)	13 (23)
Rankin 3 months = 4 or 5	4 (12)	12 (21)

COPD = Chronic obstructive pulmonary disease.

Percentages between parentheses.

Statistical analysis

We related changes in CT parameters to clinical variables by means of bivariate statistical analysis with crude odds ratios ((c)OR) with 95% confidence intervals (CI). Multivariate logistic regression analysis with adjusted odds ratios ((a)OR) determined the association of the clinical variables with 4 dependent variables: (1) progression of WMLs, (2) increased number of small deep infarcts, (3) progression of territorial infarcts, and (4) progression of both WMLs and small deep infarcts. Besides the vascular risk factors, the following clinical variables were included in various regression models: stroke subtype, presence of WMLs, silent small deep or territorial infarcts at study entry, Rankin (handicap) score at 3 months after stroke and at follow-up, and duration of follow-up. The Rankin scores were divided into 2 groups: functionally independent (Rankin ≤ 3) or dependent (Rankin = 4 or 5). Patients were categorized into 3 age groups: 60 years or younger, 61 to 67 years, and older than 67 years. The duration of follow-up was divided into 4 categories: less than 900 days, 900 to 1200 days, 1200 to 1400 days, and 1400 days or more. For all dependent variables, the 2 “higher-age” categories and the 3 “longer-duration of follow-up” categories were compared with the youngest age and shortest follow-up categories, respectively.

Results

Table 3.2 shows the baseline characteristics of the lacunar and territorial stroke patients, who participated in this study. The median age was 58 (range: 30–85) years: 58 (range: 30–85) years in lacunar and 60 (range: 37–82) years in territorial stroke patients. The number of patients in the different age groups did not differ significantly between the 2 patient groups. There was an unbalanced distribution of follow-up duration in the lacunar and territorial stroke patients in the 900- to 1200-day category (21% vs. 36%, χ^2 -test: $p=0.02$), and 1200- to 1400-day category (33% vs. 14%, χ^2 -test: $p=0.07$).

Table 3.3 and *Figure 3.1* show the results of the bivariate and multivariate logistic regression analysis of the most relevant model of clinical variables, expressed as (c)OR and (a)OR, respectively, in the 4 patient groups, i.e., those with progression of WMLs, those with progression of small deep infarcts, those with progression of both WMLs and small deep infarcts, and those with progression of territorial infarcts.

Progression of WMLs

At study entry, WMLs were equally frequent in lacunar (16%), and in territorial stroke patients (14%) (*Table 3.2*). Three lacunar and three territorial stroke patients who already had maximal extensiveness of WMLs at study entry were excluded from the analysis, because they did not show further WML progression. The WMLs progressed in 26 patients (26%): 22 with a lacunar and 4 with a territorial stroke. This means that WML progression was significantly associated with lacunar stroke ((a)OR 5.0, 95% CI 1.2–20.3). In 1

Table 3.2: Baseline characteristics of patients with a lacunar or territorial stroke participating in the follow-up study.

Baseline characteristics	Lacunar stroke N=63 (59)	Territorial stroke N=44 (41)	Total N=107
Male gender	43 (68)	27 (61)	70 (65)
Age (years)			
≤ 60	21 (33)	20 (45)	41 (38)
61–67	22 (35)	10 (23)	32 (30)
> 67	20 (32)	14 (32)	34 (32)
Hypertension	28 (44)	16 (36)	44 (41)
Diabetes mellitus	12 (19)	7 (16)	19 (18)
Hypercholesterolemia	32 (51)	18 (41)	50 (47)
Ischaemic heart disease	8 (13)	13 (30)	21 (20)
COPD	5 (8)	3 (7)	8 (7)
Smoking	20 (32)	17 (39)	37 (35)
Carotid stenosis	3 (5)	14 (32)	17 (16)
WMLs at study entry	10 (16)	6 (14)	16 (15)
Silent SDIs at study entry	10 (16)	7 (16)	17 (16)
Silent TIs at study entry	1 (2)	0	1 (1)
Rankin at 3 months = 4 or 5	2 (3)	4 (9)	6 (6)
Rankin at follow-up = 4 or 5	1 (2)	5 (11)	6 (6)
Follow-up (days)			
< 900	14 (22)	11 (25)	25 (23)
900–1200	13 (21)	16 (36)	29 (27)
1200–1400	21 (33)	6 (14)	27 (25)
> 1400	15 (24)	11 (25)	26 (24)

COPD = Chronic obstructive pulmonary disease. WMLs = White matter lesions. SDIs = Small deep infarcts. TIs = Territorial infarcts.

Percentages between parentheses.

lacunar and 1 territorial stroke patient, CT scans at study entry showed WMLs around the frontal and occipital horns, respectively, whereas follow-up CT scans were without WMLs. In 1 territorial stroke patient the CT scan at study entry showed WMLs in all regions, whereas the follow-up CT scan showed WMLs only around frontal horns and in the centrum semiovale. Besides the association with lacunar stroke, progression of WMLs was also significantly associated with silent small deep infarcts on CT at study entry ((a)OR 6.0, 95% CI 1.0–34.6), old age (age > 67 vs. age ≤ 60: (a)OR 5.5, 95% CI 1.3–23.1), and longer follow-up (follow up > 1400 vs. < 900 days: (a)OR 12.7, 95% CI 1.8–89.0). When diabetes mellitus was added to the multivariate regression model, it was associated with less progression of WMLs ((a)OR 0.03, 95% CI 0.0–0.4).

Table 3.3: Adjusted odds ratios with 95% confidence intervals of clinical variables in patients with progression of white matter lesions, small deep infarcts, both white matter lesions and small deep infarcts, or territorial infarcts.

Vascular risk factors		WML progression N=26 (26%)	SDI progression N=41 (38%)	SDI and WML progression N=16 (16%)	Tl progression N=14 (13%)
Male gender		1.2 (0.3-4.6)	2.2 (0.7-6.5)	2.3 (0.4-12.9)	1.9 (0.3-11.1)
Age (years)	61-67 vs. age $\leq$ 60	2.0 (0.4-9.0)	0.2 (0.1-0.8)	0.2 (0.02-1.6)	0.1 (0.02-1.1)
	> 67 vs. age $\leq$ 60	5.5 (1.3-23.1)	0.8 (0.2-2.9)	1.2 (0.2-7.3)	0.3 (0.05-1.6)
Lacunar stroke at study entry		5.0 (1.2-20.3)	27.7 (6.3-120.9)	34.1 (2.5-471.7)	0.1 (0.02-0.7)
Hypertension		0.9 (0.3-3.2)	1.8 (0.6-5.4)	0.4 (0.1-2.4)	3.8 (0.8-18.1)
Ischaemic heart disease		2.2 (0.4-10.8)	0.9 (0.2-4.2)	1.8 (0.2-15.3)	6.6 (1.3-34.8)
Silent SDIs at study entry		6.0 (1.0-34.6)	1.7 (0.4-7.8)	12.5 (1.4-112.0)	2.4 (0.4-16.1)
WMLs at study entry		4.9 (0.6-37.8)	4.5 (0.8-24.3)	11.0 (1.2-100.0)	3.8 (0.5-27.1)
Follow-up (days)	900-1200 vs. < 900	0.6 (0.1-5.1)	1.9 (0.4-9.1)	1.8 (0.1-25.5)	2.2 (0.3-18.2)
	900-1200 vs. < 900	0.6 (0.1-5.1)	1.9 (0.4-9.1)	1.8 (0.1-25.5)	2.2 (0.3-18.2)
	1200-1400 vs. < 900	4.7 (0.8-28.0)	1.9 (0.5-8.0)	1.7 (0.2-17.2)	2.0 (0.2-18.1)

WML = White matter lesion. SDIs = Small deep infarcts. TIs = Territorial infarcts.

95% Confidence intervals between parentheses.

Figure 3.1: Crude and adjusted odds ratios with 95% confidence intervals of clinical variables in patients with progression of white matter lesions (WMLs), small deep infarcts (SDIs), territorial infarcts (TIs), or both WMLs and SDIs.

Progression of small deep infarcts

We found progression of small deep infarcts in 41 patients (38%), 37 lacunar and 4 territorial stroke patients, which demonstrates a significant association of progression of small deep infarcts with symptomatic lacunar stroke at study entry ((a)OR 27.7, 95% CI 6.3–120.9). In 5 lacunar and 2 territorial stroke patients recurrent infarcts were symptomatic. Progression of small deep infarcts was independently associated with longer follow-up (follow-up > 1400 vs. < 900 days: (a)OR 7.7, 95% CI 1.4–41.3), and, inversely, with age between 61 and 67 years (compared with patients younger than 61: (a)OR 0.2, 95% CI 0.1–0.8). Progression of small deep infarcts was significantly associated with WML progression ((c)OR 3.6, 95% CI 1.4–9.2), but not independently ((a)OR 1.4, 95% CI 0.4–5.4). After stepwise stripping of the multivariate regression analysis model, it appeared that the type of stroke at study entry was responsible for this considerable difference in OR.

Progression of both WMLs and small deep infarcts

Six patients who had maximal extension of WMLs on CT at study entry were excluded from the analysis. Progression of both WMLs and small deep infarcts occurred in 16 patients (16%), 15 lacunar and 1 territorial stroke patient, demonstrating a significant association of progression of both WMLs and small deep infarcts with symptomatic lacunar stroke at study entry ((a)OR 34.1, 95% CI 2.5–471.7). In contrast, only 3 patients had progression of both WMLs and territorial infarcts. Progression of both WMLs and small deep infarcts was also significantly associated with silent small deep infarcts at study entry ((a)OR 12.5, 95% CI 1.4–112.0), and with longer follow-up (follow-up > 1400 vs. < 900 days: (a)OR 29.7, 95% CI 1.8–501.0).

Progression of territorial infarcts

The number of territorial infarcts increased in 14 patients (13%), of whom 3 had a lacunar and 11 a territorial stroke. The recurrent infarct was symptomatic in only 1 (territorial stroke) patient. The progression of territorial infarcts was significantly associated with symptomatic territorial stroke at study entry (lacunar vs. territorial stroke: (a)OR 0.1, 95% CI 0.02–0.7) and with a history of ischaemic heart disease ((a)OR 6.6, 95% CI 1.3–34.8).

Remarkably, the progression of small deep infarcts in lacunar stroke patients occurred significantly more than progression of territorial infarcts in territorial stroke patients ((c)OR 4.3, 95% CI 1.8–10.0).

Rankin (handicap) score

The degree of handicap as measured by the Rankin score at 3 months after initial stroke and at follow-up was not associated with progression of WMLs, small deep or territorial infarcts, or with both WMLs and small deep infarcts. The handicap increased in 36 patients (34%)

(26 with a lacunar and 10 with a territorial stroke); it decreased in 26 patients (24%) (10 with a lacunar and 16 with a territorial stroke); and it remained unchanged in 45 patients (42%) (27 with a lacunar and 18 with a territorial stroke).

Discussion

After a median follow-up of 3.0 years, WMLs had progressed in 24% of the study patients with an ischaemic stroke. This progression was much more pronounced in lacunar than in territorial stroke patients. The progression of WMLs was significantly associated with symptomatic lacunar stroke and with silent small deep infarcts at study entry. These findings are in line with those of our earlier CT study, which showed WMLs to be significantly associated with the presence of silent small deep infarcts [20]. Also, we found marked progression of small deep infarcts in lacunar stroke patients.

Not all patients initially included in our stroke registry were available for follow-up CT, which may have created bias, but, if so, the bias was most likely toward underdetection of WMLs and recurrent infarcts: most patients not investigated had died or were severely disabled; therefore, the younger and relatively less disabled patients participated in the study. The progression of WMLs and infarcts might have been even worse if more severely affected patients had also been included.

In 3 patients, the initial CT scans showed more extensive WMLs than the follow-up CT scans. In search for an explanation of this apparently odd finding, we reviewed the 2 CT scans of each patient. In these 3 patients, the follow-up CT scans showed diminished black-and-white contrast compared with the initial CT scans, which may have led to an underestimation of the extensiveness of WMLs. Furthermore, 1 of the 3 patients had WMLs around the occipital horns on the initial CT scan. The follow-up CT scan in this patient showed a large infarct in the territory of the middle cerebral artery extending around the occipital horn, which interfered with judgement of WMLs in this area. There were no signs of ventricular enlargement or changes in ventricular size in follow-up CT scans compared with the initial CT scans in these 3 patients. Therefore, intraobserver variability, rather than real change, such as might occur in periventricular WMLs related to (normal pressure) hydrocephalus [51, 56, 106, 132], may explain these discrepancies.

Progression of small deep infarcts occurred significantly more often in lacunar stroke patients, and progression of territorial infarcts in territorial stroke patients. These findings support the hypothesis of different underlying vasculopathies in small deep (lacunar) infarcts and in (non-cardio-embolic) territorial infarcts, i.e., small-vessel disease and large-vessel disease, respectively [11, 19, 97, 114, 131, 142, 178]. The association of territorial infarct progression with ischaemic heart disease also supports the relationship of territorial infarcts with generalized large-vessel atherosclerosis. The unexpected inverse association of patient age between 61 and 67 years, compared with patient age 60 years or younger,

with increase in the number of small deep infarcts is probably related to the relative small numbers of patients in the different age groups.

Most recurrent infarcts were silent. Two previous follow-up studies found similar results. In a 1-year magnetic resonance imaging follow-up study of 81 lacunar stroke patients, Samuelsson et al. [160] found 5 recurrent symptomatic strokes, 4 of which were small deep and 1 of which was territorial, and 9 new silent infarcts, 5 of which were territorial and 4 of which were small deep. In a CT follow-up study of 24 patients with vascular dementia (follow-up 42 ± 27 [mean $\pm$ SD] months) and 24 with dementia of the Alzheimer type, Meyer et al. [130] found recurrent silent infarcts in 4 patients with vascular dementia, all of which were small deep.

Several vascular risk factors have been associated with WMLs. Among these factors are increasing age [4, 30, 32, 37, 81, 87, 96, 113, 122, 171, 186, 193], hypertension [4, 15, 30, 32, 52, 112, 122, 186], heart disease [30, 52, 113, 193], hypercholesterolemia [30], diabetes mellitus [193], and carotid stenosis [52]. We could only confirm the association of increasing age with WML progression. Unexpectedly, WML progression was related to the absence of diabetes mellitus. This finding may be the result of a selection bias, but diabetes mellitus was not significantly more frequent among patients who did not participate in this study. A more likely explanation may be a random variation due to the small number of patients involved, because there was only 1 patient with diabetes mellitus among those with WML progression. We did not find an association of WML progression with other vascular risk factors, such as hypertension. Some authors also found no relationship between hypertension and WMLs [96, 193]. Possibly, hypertension may not be identified as a discriminator among a population that already has a high frequency of hypertension. Moreover, Liao et al. [112] found that the level of blood pressure is related to WMLs. So, antihypertensive treatment in our study patients may have weakened the effect of hypertension as a risk factor.

Meyer et al. [130] demonstrated that cognitive decline correlated with recurrent silent infarcts and with changes in local cerebral blood flow of the frontal white matter, thalamus and internal capsule. Both WMLs and multiple, usually silent, small deep infarcts have been associated with mental impairment and dementia [72, 94, 100, 169, 182], and with multiple neurological deficits, such as gait disorders, tendency to fall, pseudobulbar state, and incontinence [6, 94, 169]. In our study, progression of WMLs and increase in the numbers of small deep or territorial infarcts were not associated with increased handicap. However, as stated earlier, patient selection may have created bias, because patients not included were more severely disabled. Recently, we could not find an association between silent lesions in infarct patients and functional outcome at 1 year [23]. Obviously, there is no clear relationship between silent infarcts, WML progression, and functional outcome in brain infarct patients.

The marked progression of WMLs that occurred mainly in lacunar stroke patients sug-

gests that both WMLs and small deep infarcts are due to small-vessel disease, as has been suggested by others [15, 32, 87]. The impressive increase over time of WMLs and of small deep infarcts in our patients suggests that the underlying small-vessel disease is progressive. Autopsy studies in patients with WMLs on CT or magnetic resonance imaging scans showed diffuse demyelination of the white matter, multiple small deep infarcts, cystic lacunae, dilated perivascular spaces, and arteriolosclerosis [3, 27, 28, 31, 36, 41, 72, 100, 101, 125, 153, 156]. More rarely, amyloid angiopathy [73, 95] or noninflammatory collagenous thickening of venous walls resulting in severe periventricular venous stenosis [136] were found. Recently, arteriolosclerosis was suggested as the primary factor in the pathogenesis of these diffuse WMLs, whereas dilatation of perivascular spaces was considered as secondary event [187]. Fisher [55, 57] showed at autopsy that arteriolosclerosis is also related to multiple, usually silent small deep infarcts. So, these various autopsy studies showed (1) that both WMLs and multiple small deep infarcts result from a vascular disease and (2) that in most patients this vascular disease may be arteriolosclerosis. These observations are remarkable, because WMLs and small deep infarcts mainly occur in different vascular territories: small deep infarcts in the territory of small deep penetrating arteries, and WMLs in the territory of the superficial perforating branches of large cerebral arteries. The vasculopathy that results in WMLs and small deep infarcts may therefore be pathologically homogeneous but heterogeneous as to the affected cerebral vascular system. What causes deep perforating vessels to react with infarction and the superficial system with "incomplete infarction" and demyelination remains unclear, but factors such as local perfusion pressure and autoregulatory differences between the 2 systems may be involved.

Recently, Hachinski [76] pointed out that vascular dementia is currently the only preventable major cause of dementia. Prevention should be tried in patients in the "brain-at-risk" stage (e.g., patients with vascular risk factors), in patients in the predementia stage (e.g., stroke patients), and in patients who already have dementia. Our stroke patients were treated according to present standards, i.e., treatment of vascular risk factors (e.g., with antismoking advice, antihypertensives, antidiabetics, and diet) and treatment with aspirin or anticoagulants. It is both amazing and disappointing that WMLs and small deep infarcts were rapidly progressive despite this standard stroke treatment. Fisher [55, 57] suggested that severe and long-standing hypertension might be a particular cause of arteriolosclerosis. The notion that arteriolosclerosis progresses despite standard stroke treatment, including the lowering of elevated blood pressure levels, could mean that hypertensive patients should be treated more diligently or that vascular disease, once it has produced stroke, has advanced too far to be influenced significantly by therapy, although therapy reduces the risk of symptomatic recurrent stroke. Another reason may be that other, as yet unknown (environmental or genetic), factors influence the pathogenesis of cerebral arteriolosclerosis. Fortunately, despite significant progression, the vasculopathy does not seem to significantly impair the degree of handicap. Whether it may affect the degree of cognitive impairment

remains to be determined.

4

Strong association between white matter lesions and multiple small deep infarcts suggests similar type of underlying small-vessel disease

Abstract

Objectives: (1) To investigate the incidence of white matter lesions (WMLs) in first-ever ischaemic stroke patients. (2) To study WMLs in relationship with vascular risk factors, symptomatic and silent infarcts, to test the hypothesis that WMLs are especially associated with multiple, usually silent small deep infarcts.

Design: Survey of prospectively registered patients with a first-ever supratentorial ischaemic stroke, of whom vascular risk factors were registered, and whose computed tomographic (CT) scans were reviewed for presence of WMLs and silent small deep or territorial infarcts.

Setting: Primary and referral care centre.

Patients: Of 999 consecutively registered patients, 39 patients were excluded: 37 because a CT scan of the brain had not been performed, 2 because the CT scan could not be retrieved. So, 960 patients entered this study: 332 patients with a lacunar stroke, 213 with a cardio-embolic territorial stroke, and 415 with a atherothrombotic territorial stroke.

Main outcome measure: WMLs on brain CT scan.

Results: 24% of all stroke patients had WMLs. WMLs were associated with higher age, lacunar stroke and silent small deep infarcts. Furthermore, WMLs were associated with silent territorial infarcts in the atherothrombotic stroke subgroup.

Conclusions: A considerable percentage of stroke patients have WMLs, which are associated with especially silent small deep infarcts and higher age. These findings support the hypothesis that WMLs and multiple, usually silent small deep infarcts have the same vascular cause, namely arteriolosclerosis.

Introduction

Hachinski [78] was one of the first to draw attention to white matter lesions (WMLs), often called leukoaraiosis. Since then a vast amount of studies on WMLs have been published. WMLs have been studied in the general population [30, 52, 49, 113, 193], in patients with hypertension [186], in stroke patients [81, 87, 91, 96, 99], and in patients with dementia [12, 31, 32, 105, 111, 154, 169]. WMLs were found to be related to higher age [4, 30, 32, 37, 81, 87, 96, 122, 171, 193], and several vascular risk factors [4, 30, 32, 113, 122, 193].

Like small deep (lacunar) infarcts, WMLs are thought to be caused by small-vessel disease [31, 64, 66, 187]. Associations of WMLs with small deep infarcts have been found in a stroke population [87], a neurogeriatric population [32], and in neurologically nondiseased elderly subjects [193]. Pathological [34, 58] as well as clinical [20, 127] evidence points at two distinct small deep (lacunar) infarct entities: arteriolosclerosis as the cause of multiple, usually silent, small deep infarcts, whereas the somewhat larger, symptomatic ones are caused by microatheromatosis. Pathological studies showed that arteriolosclerosis is also the underlying vasculopathy in WMLs [31, 64, 66, 187]. So, one could expect that WMLs occur more frequently in patients with multiple, usually silent small deep infarcts than in those with single larger symptomatic lacunar infarcts. Furthermore, the risk factor profile of WMLs could clarify the factors involved in the development of arteriolosclerosis. The aims of this study were (1) to investigate the incidence of WMLs in patients with a first-ever ischaemic stroke, and (2) to study WMLs in relationship with vascular risk factors and with symptomatic as well as silent infarct subtypes, to test the hypothesis that WMLs are especially associated with multiple, usually silent small deep infarcts.

Patients and methods

Patients were registered at the University Hospital of Maastricht between July 1987 and January 1994 in a prospective registry of all patients, admitted or visiting the out-patient clinic, with a first-ever supratentorial brain infarct with symptoms lasting longer than 24 hours. Routine investigations included standard blood tests, electrocardiogram, chest X-ray, computed tomographic (CT) scan of the brain, and noninvasive carotid studies. Echocardiography, 24-hour ECG monitoring, and cerebral angiography were done in selected cases.

Definitions

The following possible *vascular risk factors* were recorded: age, gender, hypertension (known hypertension, or at least 2 separate blood pressure recordings of higher than 160/90 mmHg before or at least 1 week after stroke), diabetes mellitus (known diabetes mellitus, or fasting serumglucose higher than 7 mmol/l, or a postprandial serumglucose

higher than 11 mmol/l, both on at least 2 separate occasions), haematocrit at stroke onset, history of ischaemic heart disease (myocardial infarction, angina pectoris), history of chronic obstructive pulmonary disease (COPD), cardiac source of embolism (atrial fibrillation, mitral stenosis, prosthetic aortic or mitral valve, recent myocardial infarction (within 6 weeks preceding stroke), endocarditis, cardiomyopathy, left ventricular aneurysm, intraventricular thrombus), use of diuretics prior to stroke, and significant (more than 50%) carotid stenosis ipsilateral to the symptomatic stroke.

Lacunar stroke was defined (1) as an acute stroke syndrome with a CT lesion compatible with occlusion of a single perforating artery, i.e., a small, subcortical, sharply margined hypodense lesion with a diameter smaller than 20 mm (small deep infarct), or (2) as a specific lacunar syndrome (i.e., unilateral motor and/or sensory symptoms and signs that completely involve at least 2 of 3 body parts (face, arm, leg) without disturbance of consciousness or language, visual field defect or other signs of cortical dysfunction) when the CT scan showed no specific lesion.

Territorial stroke was defined (1) as an acute stroke syndrome with CT findings compatible with infarction involving the cortex, or (2) when no specific lesion was visible on CT, as a clinically identified cortical syndrome consisting of unilateral motor and/or sensory symptoms and signs in combination with signs of cortical dysfunction with or without visual field defect, or as incomplete involvement of 2 body parts, or as isolated monoparesis [16], or as isolated cortical dysfunction (usually dysphasia). Patients with a large subcortical infarct were included in the territorial stroke group because of similar pathogenesis [18, 21]. By presumed stroke cause, 3 territorial stroke subtypes were discerned: cardio-embolic, atherothrombotic, and territorial stroke with undetermined cause. Cardio-embolic territorial stroke was defined as a territorial stroke in the presence of a cardiac source of embolism. Atherothrombotic stroke was defined as a territorial stroke in the presence of a significant carotid stenosis. If neither a cardiac source of embolism nor a significant carotid stenosis was found, then the territorial stroke was classified as one with undetermined cause. The aim of this study was to investigate WMLs in 3 groups of patients, namely those with small-vessel disease (i.e., lacunar stroke), with large-vessel disease (i.e., territorial stroke due to large-vessel atherosclerosis), and those with territorial stroke due to cardiac embolism. Therefore, patients with a specific stroke cause such as vasculitis, arterial dissection etc., were not included in this study.

Silent brain infarct was defined as a low-density area on the CT scan compatible with infarction but without a history of stroke, as taken from the patient's history, from family, or any other accessible information. Also, the stroke symptoms at study entry had to be anatomically incompatible with this infarct. Old infarcts can usually be distinguished from new ones because they are more hypodense, and there may be signs of surrounding tissue loss, like retraction of brain structures towards the infarct. Silent infarcts were also categorized as small deep or territorial.

White matter lesions (WMLs) were defined as focal or diffuse hypodensities in the periventricular or deep white matter, not involving the cortex, and with ill-defined margins to distinguish them from infarction [168]. No effort was made to quantify the degree of white matter density in these different sites, as this might depend on the tuning of the CT scan.

Patient population

Of 999 consecutively registered patients, 39 patients were excluded from this study, 37 because a CT scan of the brain had not been performed, and 2 because the CT scan could not be retrieved. So, 960 patients entered this study. Median time between study entry and the CT scan was 4 (range: 0–882) days. In eleven patients this period was more than 100 days: in seven patients 100–200, in two 200–300, in one 566, and in one 882 days. Despite this long delay between stroke and the time of CT, we entered these patients in our registry because we could verify their symptomatic stroke with a compatible lesion on CT. CT scans were reviewed for the presence and extensiveness of WMLs, and the number of (symptomatic as well as silent) small deep and territorial infarcts by 2 neurologists. Only those WMLs and infarcts on which both investigators agreed were registered.

Statistical analysis

We related the presence of WMLs to clinical variables by means of bivariate statistical analysis with crude odds ratios ((c)OR) with 95% confidence intervals (CI). Multivariate logistic regression analysis with adjusted odds ratios ((a)OR) determined the association of various subsets of clinical variables with presence of WMLs. Besides the vascular risk factors, the following clinical variables were included in various regression models: stroke subtype, presence of silent small deep or territorial infarcts, and Rankin (handicap) score at study entry. The Rankin scores were divided into 2 groups: functionally independent (Rankin ≤ 3) or dependent (Rankin = 4 or 5). Patients were categorized in 4 age-groups: 64 years or younger, 65 to 71 years, 72 to 78 years, and older than 78 years. The 3 “higher-age” categories were compared with the youngest age. Haematocrit at admission was classified in 3 categories: low (men: < 0.41 l/l, women: < 0.36), normal (men: 0.41 – 0.51 , women: 0.36 – 0.46), and high (men: > 0.51 , women: > 0.46). Patients with a low or high haematocrit were compared with those with normal values.

Results

Table 4.1 shows the baseline characteristics and CT findings in the ischaemic stroke subgroups. Because the analyses showed no difference between the atherothrombotic subgroup of territorial stroke and the subgroup of territorial stroke with undetermined cause, the results are shown for these 2 groups combined. Median age was 72 (range: 24–96) years.

Table 4.1: Baseline characteristics and CT findings in the three subgroups of stroke patients.

Baseline characteristics	Total	Symptomatic stroke subgroups		
		Lacunar	Cardio-embolic	Atherothrombotic/ Undetermined cause
	N=960	N=332 (35)	N=213 (22)	N=415 (43)
Age (years)				
≤ 64	240 (25)	98 (30)	26 (12)	116 (28)
65–71	235 (24)	89 (27)	47 (22)	99 (24)
72–78	252 (26)	89 (27)	55 (26)	108 (26)
> 78	233 (24)	56 (17)	85 (40)	92 (22)
Male gender	497 (52)	185 (56)	90 (42)	222 (53)
Hypertension	435 (45)	158 (48)	102 (48)	175 (42)
Diabetes mellitus	194 (20)	65 (20)	48 (23)	81 (20)
Ischaemic heart disease	250 (26)	67 (20)	71 (33)	112 (27)
COPD	97 (10)	39 (12)	23 (11)	35 (8)
Diuretics	277 (29)	83 (25)	88 (41)	106 (26)
Haematocrit: low	150 (16)	38 (11)	45 (21)	67 (16)
normal	723 (75)	259 (78)	133 (62)	331 (80)
high	87 (9)	35 (11)	35 (16)	17 (4)
Rankin = 4 or 5	495 (52)	104 (31)	145 (68)	246 (59)
White matter lesions	235 (24)	96 (29)	46 (22)	93 (22)
Silent small deep infarcts	223 (23)	103 (31)	35 (16)	85 (20)
Silent territorial infarcts	61 (6)	14 (4)	18 (8)	29 (7)

COPD = Chronic obstructive pulmonary disease.

Percentages between parentheses.

Patients with a cardio-embolic stroke were significantly older than patients with a lacunar or atherothrombotic stroke (χ^2 -test: $p=0.00$). The Rankin score showed that lacunar stroke patients were less disabled than those with a territorial stroke (χ^2 -test: $p=0.00$). In 680 patients a noninvasive carotid study was performed, which showed a significant stenosis on the symptomatic side in 150 (22%) patients: 25 (10%) lacunar, 11 (10%) cardio-embolic, and 114 (37%) atherothrombotic stroke patients.

Both WMLs and silent small deep infarcts were found frequently in all stroke patients, 24% and 23%, respectively. Both were more frequent in the lacunar stroke subgroup (29% and 31% respectively). Silent territorial infarcts were less frequent (6% of all patients). Of patients with silent small deep infarcts 65% had only one such infarct. Multiple small deep infarcts (range: 1–8) occurred almost exclusively in lacunar stroke patients.

Table 4.2: Crude and adjusted odds ratios with 95% confidence intervals of clinical and CT-variables comparing stroke patients with white matter lesions, with stroke patients without white matter lesions.

Vascular risk factors		WMLs N=235 (24%)	No WMLs N=725 (76%)	(c)OR	95% CI	(a)OR	95% CI
Age (years)	65–71 vs. age ≤ 64	33 vs. 22	202 vs. 218	1.6	0.9–2.9	1.5	0.8–2.9
	72–78 vs. age ≤ 64	76 vs. 22	176 vs. 218	4.3	2.6–7.2	4.2	2.4–7.4
	> 78 vs. age ≤ 64	104 vs. 22	129 vs. 218	8.0	4.8–13.3	10.8	6.0–19.5
Male gender		98	399	0.6	0.4–0.8	1.3	0.9–1.9
Hypertension		116	319	1.2	0.9–1.7	1.2	0.8–1.7
Symptomatic lacunar vs. cardio-embolic stroke		96 vs. 46	236 vs. 167	1.5	1.0–2.2	2.1	1.3–3.6
Symptomatic lacunar vs. atherothrombotic stroke		96 vs. 93	236 vs. 322	1.4	1.0–2.0	1.4	0.9–2.1
Silent small deep infarcts		124	99	7.1	5.1–9.8	8.1	5.6–11.9
Silent territorial infarcts		19	42	1.4	0.8–2.5	1.7	0.9–3.2
Rankin = 4 or 5		137	358	1.4	1.1–1.9	1.1	0.8–1.6

WMLs = White matter lesions. (c)OR = Crude odds ratio. (a)OR = Adjusted odds ratio. CI = Confidence interval.

Figure 4.1: Crude and adjusted odds ratios with 95% confidence intervals of clinical and CT-variables comparing stroke patients with white matter lesions, with stroke patients without white matter lesions.

Table 4.2 and Figure 4.1 show crude and adjusted odds ratios with 95% confidence intervals comparing stroke patients with WMLs, with stroke patients without WMLs. WMLs were significantly associated with higher age (age 72–78 vs. age ≤ 64: (a)OR 4.2, 95% CI 2.4–7.4; age > 78 vs. age ≤ 64: (a)OR 10.8, 95% CI 6.0–19.5). WMLs were not associated with the Rankin (handicap) score. WMLs were related to lacunar stroke (lacunar vs. cardio-embolic stroke ((a)OR 2.1, 95% CI 1.3–3.6), lacunar vs. atherothrombotic stroke ((a)OR 1.4, 95% CI 0.9–2.1), and to silent small deep infarcts ((a)OR 8.1, 95% CI 5.6–11.9). When we analyzed patients younger than 75 years with the same model, we found the same associations as we did in the analysis of all patients. In a separate multivariate regression analysis with a model including multiple small deep infarcts (defined as more than one symptomatic or silent small deep infarct), age, gender, hypertension and Rankin score, we found that WMLs were strongly associated with both age, and multiple small deep infarcts ((a)OR 8.9, 95% CI 5.7–13.9).

Tables 4.3, 4.4, and 4.5 and Figures 4.2, 4.3, and 4.4 show crude and adjusted odds ratios with 95% confidence intervals comparing patients in each stroke subgroup with WMLs, with patients in each stroke subgroup without WMLs. Because all cardio-embolic

Table 4.3: Crude and adjusted odds ratios with 95% confidence intervals of clinical and CT-variables comparing lacunar stroke patients with white matter lesions, with lacunar stroke patients without white matter lesions.

Vascular risk factors	WMLs N=96 (29%)	No WMLs N=236 (71%)	(c)OR	95% CI	(a)OR	95% CI
Age (yrs) 65–71 vs. ≤ 64	17 vs. 12	72 vs. 86	1.7	0.8–3.8	1.4	0.6–3.4
72–78 vs. ≤ 64	35 vs. 12	54 vs. 86	4.6	2.2–9.7	4.4	1.9–10.3
> 78 vs. ≤ 64	32 vs. 12	24 vs. 86	9.6	4.3–21.3	10.5	4.0–27.3
Male gender	48	137	0.7	0.4–1.2	0.9	0.5–1.6
Hypertension	52	106	1.4	0.9–2.3	1.5	0.8–2.6
Silent small deep infarcts	63	40	9.4	5.4–16.1	10.1	5.5–18.6
Silent territorial infarcts	4	10	1.0	0.3–3.2	0.7	0.2–2.7
Rankin = 4 or 5	40	64	1.9	1.2–3.2	1.2	0.6–2.2

WMLs = White matter lesions. (c)OR = Crude odds ratio. (a)OR = Adjusted odds ratio.

CI = Confidence interval.

stroke patients with WMLs were older than 65 years, the two youngest age-groups were taken together in the analysis. In all stroke subgroups we found significant associations of WMLs with higher age (lacunar: age 72–78 vs. ≤ 64 (a)OR 4.4, 95% CI 1.9–10.3, age > 78 vs. ≤ 64 (a)OR 10.5, 95% CI 4.0–27.3; cardio-embolic: age 72–78 vs. ≤ 71 (a)OR 6.9, 95% CI 1.8–26.8, age > 78 vs. ≤ 71 (a)OR 12.7, 95% CI 3.5–46.4; atherothrombotic: age 72–78 vs. ≤ 64 (a)OR 3.5, 95% CI 1.5–8.2, age > 78 vs. ≤ 64 (a)OR 10.9, 95% CI 4.5–26.5). WMLs were also related to silent small deep infarcts in all stroke subgroups (lacunar: (a)OR 10.1, 95% CI 5.5–18.6; cardio-embolic: (a)OR 4.4, 95% CI 1.9–10.3; atherothrombotic: (a)OR 8.6, 95% CI 4.7–15.8). Furthermore, WMLs were associated with silent territorial infarcts in the atherothrombotic subgroup ((a)OR 2.7, 95% CI 1.0–6.8).

Discussion

Frequency of WMLs

We found WMLs in 24% of our ischaemic stroke patients. In a similar study Jørgensen et al. [96] found WMLs in 15% of ischaemic stroke patients. In the study of Hijdra et al. [87] the prevalence of WMLs in ischaemic stroke patients was much higher (35%), but this study may have suffered bias because only patients with a clinically relevant lesion on the CT scan were included.

Figure 4.2: Crude and adjusted odds ratios with 95% confidence intervals of clinical and CT-variables comparing lacunar stroke patients with white matter lesions, with lacunar stroke patients without white matter lesions.

Vascular risk factors

Among all vascular risk factors we only found higher age to be associated with WMLs. Hypertension was not independently associated with WMLs in this study. Also in patients younger than 75 years we found no association of WMLs with hypertension. Previous studies found WMLs to be associated with various vascular risk factors: higher age [4, 30, 32, 37, 81, 87, 96, 113, 122, 171, 193], hypertension [4, 30, 32, 112, 122], use of diuretics [32], history of heart disease [30, 113], diabetes mellitus [193], and hypoxia [37]. Some authors found no relationship between hypertension and WMLs [96, 193]. Possibly, hypertension may not be identified as a discriminator among a population which already has a high frequency of hypertension and end-organ damage due to hypertension, such as stroke. Moreover, Liao et al. [112] found in a population-based study that the level of blood pressure is related to WMLs: patients with antihypertensive treatment who still had high blood pressure, had greater odds of WMLs than those with antihypertensive treatment with a normalized blood pressure. So, antihypertensive treatment in our stroke patients may have weakened the effect of hypertension as a risk factor. Breteler et al. [30] found the association

Table 4.4: Crude and adjusted odds ratios with 95% confidence intervals of clinical and CT-variables comparing cardio-embolic territorial stroke patients with white matter lesions, with cardio-embolic territorial stroke patients without white matter lesions.

Vascular risk factors	WMLs N=46 (22%)	No WMLs N=167 (78%)	(c)OR	95% CI	(a)OR	95% CI
Age (yrs) 72–78 vs. ≤ 71	13 vs. 3	42 vs. 70	7.2	1.9–26.8	6.9	1.8–26.8
> 78 vs. ≤ 71	30 vs. 3	55 vs. 70	12.7	3.7–43.9	12.7	3.5–46.4
Male gender	14	76	0.5	0.3–1.1	0.7	0.3–1.6
Hypertension	21	81	0.9	0.5–1.7	0.7	0.3–1.5
Silent small deep infarcts	16	19	4.2	1.9–9.0	4.4	1.9–10.3
Silent territorial infarcts	5	13	1.4	0.5–4.3	1.8	0.6–6.0
Rankin = 4 or 5	33	112	1.2	0.6–2.6	0.9	0.4–2.0

WMLs = White matter lesions. (c)OR = Crude odds ratio. (a)OR = Adjusted odds ratio.

CI = Confidence interval.

between hypertension and WMLs only in subjects aged 65–74 years, not in older subjects. Their explanation for this finding was that in the very old, the importance of elevated blood pressure for the risk of vascular disease seems to diminish or even reverse [25]. Since cardiovascular risk factors are all associated with increased mortality, very old survivors with these risk factors may form a selected group resistant to the damaging effects of hypertension. Age may be a far more important risk factor in the elderly than hypertension.

Association with silent territorial infarcts

In the atherothrombotic subgroup WMLs were associated with silent territorial infarcts. No previous study found such association. Territorial infarcts may have caused Wallerian degeneration resulting in lower densities in the white matter [110]. Studies on WMLs in similar stroke populations as ours [81, 96], did not look into the association of symptomatic or silent infarcts with WMLs.

Associations with lacunar stroke and multiple, usually silent small deep infarcts

We found that WMLs were associated with symptomatic lacunar stroke, and even more with silent small deep infarcts. This association was also found in a neurogeriatric population [32], and in neurologically nondiseased elderly subjects [193]. Hijdra et al. [87], in a similar study regarding WMLs in ischaemic and haemorrhagic stroke patients, also showed that WMLs were related to small deep infarcts, but they did not differentiate between single symptomatic and multiple silent small deep infarcts.

Figure 4.3: Crude and adjusted odds ratios with 95% confidence intervals of clinical and CT-variables comparing cardio-embolic territorial stroke patients with white matter lesions, with cardio-embolic territorial stroke patients without white matter lesions.

Neuropathology

Why are small deep infarcts, and especially silent ones, associated with WMLs? Neuropathologic studies of WMLs showed demyelination [3, 28, 31, 66, 101, 161, 162, 187], axonal loss [31, 187], dilated perivascular spaces [3, 161, 187], gliosis [3, 7, 28, 31, 161, 162, 187], arteriolosclerosis [3, 7, 31, 64, 66, 101, 161, 187], and (small deep) infarcts [7, 28, 31, 161, 187]. Although a mixture of pathologic changes is found in WMLs, many authors believe that arteriolosclerosis is the primary factor in WMLs [3, 7, 28, 31, 162, 187]. The loss of myelin might simply be explained by the fact that white matter contains a lot of myelin, in contrast with the grey matter in the basal ganglia. Therefore, ischaemia due to arteriolosclerosis in the white matter will lead to demyelination. Because in both small deep infarcts and WMLs arteriolosclerosis is found, this is thought to be the common pathological cause.

Two distinct small deep infarct entities

Pathological evidence, although scarce, points at arteriolosclerosis as the cause of multiple, usually silent small deep infarcts, whereas the somewhat larger, symptomatic ones are

Table 4.5: Crude and adjusted odds ratios with 95% confidence intervals of clinical and CT-variables comparing atherothrombotic territorial stroke patients with white matter lesions, with atherothrombotic territorial stroke patients without white matter lesions.

Vascular risk factors	WMLs N=93 (22%)	No WMLs N=322 (78%)	(c)OR	95% CI	(a)OR	95% CI
Age (yrs) 65–71 vs. ≤ 64	13 vs. 10	86 vs. 106	1.6	0.7–3.8	1.6	0.6–4.2
72–78 vs. ≤ 64	28 vs. 10	80 vs. 106	3.7	1.7–8.1	3.5	1.5–8.2
> 78 vs. ≤ 64	42 vs. 10	50 vs. 106	8.9	4.1–19.2	10.9	4.5–26.5
Male gender	36	186	0.5	0.3–0.7	0.6	0.4–1.1
Hypertension	43	132	1.2	0.8–2.0	1.2	0.7–2.1
Silent small deep infarcts	45	40	6.6	3.9–11.2	8.6	4.7–15.8
Silent territorial infarcts	10	19	1.9	0.9–4.3	2.7	1.0–6.8
Rankin = 4 or 5	64	182	1.7	1.0–2.8	1.2	0.6–2.1

WMLs = White matter lesions. (c)OR = Crude odds ratio. (a)OR = Adjusted odds ratio.

CI = Confidence interval.

caused by microatheromatosis [34, 58]. Also on clinical grounds one might argue that two distinct small deep infarct entities exist. In a study on 100 lacunar infarct patients Boiten and Lodder found that WMLs were associated with silent small deep infarcts [20]. The silent infarcts differed in location (more often in the anterior limb of the internal capsule and in the caudate nucleus, less often in the posterior limb of the internal capsule), involved vascular territory (more often in the lateral and medial striate arteries territory, less often in the anterior choroidal artery territory), and volume (smaller) from the symptomatic infarcts. Furthermore, hypertension was more frequent in patients with multiple silent small deep infarcts, than in those with a single symptomatic lacunar stroke. These findings were confirmed by Mast et al. [127], who found multiple small deep infarcts, but not single ones, to be associated with hypertension and diabetes mellitus. Furthermore, cerebral blood flow in the cerebral cortex was found to be significantly lower in patients with multiple small deep infarcts than in those with a single small deep infarct [133]. These studies suggest that hypertension-associated arteriolosclerosis is the main cause of multiple (silent) small deep infarcts, which explains the association we found between WMLs and silent small deep infarcts.

Vascularisation

A further question is why arteriolosclerosis causes small deep infarcts in various deep areas and confluent lesions, which are not evident infarcts, in the regions supplied by the medullary penetrators. The basal ganglia and thalamus are supplied by deep perforating branches of the large cerebral arteries, such as the lenticulostriate, thalamoperforating, and

Figure 4.4: Crude and adjusted odds ratios with 95% confidence intervals of clinical and CT-variables comparing atherothrombotic territorial stroke patients with white matter lesions, with atherothrombotic territorial stroke patients without white matter lesions.

anterior choroidal artery [67]. Functionally, these are endarteries, although anastomoses may exist [69, 123, 157]. The centrum semiovale is supplied by long medullary arteries arising from the leptomeningeal plexus, which in turn arises from cerebral surface branches of the anterior, middle, and posterior cerebral arteries [64, 140]. Moody et al. [135] found that these medullary arteries and their arterioles have exclusive territories that border smoothly on one another, forming numerous small sequential contact zones with adjacent afferent arteriolar systems throughout the whole depth of the white matter, without interdigitation. However, Nelson et al. [140] studying fetal and neonatal brains, found interconnecting pre-capillary anastomotic channels in the cortex and white matter. They believed that these interconnections persist into adolescence. Whether these interconnecting channels also exist in older age is unknown. The basal ganglia have a greater capillary density than the white matter [135]. Terminal branches of the most lateral thalamic arteries and the lateral striate arteries of the basal ganglia border on medullary vessels in the lowest portion of the centrum semiovale. Considerable variation exists in the contributions of the anterior, middle, and posterior cerebral arteries to the blood supply of the lobar white matter and the basal ganglia [183]. So, the vasculature in the basal ganglia and thalamus, and in

the white matter are similar as to the scarcity of anastomoses. However, there are also major differences: in the white matter the capillary density is lower and consequently the supplied territory per capillary larger, than in the basal ganglia. Therefore, hypoperfusion might cause larger lesions in the white matter than in the basal ganglia.

Cerebral metabolism and regional blood flow

As grey matter metabolic rate is higher than that in white matter, basal ganglia metabolic rate is higher than that in the periventricular white matter region [135]. Areas with a higher metabolic rate have a higher regional cerebral blood flow (CBF), which makes these areas more vulnerable to ischaemia, e.g., during hypotension [190]. While the cerebral cortex shows evidence of damage with flow below 17 ml/100g/min., flows of 6 to 8 ml/100g/min. can be tolerated for 1 hour before evidence of infarction appears in deep white matter [190]. Do these differences in metabolism and CBF between basal ganglia and white matter explain why as a result of ischaemia small deep infarcts develop in one region and more confluent lesions in the other? PET-studies showed that WMLs were associated with a reduced CBF [82, 129], and reduced cortical metabolism [42, 82, 172]. However, SPECT-studies in general population showed no association between WMLs and CBF [38, 104], whereas silent small deep infarcts were related to a significant decrease in mean regional CBF [104]. These studies can not answer the question whether decreased CBF caused the lesions, or the other way around. A PET-study in asymptomatic subjects with cerebrovascular risk factors showed that although resting grey matter CBF was not significantly correlated with the severity of WMLs, impaired autoregulation mechanisms such as lowered vasodilatory capacity, and decreased vasodilation compensatory to the fall of cerebral perfusion pressure occurred in the cerebral cortex [93]. One could hypothesize that in these asymptomatic subjects disturbance of autoregulation causes WMLs by making the brain vulnerable to minor hypotensive episodes, whereas actual changes in CBF can not be measured yet. This hypothesis is supported by the association between WMLs and reduced compensatory mechanisms of the brain to cerebral perfusion pressure falls in patients with symptomatic carotid occlusion [92]. Although Fazekas et al. [52] found that carotid stenosis was associated with WMLs, we found in agreement with a recent large carotid endarterectomy trial [171], no association between WMLs and carotid stenosis. In another large carotid surgery trial an association was found between small infarcts in the white matter (so-called small centrum ovale infarcts) and carotid stenosis [21]. Possibly, carotid large-vessel disease is associated with small infarcts and not with more confluent lesions in the white matter. As no clear association exists between carotid stenosis and WMLs, carotid stenosis does probably not contribute to chronic impairment of white-matter-CBF, but in some patients it may cause (temporary) hypoperfusion. More likely, arteriolosclerosis causes impairment of white-matter-CBF-regulation, thereby causing WMLs.

Blood-brain barrier

Caplan et al. [36] have hypothesized that WMLs may be due to hypertension and subsequent local fluid transudation and focal cerebral edema, leading to loss of tissue with gliosis. Indeed Tomimoto et al. [181] found a dysfunction of the blood-brain barrier in ischaemic stroke patients with WMLs.

Excitotoxicity

Contrary to grey matter, white matter lacks glutaminergic synapses [54]. Glutamate plays a crucial role in excitotoxicity. Therefore, differences in the effects of excitotoxicity during ischaemia may also be involved in causing "incomplete infarction" in the white matter and infarcts in the grey matter. However, this has hardly been investigated.

In conclusion, we found that a considerable percentage of stroke patients have WMLs, which are associated with (especially silent) small deep infarcts and higher age. This study supports the idea that WMLs and multiple, mostly silent small deep infarcts have the same vascular cause, namely arteriolosclerosis. However, because of differences between basal ganglia and white matter in vascular anatomy and CBF regulation, vascular insufficiency of the small vessels may lead to small infarcts in the basal ganglia, and to confluent areas of demyelination, axonal loss, dilated perivascular spaces, and gliosis in the white matter.

5

Interobserver agreement in the assessment of cerebral atrophy on CT using bicaudate and Sylvian fissure ratios

Abstract

Objectives: To assess and compare the interobserver variability of 2 cerebral-atrophy measures on computed tomographic (CT) scans.

Design: Measurements of the bicaudate ratio (BCR) and the Sylvian fissure ratio (SFR) on 20 CT scans of ischaemic stroke patients by 3 investigators.

Results: The intraclass correlation coefficient of BCR measurements was 0.82 (95% confidence interval (CI) 0.75–0.94), and of SFR measurements 0.69 (95% CI 0.57–0.89). The range of pairwise calculated Pearson correlation coefficients was smaller in the measurements of the BCR (0.89 to 0.92), than in the SFR measurements (0.66 to 0.84).

Conclusions: The interobserver agreement of the BCR measurements was excellent and that of the SFR measurements moderate.

Introduction

Cerebral atrophy may significantly contribute to cognitive impairment [29, 71, 98, 115, 150, 176]. Many ways of measuring cerebral atrophy on CT have been used [70, 128, 158]. Only a few studies reported on interobserver agreement in measuring cerebral atrophy [89, 108, 109], but none investigated the bicaudate ratio (BCR) or the Sylvian fissure ratio (SFR) which we often use to quantify the degree of cerebral atrophy. However, despite the absence of data on interobserver variability of the BCR, major decisions, such as shunting hydrocephalus in subarachnoid haemorrhage patients, may partly depend on the value of the BCR [184]. Because we wanted to study the relationship between cerebral atrophy and white matter lesions (see Chapter 6), we first determined the interobserver agreement in measuring the BCR and SFR.

Patients and methods

Patients were registered at the University Hospital of Maastricht between July 1987 and January 1994 in a prospective registry of all patients with a first-ever supratentorial brain infarct with symptoms lasting longer than 24 hours. From the brain CT scans of 999 registered patients, 20 CT scans were randomly selected. Brain CT scans were performed with the scanning plane parallel to the orbitomeatal line, with consecutive 10 mm slices. In some patients the orbitomeatal scanning plane could not be used because of their bad medical condition or restlessness. To measure cerebral atrophy we used 2 linear measurements: (1) as measure of internal cerebral atrophy we used the bicaudate ratio (BCR), which was measured at the level that most prominently depicted the heads of the caudate nuclei. The BCR is the minimal distance between the caudate indentations of the frontal horns divided by the distance between the inner tables of the skull along the same line [70]. (2) As measure of external cerebral atrophy we chose the Sylvian fissure ratio (SFR), which is the average of the 2 maximal Sylvian fissure widths taken from the CT slice showing the widest Sylvian fissures, divided by the transpineal coronal inner table diameter [70]. To increase reliability of the measurements, the CT scans were projected on the wall with an overhead projector, with a 10-fold magnification. The measurements of the BCR and SFR as defined above were practised in a few CT scans by 3 investigators together. Subsequently, the 3 investigators independently measured both ratios in 20 CT scans.

Statistical analysis

We assessed the interobserver agreement between the 3 investigators of the BCR and SFR by means of intraclass correlation coefficients with 95% confidence intervals (CI), computed by oneway analysis of variance (ANOVA) [166]. Pearson correlation coefficients were computed to assess the interobserver agreement between all pairs of investigators.

To detect significant differences in interobserver agreement between the pairs of investigators, the Pearson correlation coefficients were tested taking into account their mutual dependence [24].

Results

The intraclass correlation coefficient of BCR measurements was 0.82 (95% CI 0.75–0.94), and of SFR measurements 0.69 (95% CI 0.57–0.89).

Figure 5.1: Distribution of the bicaudate ratio in the measurements of 3 investigators.

Figures 5.1 and 5.2 show the distribution of the BCR and of the SFR, respectively, as measured by the 3 investigators. In Table 5.1 the Pearson correlation coefficients comparing all pairs of investigators in measuring cerebral atrophy are listed. The range of pairwise calculated Pearson correlation coefficients was smaller in the measurements of the BCR (0.89 to 0.92), than in the SFR measurements (0.66 to 0.84). The correlation coefficients of the measurements of investigator 1 and 3 were for both atrophy measures higher than those in the other pairs of investigators, but these differences in interobserver agreement between the pairs of investigators were not statistically significant.

Figure 5.2: Distribution of the Sylvian fissure ratio in the measurements of 3 investigators.

Discussion

We found an excellent interobserver agreement in the measurement of the BCR and a moderate agreement in the measurement of the SFR. The Sylvian fissure was visible on several CT slices with different widths on each slice. This may have increased interobserver variability by measuring the SFR on different CT slices by the 3 investigators. The finding that there was no significant difference in interobserver agreement between all pairs of investigators may be due to the small number of measurements.

We decided only to use the BCR as measure of internal atrophy (see Chapter 6), and not to measure external cerebral atrophy by means of the SFR, firstly, because the interobserver agreement of the BCR compared to that of the SFR was higher. Moreover, Coffey et al. [39] found in a volumetric magnetic resonance imaging (MRI) study that ventricular enlargement provides a more sensitive index of declining brain volume than does cortical atrophy.

We are not aware of an earlier study on interobserver agreement in the measurement of the BCR and SFR on CT. Only a few CT studies have been published on interobserver variability quantifying atrophy. For subjectively quantifying cerebral atrophy a low kappa (κ) of 0.24 [109], and of 0.55 [89] was found. Furthermore, a κ of 0.59 was found for the subjective rating of type (cortical/subcortical) of atrophy [109]. The interobserver correlation in subjective evaluation of Sylvian sulci on CT was in the study of Lee et al. [108]

Table 5.1: Pearson correlation coefficients comparing all pairs of investigators in measuring cerebral atrophy.

Cerebral-atrophy measures	Pearson correlation coefficient		
	Investigator 1 and 2	Investigator 1 and 3	Investigator 2 and 3
Bicaudate ratio	0.89	0.92	0.89
Sylvian fissure ratio	0.72	0.84	0.66

not significant. Staal et al. [167] assessed the degree of atrophy on CT subjectively, because an interobserver study of 60 normal CT scans did not produce reliable measurements. They do not mention an interobserver agreement on this subjective method. The interobserver agreements we found in objective measurements of the BCR and the SFR were clearly higher than in these studies which used subjective methods to quantify cerebral atrophy.

Apart from interobserver variability, possible errors in linear measurements of atrophy on CT depend on thickness (partial volume effect) and the interval of the slices [158]. Other methods have been used to measure cerebral atrophy on CT [158], such as planimetric methods, direct calculation of ventricle volume, and computed methods. Which method is most suitable and sufficiently operational for research remains unstudied.

With MRI scans slightly better interobserver agreements ($\kappa=0.48-0.67$) in subjective quantification of cerebral atrophy were found [148, 163]. Measurements of regional brain volume on MRI are highly reliable, with intraclass correlation coefficients for interrater reliability of 0.88–0.99, and for intrarater reliability of 0.93–0.99 [39].

Our study can not provide the normal values of the BCR and SFR. Others [184] combined two studies [46, 128] on BCR measurements in neurologically healthy individuals to derive upper limits for normal values (95th percentile) in several age-groups, but did not clearly state how they arrived at these 95th percentile values, especially for the higher age-group (age > 70 years). On the other hand, no better estimations of normal BCR values are presently known.

In conclusion we found that the interobserver agreement of the BCR on CT in our stroke patients was excellent, and that of the SFR moderate. No accurate normal values of these atrophy measurements exist.

6

Cerebral ventricular enlargement in stroke patients is not specifically associated with either small- or large-vessel disease

Abstract

Objectives: To investigate whether in ischaemic stroke patients cerebral atrophy, as measured by the degree of ventricular enlargement, is associated with presence and site of white matter lesions (WMLs), stroke subtype, or silent brain infarcts.

Design and Patients: (1) Ventricular enlargement was measured with the bicaudate ratio (BCR) on the computed tomographic (CT) scans of 917 patients with a first-ever supratentorial ischaemic stroke. Linear regression analysis determined the association of vascular risk factors and CT variables with the BCR. (2) CT scans of 954 first-ever supratentorial ischaemic stroke patients were reviewed for presence of deep or periventricular WMLs. By means of multivariate logistic regression analysis we determined the associations of vascular risk factors and CT variables with deep or periventricular WMLs.

Results: Ventricular enlargement was associated with higher age, male gender, use of diuretics, WMLs, and with silent small deep and territorial infarcts. Both periventricular and deep WMLs were associated with higher age, silent small deep infarcts, and with lacunar stroke compared with cardio-embolic stroke.

Conclusions: (1) As ventricular enlargement in ischaemic stroke patients is associated with WMLs and silent small deep and territorial infarcts, we conclude that ventricular enlargement is merely due to tissue loss and not specifically associated with either small- or large-vessel disease. (2) Deep and periventricular WMLs had similar risk factor profiles and were both related to ventricular enlargement, which points at a similar, presumably vascular, pathogenesis.

Introduction

Cerebral atrophy is a clinically important finding as it is related to cognitive impairment [29, 71, 98, 115, 150, 176]. Several studies, in elderly [29, 79, 102, 122, 193], hypertensive [159, 165], demented [115], and stroke patients [81, 86, 116, 147, 150, 176], pointed at hypertension as a risk factor for cerebral atrophy. Furthermore, vascular cerebral lesions such as symptomatic stroke, multiple cerebral infarcts on neuroimaging, and white matter lesions (WMLs) were associated with cerebral atrophy. The degree of cerebral atrophy in stroke patients may depend on the underlying vascular cause, such as small- or large-vessel disease, or cardiac embolism. Such a relationship could give more insight, although indirectly, into the pathogenesis of cerebral atrophy and would stress the importance of lowering the risk of stroke recurrences in specific stroke subgroups. Therefore, the first objective of this study was to study cerebral atrophy in a large stroke population, focusing on associations with vascular risk factors, CT findings, and clinical stroke subtype.

Cerebral ventricular enlargement may especially be associated with periventricular hypodensities on CT in the syndrome of normal pressure hydrocephalus [56, 155]. Such hypodensities are thought to be the result of leakage of cerebrospinal fluid (CSF) into the adjacent brain parenchyma, whereas WMLs in stroke patients are more likely the result of small-vessel disease of the white matter arterioles [31, 64, 65, 187]. Consequently, an eventual association between ventricular enlargement and periventricular WMLs could point at the presence of normal pressure hydrocephalus among stroke patients. Testing this hypothesis we compared vascular risk factor profiles of patients with deep or periventricular WMLs to gain indirect clues pointing at the alleged distinct pathogenesis in these two types of WMLs.

Patients and methods

Patients were registered at the University Hospital of Maastricht between July 1987 and January 1994 in a prospective registry of all patients with a first-ever supratentorial brain infarct with symptoms lasting longer than 24 hours, admitted or visiting the out-patient clinic. Routine investigations included standard blood tests, electrocardiogram, chest X-ray, CT scan of the brain, and noninvasive carotid studies. Echocardiography, 24-hour ECG monitoring, and cerebral angiography were done in selected cases.

Definitions

The following possible *vascular risk factors* were recorded: age, gender, hypertension (known hypertension, or at least 2 separate blood pressure recordings of higher than 160/90 mmHg before or at least 1 week after stroke), diabetes mellitus (known diabetes mellitus, or fasting serumglucose higher than 7 mmol/l, or a postprandial serumglucose

higher than 11 mmol/l, both on at least 2 separate occasions), haematocrit at stroke onset, history of ischaemic heart disease (myocardial infarction, angina pectoris), history of chronic obstructive pulmonary disease (COPD), cardiac source of embolism (atrial fibrillation, mitral stenosis, prosthetic aortic or mitral valve, recent myocardial infarction (within 6 weeks preceding stroke), endocarditis, cardiomyopathy, left ventricular aneurysm, intraventricular thrombus), use of diuretics prior to stroke, and significant (more than 50%) carotid stenosis ipsilateral to the symptomatic stroke.

Lacunar stroke was defined as an acute symptomatic stroke syndrome with a CT lesion compatible with occlusion of a single perforating artery, i.e., a small, subcortical, sharply margined hypodense lesion with a diameter smaller than 20 mm (small deep infarct), or in case of a specific lacunar syndrome (unilateral motor and/or sensory symptoms and signs that completely involve at least 2 of 3 body parts (face, arm, and leg) without disturbance of consciousness or language, visual field defect or other signs of cortical dysfunction) when the CT scan showed no specific lesion.

Territorial stroke was defined (1) as an acute stroke syndrome with CT findings compatible with infarction involving the cortex, or (2) when no specific lesion was visible on CT, as a clinically identified cortical syndrome consisting of unilateral motor and/or sensory symptoms and signs in combination with signs of cortical dysfunction with or without visual field defect, or as incomplete involvement of 2 body parts, or as isolated monoparesis [16], or as isolated cortical dysfunction (usually dysphasia). Patients with a large subcortical infarct were included in this group because of similar pathogenesis [18, 21]. By presumed stroke cause, 3 territorial stroke subtypes were discerned: cardio-embolic, atherothrombotic, and territorial stroke with undetermined cause. Cardio-embolic territorial stroke was defined as a territorial stroke in the presence of a cardiac source of embolism. Atherothrombotic stroke was defined as a territorial stroke in the presence of a significant carotid stenosis. If neither a cardiac source of embolism nor a significant carotid stenosis was found, then the territorial stroke was classified as one with undetermined cause. Because the analyses showed no difference between the atherothrombotic subgroup of territorial stroke, and that with undetermined cause, the results are shown for these 2 groups combined. The aim of this study was to investigate ventricular enlargement as measure of cerebral atrophy, and WMLs in 3 groups of patients, namely those with small-vessel disease (i.e., lacunar stroke), with large-vessel disease (i.e., territorial stroke due to large-vessel atherosclerosis), and those with territorial stroke due to cardiac embolism. Therefore, patients with a specific stroke cause such as vasculitis, arterial dissection etc., were not included in this study.

Silent brain infarct was defined as a low-density area on the CT scan compatible with infarction but without a history of stroke, as taken from the patient's history, from family, or any other accessible information. Also, the stroke symptoms at study entry had to be anatomically incompatible with this infarct. Old infarcts can usually be distinguished

from new ones because they are more hypodense, and there may be signs of surrounding tissue loss, like retraction of brain structures towards the infarct. Silent infarcts were also categorized as small deep or territorial.

White matter lesions (WMLs) were defined as focal or diffuse hypodensities in the periventricular or deep white matter, not involving the cortex, and with ill-defined margins to distinguish them from infarction [168]. Presence of WMLs around frontal or occipital horns, or in the centrum semiovale were rated separately. Patients with WMLs were divided in 2 subgroups: (1) patients with WMLs in the centrum semiovale with or without WMLs around frontal or occipital horns (deep WMLs), and (2) patients with WMLs limited to the area around the frontal or occipital horns (periventricular WMLs). No effort was made to quantify the degree of white matter density in these different sites as this may depend on the tuning of the CT scan.

CT analysis

CT scans were performed with the scanning plane parallel to the orbitomeatal line, with consecutive 10 mm slices. In some patients the orbitomeatal scanning plane could not be used because of their bad medical condition or restlessness. For the atrophy-study we assessed ventricular enlargement by means of the bicaudate ratio (BCR), which was measured on the CT slice that most prominently depicted the heads of the caudate nuclei (see Chapter 5). The BCR is the minimal distance between the caudate indentations of the frontal horns divided by the distance between the inner tables of the skull along the same line [70]. Furthermore, the CT scans were reviewed for presence and extensiveness of WMLs, and number of (symptomatic as well as silent) small deep and territorial infarcts by 2 neurologists. Only those WMLs and infarcts on which both neurologists agreed were registered.

Patient population

Of 999 consecutively registered patients, 37 patients were excluded because a CT scan of the brain had not been performed. Of the remaining 962 patients 45 were excluded for the first part of this study (measuring ventricular enlargement as measure of cerebral atrophy): in 34 patients the CT scan could not be retrieved, in 6 patients the BCR could not be measured because of edema caused by the ischaemic stroke, and in 5 patients not all vascular risk factors were known. So, 917 patients entered the atrophy-study.

For the second part of the study (studying the vascular risk factors leading to deep or periventricular WMLs) 8 of the 962 patients were excluded: 2 because the CT scan could not be retrieved, and 6 because not all vascular risk factors were known. So, 954 patients entered the WML-study. Of all patients included in the Maastricht Stroke Registry CT scans are routinely examined for infarcts and WMLs. The atrophy-measurements were done at a later stage. This explains why more CT scans could not be retrieved in the

atrophy-study.

Median time between study entry and CT scan was 5 days for the atrophy-study, and 4 days for the WML-study (range: 0–882). In respectively ten and eleven patients this period was more than 100 days: in six and seven respectively 100–200, in two 200–300, in one 566, and in one 882 days. Despite this long delay between stroke and the time of CT, we entered these patients in our registry because we could verify their symptomatic stroke with a compatible lesion on CT.

Statistical analysis

For the atrophy-study, linear regression analysis, in which the BCR was the dependent variable, determined the association of the BCR with various subsets of clinical and CT variables.

For the WML-study, we related presence of deep and periventricular WMLs to clinical and CT variables by means of bivariate statistical analysis with crude odds ratios ((c)OR) with 95% confidence intervals (CI). Multivariate logistic regression analysis with adjusted odds ratios ((a)OR) determined the association of various subsets of clinical and CT variables with presence of deep or periventricular WMLs.

Patients were categorized in 4 age-groups: 64 or younger, 65 to 71, 72 to 78, and older than 78 years. The 3 “higher-age” categories were compared with the youngest age. Haematocrit at admission was classified in 3 categories: low (men: < 0.41 l/l, women: < 0.36), normal (men: 0.41–0.51, women: 0.36–0.46), and high (men: > 0.51, women: > 0.46). Patients with low and high haematocrit were compared with those with normal values. The Rankin (handicap) score at study entry was dichotomized in 2 groups: functionally independent (Rankin $\leq$ 3) or dependent (Rankin = 4 or 5).

Results

Ventricular enlargement as measure of cerebral atrophy

Figure 6.1 depicts the distribution of the BCR in all stroke patients. The median value of the BCR was 0.14 (range: 0.04–0.32). The distribution of the BCR in this stroke population was fairly normal. In *Figure 6.2* the mean BCR is depicted in all age-groups. This shows the gradual increase of the BCR with increasing age. In patients younger than 31 years the BCR was relatively high. However, this group consisted only of 5 patients.

Table 6.1 shows the baseline characteristics and CT findings in the 3 subgroups of stroke patients in the atrophy-study. Median age was 72 (range: 24–95) years. Patients with a cardio-embolic stroke were significantly older than patients with a lacunar or atherothrombotic stroke (χ^2 -test: $p < 0.001$). In 652 patients a noninvasive carotid study was performed, which showed a significant stenosis on the symptomatic side in 147 (23%) patients: 25 (10%) lacunar, 11 (11%) cardio-embolic, and 111 (37%) atherothrombotic stroke patients.

Figure 6.1: Distribution of the bicaudate ratio in 917 ischaemic stroke patients.

Table 6.2 and Figure 6.3 show the results of linear regression analysis with the BCR as dependent variable. Among the clinical variables higher age (age 65–71 vs. ≤ 64 : regression coefficient (B) = 0.014, 95% CI 0.008–0.021; age 72–78 vs. ≤ 64 : $B=0.032$, 95% CI 0.026–0.039; age > 78 vs. ≤ 64 : $B=0.038$, 95% CI 0.030–0.045), male gender ($B=0.014$, 95% CI 0.009–0.019), and use of diuretics ($B=0.006$, 95% CI 0.000–0.011) were associated with a higher BCR. Of the CT variables WMLs ($B=0.013$, 95% CI 0.007–0.019), silent small deep infarcts ($B=0.006$, 95% CI 0.000–0.012), and silent territorial infarcts ($B=0.018$, 95% CI 0.008–0.027) were associated with a higher BCR. The type of symptomatic stroke did not influence the BCR significantly. In another linear regression model we added deep and periventricular WMLs separately as risk factor. Both types of WMLs were associated with a higher BCR (deep: $B=0.012$, 95% CI 0.005–0.020; periventricular: $B=0.014$, 95% CI 0.006–0.022).

Deep and periventricular WMLs

In Table 6.3 the baseline characteristics and CT findings in the 3 subgroups of stroke patients in the WML-study are listed. Median age was 72 (range: 24–96) years. Patients with a cardio-embolic stroke were significantly older than patients with lacunar or atherothrombotic stroke (χ^2 -test: $p=0.00$). In 676 patients a noninvasive carotid study was performed, which showed a significant stenosis on the symptomatic side in 149 (22%) patients: 25 (10%) lacunar, 11 (10%) cardio-embolic, and 113 (37%) atherothrombotic stroke patients.

Figure 6.2: Bicaudate ratio distribution in age-groups.

Table 6.4 and Figure 6.4 show crude and adjusted odds ratios with 95% confidence intervals comparing patients with deep WMLs (WMLs in the centrum semiovale with or without WMLs around frontal or occipital horns) with those without WMLs, and patients with periventricular WMLs (WMLs limited to the area around frontal or occipital horns) with those without WMLs. Both WML-subgroups were associated with higher age (deep WMLs: age 72–78 vs. ≤ 64 (a)OR 5.0, 95% CI 2.3–10.8, age > 78 vs. ≤ 64 (a)OR 12.4, 95% CI 5.6–27.7; periventricular WMLs: age 72–78 vs. ≤ 64 (a)OR 3.4, 95% CI 1.6–7.1, age > 78 vs. ≤ 64 (a)OR 9.2, 95% CI 4.3–19.6), with silent small deep infarcts (deep WMLs: (a)OR 7.4, 95% CI 4.6–12.0; periventricular WMLs: (a)OR 8.4, 95% CI 5.2–13.3), and with lacunar stroke compared with cardio-embolic stroke (deep WMLs: (a)OR 2.2, 95% CI 1.1–4.2; periventricular WMLs: (a)OR 2.3, 95% CI 1.2–4.3). Periventricular WMLs were also related to lacunar stroke compared with atherothrombotic stroke ((a)OR 1.9, 95% CI 1.1–3.2). Finally, deep WMLs were less strongly associated with male than female gender ((a)OR 0.6, 95% CI 0.3–0.9).

Discussion

Cerebral atrophy and vascular risk factors

In our study ventricular enlargement as measure of cerebral atrophy was related to higher age, male gender, and use of diuretics. Several authors [39, 75, 80, 86, 122, 147] also found the association with higher age and with male gender [75, 122]. Unfortunately,

Table 6.1: Baseline characteristics and CT findings in the 3 subgroups of stroke patients in the atrophy-study.

Baseline characteristics	Total	Symptomatic stroke subgroups		
		Lacunar	Cardio-embolic	Atherothrombotic/ Undetermined cause
	N=917	N=320 (35)	N=196 (21)	N=401 (44)
Age (years)				
≤ 64	231 (25)	96 (30)	25 (13)	110 (27)
65–71	224 (24)	84 (26)	44 (22)	96 (24)
72–78	242 (26)	86 (27)	50 (26)	106 (26)
> 78	220 (24)	54 (17)	77 (39)	89 (22)
Male gender	478 (52)	179 (56)	86 (44)	213 (53)
Hypertension	416 (45)	152 (48)	94 (48)	170 (42)
Diabetes mellitus	184 (20)	62 (19)	44 (22)	78 (19)
Ischaemic heart disease	240 (26)	63 (20)	68 (35)	109 (27)
COPD	93 (10)	39 (12)	20 (10)	34 (8)
Diuretics	261 (28)	80 (25)	78 (40)	103 (26)
Haematocrit: low	142 (15)	34 (11)	44 (22)	64 (16)
normal	691 (75)	251 (78)	120 (61)	320 (80)
high	84 (9)	35 (11)	32 (16)	17 (4)
Rankin = 4 or 5	466 (51)	100 (31)	130 (66)	236 (59)
White matter lesions	228 (25)	95 (30)	44 (22)	89 (22)
Silent small deep infarcts	211 (23)	100 (31)	31 (16)	80 (20)
Silent territorial infarcts	58 (6)	14 (4)	17 (9)	27 (7)

COPD = Chronic obstructive pulmonary disease.

Percentages between parentheses.

use of alcohol, which is associated with cerebral atrophy [141, 147], could not be reliably registered in our patients. A possible higher alcohol consumption among men could explain the relationship with male gender, but this remains speculative.

We found no association between ventricular enlargement and hypertension. Two studies [159, 165, 170] in which hypertensive patients without stroke were compared with normal control subjects, showed that ventricular enlargement was related to hypertension. Hypertension may not be identified as a discriminator among a stroke population, which already has a high frequency of hypertension and hypertensive end-organ damage.

In contrast with Manolio et al. [122], we found ventricular enlargement related to the use of diuretics. This finding is all the more surprising realizing that diuretics are sometimes used to diminish CSF production in hydrocephalus. One could speculate that diuretics lead to dehydration of the brain and thereby to ventricular enlargement. Especially in view of the connection between cerebral atrophy and dementia [29, 71, 150, 176], this

Table 6.2: Linear regression coefficients with 95% confidence intervals of clinical and CT variables in relation to the bicaudate ratio as dependent variable, in 917 stroke patients.

Vascular risk factors	B	95% CI	p-value
Age (years) 65–71 vs. age $\leq$ 64	0.014	0.008 – 0.021	0.00
72–78 vs. age $\leq$ 64	0.032	0.026 – 0.039	0.00
> 78 vs. age $\leq$ 64	0.038	0.030 – 0.045	0.00
Male gender	0.014	0.009 – 0.019	0.00
Hypertension	–0.003	–0.008 – 0.002	0.22
Diabetes mellitus	0.003	–0.003 – 0.009	0.37
Diuretics	0.006	0.000 – 0.011	0.05
White matter lesions	0.013	0.007 – 0.019	0.00
Symptomatic lacunar vs. cardio-embolic stroke	0.001	–0.006 – 0.008	0.76
Symptomatic lacunar vs. atherothrombotic stroke	0.004	–0.001 – 0.009	0.15
Silent small deep infarcts	0.006	0.000 – 0.012	0.05
Silent territorial infarcts	0.018	0.008 – 0.027	0.00
Rankin = 4 or 5	0.004	–0.001 – 0.009	0.14

B = Regression coefficient. CI = Confidence interval.

finding deserves further study.

Cerebral atrophy and multiple, usually silent infarcts

In our stroke population ventricular enlargement was associated with silent small deep and silent territorial infarcts. Type of symptomatic stroke was of no influence, in agreement with the study of Hijdra et al. [86]. Previously, cerebral atrophy was found to be related to multi-infarct dementia [71, 98], and prior stroke [122, 147]. We are not aware of a study on the relationship between silent infarcts and cerebral atrophy. Because both types of silent infarcts were related to ventricular enlargement, we do not think that a specific type (small- or large-vessel) of vasculopathy gives rise to ventricular enlargement. Merely, loss of cerebral tissue by multiple infarcts, leading to a “hydrocephalus ex vacuo”, seems a more probable hypothesis to explain this association.

Cerebral atrophy and WMLs

The association between cerebral atrophy and WMLs confirms the results of several other studies [5, 42, 81, 86, 89, 103, 132, 174, 193]. An increase in the BCR is a measure of ventricular enlargement which can point at either cerebral atrophy, or (normal pressure) hydrocephalus. Some authors [56, 155] suggest that CSF leakage into the adjacent periventricular brain parenchyma, and not a breakdown of myelin sheaths, may cause periventricular WMLs. This mechanism might play a role in the development of periventricular

Figure 6.3: Linear regression coefficients with 95% confidence intervals of clinical and CT variables in relation to the bicaudate ratio as dependent variable, in 917 stroke patients.

WMLs in (normal pressure) hydrocephalus, but can not explain deep WMLs. However, in our stroke patients this mechanism did probably not play a role in causing WMLs. Firstly, in our study both deep and periventricular WMLs were associated with ventricular enlargement, a finding that suggests similar causes for deep and periventricular WMLs in stroke patients. Secondly, similar vascular risk factor profiles in deep and periventricular WMLs do not argue in favour of a difference in pathogenesis between these two WML-types. Finally, none of our patients entered the study with the clinical syndrome of normal pressure hydrocephalus.

Mild periventricular hyperintensities on magnetic resonance imaging (MRI) scans are of no pathological significance and not associated with (normal pressure) hydrocephalus or vascular risk factors [49, 111, 120, 161, 197]. These periventricular hyperintensities seen on MRI are hardly visible on CT. The association between small deep infarcts and periventricular WMLs on CT suggests that these WMLs have a vascular cause.

Probably, also the association between ventricular enlargement and WMLs is based on loss of white matter. This hypothesis is supported by a magnetic resonance spectroscopy study in patients with subcortical ischaemic vascular dementia [121], which showed a significant association between cerebral atrophy and a lower ratio of N-acetylaspartate and

Table 6.3: Baseline characteristics and CT findings in the 3 subgroups of stroke patients in the WML-study.

Baseline characteristics		Total	Symptomatic stroke subgroups		
			Lacunar	Cardio-embolic	Atherothrombotic/ Undetermined cause
		N=954	N=330 (35)	N=210 (22)	N=414 (43)
Age (years)	≤ 64	239 (25)	98 (30)	26 (12)	115 (28)
	65–71	234 (25)	89 (27)	46 (22)	99 (24)
	72–78	250 (26)	88 (27)	54 (26)	108 (26)
	> 78	231 (24)	55 (17)	84 (40)	92 (22)
Male gender		495 (52)	185 (56)	89 (42)	221 (53)
Hypertension		435 (46)	158 (48)	102 (49)	175 (42)
Diabetes mellitus		191 (20)	65 (20)	46 (22)	80 (19)
Ischaemic heart disease		249 (26)	66 (20)	71 (34)	112 (27)
COPD		96 (10)	39 (12)	22 (10)	35 (8)
Diuretics		277 (29)	83 (25)	88 (42)	106 (26)
Haematocrit:	low	149 (16)	37 (11)	45 (21)	67 (16)
	normal	718 (75)	258 (78)	130 (62)	330 (80)
	high	87 (9)	35 (11)	35 (17)	17 (4)
Rankin = 4 or 5		491 (51)	103 (31)	143 (68)	245 (59)
WMLs:	total	234 (25)	95 (29)	46 (22)	93 (22)
	deep	117 (12)	46 (14)	20 (10)	51 (12)
	periventricular	117 (12)	49 (15)	26 (12)	42 (10)
Silent small deep infarcts		221 (23)	101 (31)	35 (17)	85 (21)
Silent territorial infarcts		61 (6)	14 (4)	18 (9)	29 (7)

COPD = Chronic obstructive pulmonary disease. WML = White matter lesion.

Percentages between parentheses.

creatinine-containing metabolites in frontal white matter. This low ratio of metabolites is probably due to loss of, or injury to axons. Furthermore, Yamaguchi et al. [191] found decreased cerebral blood flow to be correlated with severe cerebral atrophy. They hypothesize the reduction of cerebral blood flow to be an adaptation to diminished metabolic demand, corresponding to loss of brain substance.

Cerebral atrophy and cognitive impairment

Several studies showed an association between cerebral atrophy and cognitive impairment [29, 42, 71, 115, 116, 150, 176]. Furthermore, Loeb et al. [115] found that patients with multi-infarct dementia had a slightly greater loss of cerebral substance, due to ischaemic lesions, than nondemented subjects with multiple infarcts. So, patients with a

Figure 6.4: Crude and adjusted odds ratios with 95% confidence intervals of clinical and CT variables comparing stroke patients with deep or periventricular white matter lesions, with stroke patients without white matter lesions.

larger loss of cerebral tissue could be more at risk of developing dementia.

We may conclude, firstly, that ventricular enlargement in ischaemic stroke patients is merely due to cerebral tissue loss, and not specifically associated to either small- or large-vessel disease; secondly, the findings that deep and periventricular WMLs had similar risk factor profiles and were both related to ventricular enlargement, point at a similar, presumably vascular, pathogenesis. Cerebral atrophy in stroke patients seems to be due to different types of sustained injury to the brain, such as multiple small deep and territorial infarcts, or more diffuse injury due to WMLs. The type of underlying vascular pathology such as deep small-vessel disease, large-vessel thrombo-embolism, cardiogenic embolism, or arteriolosclerosis in the large-vessel territories in case of WMLs, had no specific effect on the degree of cerebral atrophy measured on CT shortly after stroke. Whether future cerebral tissue loss in stroke patients does not differ between stroke subtypes, remains to be studied. Treatment of vascular risk factors is not only important to reduce the incidence of recurrent stroke, it may also prevent further cerebral tissue loss and consequent cognitive decline.

Table 6.4: Crude and adjusted odds ratios with 95% confidence intervals of clinical and CT variables comparing stroke patients with deep or periventricular WMLs with those without WMLs.

Vascular risk factors	Deep WMLs N=117 (13%)			Periventricular WMLs N=117 (13%)		
	(c)OR	(95% CI)	(a)OR	(95% CI)	(c)OR	(95% CI)
Age (years)						
65-71 vs. age $\leq$ 64	1.6	(0.7-3.7)	1.5	(0.6-3.6)	1.6	(0.8-3.4)
72-78 vs. age $\leq$ 64	5.2	(2.5-10.7)	5.0	(2.3-10.8)	3.4	(1.7-6.8)
> 78 vs. age $\leq$ 64	8.5	(4.2-17.4)	12.4	(5.6-27.7)	7.7	(4.0-14.9)
Male gender	0.5	(0.3-0.7)	0.6	(0.3-0.9)	0.7	(0.5-1.1)
Hypertension	1.3	(0.9-2.0)	1.3	(0.8-2.2)	1.2	(0.8-1.7)
Diabetes mellitus	1.1	(0.7-1.8)	0.8	(0.5-1.4)	1.3	(0.8-2.0)
Diuretics	1.0	(0.7-1.6)	0.7	(0.4-1.2)	1.3	(0.8-1.9)
Symptomatic lacunar vs. cardio-embolic stroke	1.6	(0.9-2.8)	2.2	(1.1-4.2)	1.3	(0.8-2.2)
Symptomatic lacunar vs. atherothrombotic stroke	1.2	(0.8-1.9)	1.1	(0.7-1.9)	1.6	(1.0-2.5)
Silent small deep infarcts	6.7	(4.4-10.2)	7.4	(4.6-12.0)	7.4	(4.9-11.3)
Silent territorial infarcts	1.5	(0.7-3.1)	1.6	(0.7-3.7)	1.3	(0.6-2.8)
Rankin = 4 or 5	1.2	(0.8-1.7)	0.8	(0.5-1.3)	1.8	(1.2-2.6)

WMLs = White matter lesions. (c)OR = Crude odds ratio. (a)OR = Adjusted odds ratio. CI = Confidence interval.

7

Gait disorder and parkinsonian signs in patients with stroke relate to small deep infarcts and white matter lesions

Adapted from:

Van Zagten M, Lodder J, Kessels F. Gait disorder and parkinsonian signs in patients with stroke relate to small deep infarcts and white matter lesions. *Mov Disord* In press.

Abstract

Objectives: To study the prevalence of parkinsonian features (bradykinesia, rigidity, tremor, and gait disorder) in ischaemic stroke patients and their relationship with small deep or territorial infarcts, and white matter lesions (WMLs).

Design: Computed tomographic (CT) and clinical follow-up study in a cohort of 103 ischaemic stroke patients (median follow-up 3.0 years).

Setting: Primary and referral care centre.

Patients: Sixty-two of 144 registered patients with a first-ever symptomatic lacunar stroke and 41 of 155 with a territorial stroke not due to cardiac embolism, entered this study. Forty-seven (33%) of the non-participating patients with a lacunar stroke and 54 (35%) of those with a territorial stroke had died, 34 (24%) and 57 (37%), respectively, refused CT follow-up, and of 1 and 3 patients, respectively, the results of the neurologic examination were insufficient.

Main outcome measures: Parkinsonian features (bradykinesia, tremor, rigidity, and gait disorder) at follow-up, and the extent of WMLs, and the number of small deep and territorial infarcts on CT scans at study entry and at follow-up.

Results: One or more parkinsonian signs were found in 36% of the patients; 11% clinically had parkinsonism. Parkinsonian signs were more frequent in lacunar than in territorial stroke patients: bradykinesia in 45% and 7%, rigidity in 13% and 7%, tremor in 6% and 7%, gait disorder in 16% and 7%, respectively. Patients with WMLs at study entry (N=16) were compared with those without (N=87): 56% and 25% had bradykinesia, 25% and 8% rigidity, 25% and 3% tremor, 38% and 8% gait disorder, respectively. Multivariate regression analysis showed that WMLs at study entry were associated with bradykinesia, gait disorder, and tremor. Bradykinesia was associated with lacunar stroke at study entry.

Conclusions: One third of our stroke patients had one or more parkinsonian signs. Ten percent clinically had a parkinsonian syndrome, that differed from Lewy-body parkinsonism: infrequent resting tremor, but frequent gait disorder. Parkinsonian signs were associated with WMLs, and lacunar stroke. Therefore, this study favours a distinct vascular parkinsonian syndrome.

Introduction

The concept of vascular parkinsonism is still a matter of debate. Following the original description as a distinct syndrome by Critchley [40] it met much resistance until the introduction of computed tomography (CT) and later magnetic resonance imaging (MRI). These neuroimaging studies [149, 196] found vascular lesions, mainly small deep infarcts or white matter lesions (WMLs), to be related to certain parkinsonian features, which were considered to indicate a vascular cause of the syndrome. These features included: lower body parkinsonism [61], lack of resting tremor [88], marked gait difficulty [8, 126, 168], and L-dopa unresponsiveness [61]. However, most studies were done in selected parkinsonian patients who were compared with different types of controls, sometimes in rather small series. Patients at high risk of future progression of small deep infarcts or WMLs are those who suffered a symptomatic brain infarct [188]. If the proposed clinical signs of vascular parkinsonism would be related to (an increase of) especially small deep infarcts, WMLs, or both, this would strengthen the concept of vascular parkinsonism. Therefore, we studied the prevalence of parkinsonian features, including gait disorder, in stroke patients selected for repeated CT at least 1 year after stroke. We related parkinsonian features to small deep infarcts and WMLs on CT.

Patients and methods

Patients were registered at the University Hospital of Maastricht between July 1987 and June 1992 in a prospective registry of all patients, admitted or visiting the out-patient clinic, with a first-ever supratentorial brain infarct with symptoms lasting longer than 24 hours. Routine investigations included standard blood tests, electrocardiogram, chest X-ray, CT scan of the brain, and noninvasive carotid studies. Echocardiography, 24-hour ECG monitoring, and cerebral angiography were done in selected cases.

Definitions

The following *vascular risk factors* were recorded: age, gender, hypertension (known hypertension, or at least 2 separate blood pressure recordings of higher than 160/90 mmHg before or at least 1 week after stroke), diabetes mellitus (known diabetes mellitus, or fasting serumglucose higher than 7 mmol/l, or a postprandial serumglucose higher than 11 mmol/l, both on at least 2 separate occasions), hypercholesterolemia (known hypercholesterolemia, or serumcholesterol higher than 6.4 mmol/l), history of ischaemic heart disease (myocardial infarction, angina pectoris), and cardiac source of embolism (atrial fibrillation, mitral stenosis, prosthetic aortic or mitral valve, recent myocardial infarction (within 6 weeks preceding stroke), endocarditis, cardiomyopathy, left ventricular aneurysm, intraventricular thrombus).

Lacunar stroke was defined (1) as an acute stroke syndrome with CT findings compatible with occlusion of a single perforating artery, i.e., a small, subcortical, sharply marginated hypodense lesion with a diameter smaller than 20 mm (small deep infarct), or (2) as a specific lacunar syndrome (i.e., unilateral motor and/or sensory symptoms and signs that completely involve at least 2 of 3 body parts (face, arm, and leg) without disturbance of consciousness or language, visual field defect or other signs of cortical dysfunction) when the CT scan showed no specific lesion.

Territorial stroke was defined (1) as an acute stroke syndrome with CT findings compatible with infarction involving the cortex, or (2) when no specific lesion was visible on CT, as a clinically identified cortical syndrome consisting of unilateral motor and/or sensory symptoms and signs in combination with signs of cortical dysfunction with or without visual field defect, or as incomplete involvement of 2 body parts, or as isolated monoparesis [16], or as isolated cortical dysfunction (usually dysphasia). Patients with a large subcortical infarct were included in the territorial stroke group because of similar pathogenesis [18, 21]. For the aim of this study we included patients with lacunar stroke, presumably due to small-vessel occlusion, and patients with territorial stroke presumably due to large-vessel atherosclerosis. Patients with a cardiac source of embolism or a specific stroke cause such as vasculitis, arterial dissection etc., were therefore not included in this study.

Silent brain infarct was defined as a low-density area on CT compatible with infarction but without a history of stroke, as taken from the patient's history, from family, or any other accessible information. Also, the stroke symptoms at study entry had to be anatomically incompatible with this infarct. Old infarcts can usually be distinguished from new ones because they are more hypodense, and there may be signs of surrounding tissue loss, like retraction of brain structures towards the infarct. Silent infarcts were also categorized as small deep or territorial.

Progression of small deep or territorial infarcts was defined as new symptomatic or silent infarcts visible on CT at follow-up, which were not visible on CT at study entry.

White matter lesions were defined as focal or diffuse hypodensities in the periventricular or deep white matter, not involving the cortex, and with ill-defined margins to distinguish them from infarction [168]. The presence of WMLs around frontal or occipital horns or in the centrum semiovale was noted separately. No effort was made to quantify the degree of white matter density in these different sites, as this might depend on the tuning of the CT scan. Patients were said to have *WML progression* when the CT at study entry showed no WMLs, whereas the CT at follow-up did show WMLs, or when patients who had WMLs at study entry had new WMLs in other areas on the CT at follow-up.

Bradykinesia was defined as slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions [68].

Tremor was defined as any rhythmical oscillatory movement, not elicited by action or position [144].

Rigidity was defined as an increased, waxlike or viscous resistance of a limb during the whole range of a passive movement [137]. Rigidity was differentiated from hypertonia, which in contrast with rigidity is a velocity-dependent resistance to passive movement, and paratonia, which is an uneven resistance to passive movement [144]. If doubt existed between hypertonia and rigidity, which was sometimes the case on the stroke-affected side, the findings on the not-affected side were taken as decisive.

Gait disorder was defined as a gait disturbance characterized by variable base, shuffling, short steps, start and turn hesitation, and moderate disequilibrium [145], not caused by paresis.

Patient population

Of 144 consecutively registered patients with a symptomatic lacunar and 155 with a symptomatic territorial stroke, 63 and 44, respectively, entered this follow-up study. Four patients were excluded from the analysis, because the results of neurologic examination were insufficient, leaving 103 patients (62 lacunar and 41 territorial stroke). Of the 81 registered lacunar and 111 territorial stroke patients who did not participate in this follow-up study, 47 lacunar and 54 territorial stroke patients had died, and 34 and 57, respectively, refused follow-up CT mainly because they were unable to visit the out-patient clinic due to severe disablement. At follow-up we examined patients neurologically focusing on the following signs: bradykinesia, tremor, rigidity, and gait disorder. Presence or absence of these signs was judged clinically, by routine neurological physical exam at our out-patient clinic. Medication used at follow-up was recorded. Median follow-up was 3.0 (range: 1.2–4.7) years: 2.8 (range: 1.2–4.3) years in the lacunar and 3.2 (range: 1.7–4.7) years in the territorial stroke patients. All patients had CT at study entry and at follow-up. The median time between CT at study entry and at follow-up was 2.9 (range: 1.1–4.7) years: 2.8 (range: 1.2–4.3) years in the lacunar and 2.9 (range: 1.1–4.7) years in the territorial stroke patients. The CT scans made at study entry and at follow-up were mixed together and then reviewed for the presence and extensiveness of WMLs and for the number of small deep and territorial infarcts by 2 neurologists who were blind to the patients' identity and the timing of the CT. Only those WMLs and infarcts on which both investigators agreed were registered. A third investigator analyzed whether the extensiveness of WMLs and/or the number of infarcts had changed during follow-up.

Statistical analysis

We described the relationship between the presence of each recorded sign (bradykinesia, tremor, rigidity, gaitapraxia) and the clinical variables and CT features by means of bivariate statistical analysis with crude odds ratios ((c)OR) and 95% confidence intervals

(CI) and by means of multivariate logistic regression analysis with adjusted odds ratios ((a)OR). Because presence of 2 of the 3 investigated parkinsonian signs (bradykinesia, rigidity, tremor) is considered obligatory for the diagnosis of parkinsonism [144], the presence of 2 of these signs was analyzed separately. Besides the vascular risk factors, the following clinical variables were included in various regression models: stroke subtype, Rankin (handicap) score at 3 months after stroke and at follow-up, duration of follow-up, presence of WMLs at study entry, presence of silent small deep or territorial infarcts at study entry, progression of WMLs, and progression of silent small deep or territorial infarcts. The Rankin scores were divided into 2 groups: functionally independent (Rankin ≤ 3) or dependent (Rankin = 4 or 5). Patients were categorized in 2 age-groups: 67 years or younger, and older than 67 years. We divided duration of follow-up in 3 categories: less than 1200 days, 1200 to 1400 days, and more than 1400 days. For all dependent variables, the older patients and the 2 "longer-duration of follow-up" categories were compared with the youngest patients and shortest follow-up category, respectively.

Results

In total, 37 patients (36%) had one or more of the registered signs, and 11% had at least 2 parkinsonian signs (bradykinesia, rigidity, tremor), justifying the "diagnosis" parkinsonism. Clinical and CT features of the lacunar and territorial stroke patients are listed in *Table 7.1*, and *Table 7.2* shows the clinical and CT features in patients with parkinsonian signs. Bradykinesia was found in 45% of lacunar stroke patients, and in only 7% of territorial stroke patients. Rigidity was slightly more frequent in lacunar stroke patients: 13% vs. 7% in territorial stroke patients. Tremor was evenly distributed in the 2 stroke subgroups (6% in lacunar, and 7% in territorial stroke patients). In all cases it was a minor resting tremor, without specific parkinsonian aspects, such as "pill rolling". In 16% of lacunar stroke patients, and only 2% of territorial stroke patients, we found 2 of 3 parkinsonian signs, justifying the "diagnosis" of parkinsonism. Gait disorder was present in 16% of lacunar, and 7% of territorial stroke patients. In 1 patient gait was not assessable because of amputation of one leg. Median age was 58 (range: 30–85) years: 58 (range: 30–85) years in lacunar, and 60 (range: 37–82) years in territorial stroke patients. The number of patients in the different age-groups did not differ significantly between the 2 patient groups. There was an unbalanced distribution of follow-up duration between lacunar and territorial stroke patients in the category follow-up shorter than 1200 days (44% vs. 61%, χ^2 -test: $p=0.08$), and in the category 1200 to 1400 days (32% vs. 12%, χ^2 -test: $p=0.02$), respectively. None of the patients used antiparkinsonism medication or medication known to cause parkinsonian signs.

In *Table 7.1* also clinical and CT features are listed in patients with and without WMLs at study entry. WMLs occurred in 16% of all patients. WMLs were much more frequent in

Table 7.1: Clinical and CT characteristics of patients with lacunar or territorial stroke, and of patients with and without white matter lesions at study entry.

Clinical and CT characteristics	Symptomatic stroke subgroups		WMLs at study entry		Total N=103
	Lacunar N=62 (60)	Territorial N=41 (40)	Present N=16 (16)	Absent N=87 (84)	
Elderly patients (> 67 yrs)	20 (32)	12 (29)	7 (44)	25 (29)	32 (31)
Male gender	42 (68)	25 (61)	11 (69)	56 (64)	67 (65)
Hypertension	28 (45)	15 (37)	10 (63)	33 (38)	43 (42)
Diabetes mellitus	11 (18)	6 (15)	2 (13)	15 (17)	17 (17)
Ischaemic heart disease	7 (11)	13 (32)	5 (31)	15 (17)	20 (19)
Bradykinesia	28 (45)	3 (7)	9 (56)	22 (25)	31 (30)
Rigidity	8 (13)	3 (7)	4 (25)	7 (8)	11 (11)
Tremor	4 (6)	3 (7)	4 (25)	3 (3)	7 (7)
2 of 3 Parkinsonian signs*	10 (16)	1 (2)	6 (38)	5 (6)	11 (11)
Gait disorder	10 (16)	3 (7)	6 (38)	7 (8)	13 (13)
Silent SDIs at study entry	10 (16)	7 (17)	7 (44)	10 (11)	17 (17)
Silent TIs at study entry	1 (2)	0	0	1 (1)	1 (1)
WML progression	22 (35)	4 (10)	6 (38)	20 (23)	26 (27)
SDI progression	36 (58)	4 (10)	9 (56)	31 (36)	40 (39)
TI progression	3 (5)	11 (27)	4 (25)	10 (11)	14 (14)
Follow-up duration					
< 1200 days	27 (44)	25 (61)	9 (56)	43 (49)	52 (50)
1200–1400 days	20 (32)	5 (12)	4 (25)	21 (24)	25 (24)
> 1400 days	15 (24)	11 (27)	3 (19)	23 (26)	26 (25)

WMLs = White matter lesions. SDI = Small deep infarct. TI = Territorial infarct.

* Parkinsonian signs: bradykinesia, rigidity, tremor. Percentages between parentheses.

patients with bradykinesia (56%), rigidity (25%), tremor (25%), gait disorder (38%), and with presence of 2 or 3 parkinsonian signs (38%). Hypertension, ischaemic heart disease, and silent small deep infarcts at study entry were more frequently found in patients with WMLs, compared with those without. We did not find lesions involving the substantia nigra. However, CT is not very reliable in finding or excluding lesions in this area, because of frequent artefacts.

Table 7.3 and Figures 7.1 and 7.2 show the results of the bivariate and multivariate logistic regression analysis of the most relevant model of clinical variables, expressed as crude and adjusted odds ratios, respectively, with bradykinesia, tremor, rigidity, gait disorder, or with the combination of at least 2 parkinsonian signs as dependent variables. In the analysis of tremor WML progression was left out as clinical variable because no patient with tremor had WML progression. Bradykinesia was associated with higher age ((a)OR 4.1,

Table 7.2: Clinical and CT features in patients with parkinsonian signs.

Clinical and CT characteristics	Bradykinesia N=31 (30)	Rigidity N=11 (11)	Tremor N=7 (7)	2 of 3 Parkinsonian signs* N=11 (11)	Gait disorder N=13 (13)	Total N=103
Elderly patients (age > 67 years)	14 (45)	6 (55)	4 (57)	7 (64)	8 (62)	32 (31)
Male gender	22 (71)	8 (73)	4 (57)	8 (73)	9 (69)	67 (65)
Hypertension	14 (45)	6 (55)	5 (71)	8 (73)	6 (46)	43 (42)
Diabetes mellitus	9 (29)	1 (9)	1 (14)	1 (9)	2 (15)	17 (17)
Ischaemic heart disease	4 (13)	0	1 (14)	0	3 (23)	20 (19)
Lacunar stroke at study entry	28 (90)	8 (73)	4 (57)	10 (91)	10 (77)	62 (60)
WMLs at study entry	9 (29)	4 (36)	4 (57)	6 (55)	6 (46)	16 (16)
Silent SDIs at study entry	5 (16)	3 (27)	1 (14)	3 (27)	3 (23)	17 (17)
Silent TIs at study entry	0	0	0	0	0	1 (1)
WML progression	10 (32)	3 (27)	0	3 (27)	4 (31)	26 (27)
SDI progression	19 (61)	6 (55)	4 (57)	8 (73)	9 (69)	40 (39)
TI progression	3 (10)	1 (9)	2 (29)	1 (9)	1 (8)	14 (14)

WMLs = White matter lesions. SDI = Small deep infarct. TI = Territorial infarct.

* Parkinsonian signs: bradykinesia, rigidity, tremor. Percentages between parentheses.

Figure 7.1: Crude and adjusted odds ratios with 95% confidence intervals of clinical variables in patients with bradykinesia, gait disorder, rigidity, and 2 of 3 parkinsonian signs. WMLs = White matter lesions. SDI = Small deep infarct. Parkinsonian signs: bradykinesia, rigidity, tremor.

Figure 7.2: Crude and adjusted odds ratios with 95% confidence intervals of clinical variables in patients with tremor. WMLs = White matter lesions. SDI = Small deep infarct.

95% CI 1.2–13.9), diabetes mellitus ((a)OR 9.2, 95% CI 1.9–43.7), lacunar stroke at study entry ((a)OR 11.5, 95% CI 2.4–54.9), and with WMLs at study entry ((a)OR 8.0, 95% CI 1.6–41.6). Gait disorder was related to higher age ((a)OR 4.0, 95% CI 1.0–16.8), and WMLs at study entry ((a)OR 7.1, 95% CI 1.5–33.7). Tremor was associated with WMLs at study entry ((a)OR 7.0, 95% CI 1.2–40.3). No clinical variable was significantly related to rigidity. Two out of three parkinsonian signs (bradykinesia, tremor, rigidity) were associated with higher age ((a)OR 6.7, 95% CI 1.1–42.4), lacunar stroke at study entry ((a)OR 16.4, 95% CI 1.0–271.9), and WMLs at study entry ((a)OR 12.6, 95% CI 1.8–87.7). Eight of these patients also had gait disorder. There was a negative association between the presence of at least 2 parkinsonian signs and WML progression ((a)OR 0.08, 95% CI 0.01–1.0).

Discussion

We found that more than one third of patients with a first cerebral infarct, after a median follow-up of 3 years, had parkinsonian signs, and in 10% of the patients there was a parkinsonian syndrome. Bradykinesia, gait disorder, and rigidity were more frequent among lacunar, than among territorial stroke patients. Patients with WMLs at study entry had

more than twice as often parkinsonian signs than patients without WMLs. Parkinsonian signs were associated with WMLs at study entry, lacunar stroke at study entry, and higher age.

Not all patients initially included in our stroke registry were available for follow-up, which may have created bias, but if so, most likely towards underdetection of parkinsonian signs: most patients not investigated had died, or were severely disabled, because of which the younger and relatively less disabled patients participated in the study. We judged the presence of parkinsonian signs clinically, without quantification, merely to measure the frequency of parkinsonian features to study the development of "vascular parkinsonism" in stroke patients. Unfortunately we had no information on the presence of parkinsonian signs at stroke onset.

In 3 patients, the initial CT scans showed more extensive WMLs than the follow-up CT scans. In search for an explanation of this apparently odd finding, we reviewed the 2 CT scans of each patient. In these 3 patients, the follow-up CT scans showed diminished black-and-white contrast compared with the initial CT scans, which may have led to an underestimation of the extensiveness of WMLs. Furthermore, 1 of the 3 patients had WMLs around the occipital horns on the initial CT scan. The follow-up CT scan in this patient showed a large infarct in the territory of the middle cerebral artery extending around the occipital horn, which interfered with judgement of WMLs in this area. There were no signs of ventricular enlargement or changes in ventricular size in follow-up CT scans compared with the initial CT scans in these 3 patients. Therefore, intra-observer variability, rather than real change, such as might occur in periventricular WMLs related to (normal pressure) hydrocephalus [51, 56, 106, 132], may explain these discrepancies.

The absence of resting tremor [88], so-called lower body parkinsonism (marked gait disorder with minimal upper limb involvement), and L-dopa unresponsiveness are often considered to point at a vascular cause [61], but not always [88]. In our study only 19% of patients with one or more parkinsonian signs had a resting tremor, none of which had the typical "pill-rolling" aspect. Gait disorder was found in 35% of patients with one or more parkinsonian sign.

Whether a non-Lewy-body-related, vascular parkinsonism exists can not easily be inferred from studying patients with Parkinson's disease. Although such patients may have vascular lesions, it remains difficult to identify the relevance of such lesions as a cause of the clinical signs. Studying parkinsonian signs in vascular compromised patients would be more appropriate, but such studies have scarcely been performed except for a few case reports [138, 180]. Reider-Groswasser et al. [152] found in 45 patients with small deep (lacunar) infarcts in the basal ganglia on CT, in 38% parkinsonism, 31% hemiparesis, and in 20% both parkinsonism and hemiparesis. In our study, of all parkinsonian signs only bradykinesia and presence of 2 out of 3 parkinsonian signs were associated with lacunar stroke at study entry. No parkinsonian sign was associated with progression of small deep

infarcts. Because of a strong relationship between WMLs and small deep infarcts [188] and the fact that both these features were entered in our regression model, any correlation between parkinsonian signs other than bradykinesia and presence of 2 out of 3 parkinsonian signs, and small deep infarcts may have been masked.

Several authors investigated neuroimaging findings in patients with a parkinsonian syndrome or gait disorder. Zijlmans et al. [196] found significantly more subcortical white or grey matter lesions on MRI scans in patients with suspected vascular parkinsonism than in patients with Parkinson's disease or those with hypertension. Piccini et al. [149] found significantly more often WMLs on MRI scans in patients with Parkinson's disease than in healthy subjects. In 33% of patients with progressive supranuclear palsy a multi-infarct state was found [44]. WMLs were also frequent in patients with gait and balance disorders [8, 126, 168], in multi-infarct dementia patients with gait disorder [179], and in patients with Alzheimer disease and gait disorder [12]. These studies, including ours, point at a relationship between cerebral ischaemia and parkinsonian features including gait disorder, whereas the clinical syndrome differs from that of Lewy-body Parkinson's disease. This makes a syndrome of "vascular parkinsonism" very likely.

Why are WMLs and lacunar stroke associated with parkinsonian signs? Both small deep (lacunar) infarcts and WMLs, but not territorial infarcts, may damage the basal ganglia-thalamocortical circuit, resulting in parkinsonian signs. In patients with striatal infarcts Nakane et al. [139] showed degenerative change in the ipsilateral substantia nigra 2 weeks after stroke, as a possible result from excessive excitation due to loss of inhibitory γ -aminobutyric acid (GABA)ergic input. However, in another study [192] in vascular-parkinsonism patients not a significant decrease in number of pigmented neurons in the substantia nigra, but less oligodendrocytes in the frontal white matter were found. Small deep (lacunar) infarcts and WMLs are both thought to be caused by small-vessel disease [3, 7, 28, 31, 162, 187]. The presence of both small deep infarcts and WMLs may reflect a more advanced stage of small-vessel disease, with consequently more seriously affected patients.

We found WMLs at study entry but not WML progression associated with parkinsonian signs. It could be that the period during which WMLs progressed in our study was too short for the development of parkinsonian signs, whereas WMLs at study entry might have existed for a longer time. As we are not informed about how long WMLs at study entry existed, this remains speculative.

In conclusion: one third of our stroke patients had one or more parkinsonian signs, 10% had the clinical syndrome of parkinsonism. Clinically the parkinsonian syndrome in these stroke patients differed from that in Lewy-body parkinsonism: resting tremor was infrequent, whereas gait disorder was often found. As parkinsonian signs were associated with WMLs and lacunar stroke, small-vessel disease located in either the deep structures or the white matter may be the major cause of "vascular parkinsonism".

Table 7.3: Adjusted odds ratios with 95% confidence intervals of clinical variables in patients with bradykinesia, rigidity, tremor, 2 of 3 parkinsonian signs, and gait disorder.

Vascular risk factors	Bradykinesia N=31 (30%)	Rigidity N=11 (11%)	Tremor N=7 (7%)	2 of 3 Parkinsonian signs* N=11 (11%)	Gait disorder N=13 (13%)
Male gender	1.3 (0.4-4.1)	1.6 (0.3-7.7)	0.7 (0.1-4.2)	1.8 (0.3-12.9)	1.0 (0.2-4.4)
Age (years) > 67 vs. age ≤ 60	4.1 (1.2-13.9)	2.9 (0.7-12.8)	2.6 (0.5-15.0)	6.7 (1.1-42.4)	4.0 (1.0-16.8)
Hypertension	0.5 (0.2-1.6)	1.5 (0.3-6.6)	2.9 (0.5-19.3)	3.4 (0.6-20.2)	0.6 (0.1-2.5)
Diabetes mellitus	9.2 (1.9-43.7)	0.4 (0.04-3.6)	1.0 (0.05-7.4)	0.1 (0.005-2.7)	1.1 (0.2-7.8)
Lacunar stroke at study entry	11.5 (2.4-54.9)	2.7 (0.5-16.0)	0.3 (0.04-3.4)	16.4 (1.0-271.9)	1.7 (0.3-10.3)
WMLs at study entry	8.0 (1.6-41.6)	3.7 (0.7-18.5)	7.0 (1.2-40.3)	12.6 (1.8-87.7)	7.1 (1.5-33.7)
WML progression	0.6 (0.1-2.3)	0.4 (0.05-2.6)		0.08 (0.01-1.0)	0.4 (0.06-2.8)
SDI progression	1.6 (0.5-5.4)	1.1 (0.2-6.1)	2.2 (0.2-20.2)	1.3 (0.2-9.8)	3.2 (0.6-17.2)
Follow-up (days)	1200-1400 vs. < 1200	2.6 (0.6-10.5)	0.3 (0.03-3.0)	1.2 (0.1-10.2)	0.8 (0.1-4.9)
	> 1400 vs. < 1200	1.3 (0.3-5.9)	2.3 (0.4-12.8)	0.5 (0.04-5.7)	1.0 (0.2-6.5)

WMLs = White matter lesions. SDI = Small deep infarct. * Parkinsonian signs: bradykinesia, rigidity, tremor.

95% Confidence intervals between parentheses.

8

General discussion

Now it is time to see whether we succeeded in trying to shed more light on cerebral small-vessel disease. Is cerebral small-vessel disease an entity or must it according to pathogenesis be further differentiated?

Cerebral small-vessel disease, its pathogenesis and vascular risk factors

Distinguishing types of cerebral small-vessel disease may be important in the planning of stroke treatment trials. Although additional pathologic studies would be of great value they are difficult to perform because of the low early case-fatality rate and consequently the low autopsy rate for lacunar stroke patients [10, 114]. Therefore, we need to use other methods of examining whether two types of small-vessel disease can be distinguished. Comparing the vascular risk factor profiles, clinical manifestations and disease progression in patients with different types of lesions caused by small-vessel disease could add to our understanding of cerebral small-vessel disease. Furthermore, in this way tools may be gathered to recognize patients with different types of small-vessel disease by looking at their vascular risk factors and their symptoms and signs.

This study showed a clear relationship between WMLs and small deep (lacunar) infarcts. WMLs were especially associated with multiple, mostly silent small deep infarcts. WMLs are thought to result from arteriolosclerosis. Two distinct types of small-vessel disease seem to be involved in small deep (lacunar) infarcts. Single symptomatic small deep (lacunar) infarcts are thought to be caused by microatheromatosis, whereas the somewhat smaller, silent ones are probably caused by arteriolosclerosis. The strong association we found between WMLs and multiple, usually silent small deep infarcts supports the idea of arteriolosclerosis causing WMLs and multiple, usually silent small deep infarcts.

In primary intracerebral haemorrhage, mostly located in the basal ganglia and thalamus, arteriolosclerosis is also the most prevalent vasculopathy, as shown in post-mortem studies. The risk factor profile of patients with primary intracerebral haemorrhage differed in our study from that in symptomatic lacunar stroke patients. Although indirectly, this finding also adds evidence to the idea of two distinct types of small-vessel disease: primary intracerebral haemorrhage is probably caused by arteriolosclerosis, and most symptomatic lacunar stroke by the other type of small-vessel disease, i.e., microatheromatosis. So, arteriolosclerosis may lead both to primary intracerebral haemorrhage, and to multiple, usually silent small deep infarcts. In both hypertension is the most important risk factor. However, what other factors play a role in causing either an ischaemic lesion or a haemorrhage in patients with this small-vessel disease is unknown. Duration and severity of hypertension, daily blood pressure fluctuations (e.g., a sudden rise of blood pressure) and effects of treatment may be relevant in this respect. Constitutional factors may also be involved.

The relationship between WMLs and multiple, usually small deep infarcts is remarkable, because they occur in different vascular territories: multiple silent small deep infarcts in the territory of small deep penetrating arteries, and WMLs in the territory of the superficial

perforating branches of large cerebral arteries. The vasculopathy that results in WMLs and multiple silent small deep infarcts may therefore be pathologically homogeneous but heterogeneous as to the affected cerebral vascular system. What causes deep perforating vessels to react with infarction and the superficial system with "incomplete infarction" and demyelination remains unclear. Hypothetically, because of differences between basal ganglia and white matter in vascular anatomy and cerebral blood flow regulation, vascular insufficiency might lead to small infarcts in the basal ganglia, and to confluent areas of demyelination, axonal loss, dilated perivascular spaces, and gliosis in the white matter.

In our study, in accordance with several other studies, the association between WMLs and hypertension could not be confirmed. Several reasons may be responsible for this finding. Firstly, hypertension may not be identified as a discriminator in the different subgroups of a stroke population which already has a high frequency of hypertension and end-organ damage due to hypertension. Secondly, antihypertensive treatment in our stroke patients may have weakened the effect of hypertension as a risk factor. Furthermore, in the very old, the importance of elevated blood pressure for the risk of vascular disease seems to diminish or even reverse. Since cardiovascular risk factors are all associated with increased mortality, very old survivors with these risk factors may form a selected group resistant to the damaging effects of hypertension. Age may be a far more important risk factor in the elderly than hypertension.

We found that both multiple, usually silent small deep infarcts and WMLs occur mostly in lacunar stroke patients. This suggests that the two distinct entities of small-vessel disease often occur simultaneously, for both multiple, usually silent small deep infarcts and WMLs are probably due to arteriolosclerosis, whereas symptomatic lacunar stroke is mostly caused by microatheromatosis. The reasons for small deep infarcts caused by arteriolosclerosis to be usually silent, are probably that these infarcts are often smaller than symptomatic small deep (lacunar) infarcts, and located in "neurologically silent" areas. Hypertension probably is the common risk factor in both these types of small-vessel disease, whereas more severe hypertension may result in arteriolosclerosis.

Although symptomatic lacunar stroke is thought to be caused by atheromatosis of the small vessels, lacunar stroke patients usually do not have evidence of atheromatosis of the large vessels (e.g., carotid stenosis). Why atheromatosis affects large (e.g., carotid) arteries in some patients and small arteries in others is not known. Maybe race is of influence here: Caucasians more often have extracranial vasculopathy, whereas Asiatics more frequently suffer from intracranial vasculopathy. Here also, more effort should be devoted to study the severity of hypertension as an independent predictor of stroke subtype as some patients may need more diligent antihypertensive treatment. Regular treatment may not suffice as arteriolosclerosis may progress despite such treatment, as we showed.

Progression of cerebral small-vessel disease and its long-term sequelae

We found, 3 years after the first-ever stroke, in 26% of ischaemic stroke patients progression of WMLs and in 38% progression of small deep infarcts. Both occurred mainly in lacunar stroke patients. It is both amazing and disappointing that WMLs and small deep infarcts were rapidly progressive despite standard stroke treatment. Our stroke patients were treated according to present standards, i.e., treatment of vascular risk factors (e.g., with antismoking advise, antihypertensives, antidiabetics, and diet) and treatment with aspirin or anticoagulants. Possibly, antihypertensive treatment was not sufficient, or at the time the treatment was started end-organ damage had advanced too far. However, we do not have detailed information on blood pressure over time in our patients, such as the duration and severity of hypertension, daily blood pressure fluctuations and effects of treatment, partly because the treatment was usually done by the general practitioner, cardiologist or specialist for internal diseases. Currently a study is ongoing in our department regarding these aspects of hypertension and its effects on WMLs. However, it could be that hypertension is not really the causative factor in arteriolosclerosis. Hypothetically, both hypertension and arteriolosclerosis may result from another yet unknown (e.g., genetic or environmental) factor.

Apart from morbidity directly caused by the stroke, we showed that one third of ischaemic stroke survivors examined 3 years after stroke had additional morbidity due to parkinsonian signs. Ten percent actually had the clinical syndrome of parkinsonism. Clinically the parkinsonian syndrome in these stroke patients differed from that in Lewy-body parkinsonism: resting tremor was infrequent, whereas gait disorder was often found. These parkinsonian signs were associated with WMLs and lacunar stroke, and therefore probably result from cerebral small-vessel disease. We think that WMLs and lacunar stroke cause multiple lesions in the basal ganglia-thalamocortical circuit, resulting in parkinsonian signs. Our study supports the idea of "vascular parkinsonism" as a distinct parkinsonian syndrome with specific symptoms and signs, and etiology. We found WMLs at study entry but not WML progression associated with parkinsonian signs. It could be that the period during which WMLs progressed in our study was too short for the development of parkinsonian signs, whereas WMLs at study entry might have existed for a longer time. As we are not informed about how long WMLs at study entry existed, this remains speculative. For this reason a prospective follow-up study of first-ever ischaemic stroke patients will soon start in our department, that aims at a more extensive investigation of the prevalence and causes of parkinsonian signs in stroke patients.

Cerebral ventricular enlargement in ischaemic stroke patients was not associated with a specific ischaemic stroke subtype. Probably, ventricular enlargement is merely due to cerebral tissue loss, irrespective of the causative factor. In view of the relation between cerebral atrophy and cognitive impairment, prevention of any type of stroke might be an important issue. Furthermore, we found that both deep and periventricular WMLs

had similar risk factor profiles, and were both related to ventricular enlargement. Some authors suggest that periventricular WMLs in normal pressure hydrocephalus may result from leakage of cerebrospinal fluid into the adjacent periventricular brain parenchyma, and thus may not result from a vascular cause. Our results indicate that this mechanism is not frequent in periventricular WMLs in stroke patients.

As stated in the general introduction, the aim of the studies described in this thesis was to investigate clinically whether heterogeneity of cerebral vascular lesions (intracerebral haemorrhage, different types of small deep infarcts, and WMLs) coincided with homogeneity as to the underlying type of cerebral vascular disease. It may be concluded that this is largely the case; except for single, symptomatic lacunar infarcts (due to small-vessel atheromatosis) the remaining lesions are caused by arteriolosclerosis. Further study of factors determining the heterogeneity in cerebral lesions remains of utmost importance in aiming to arrive at a better treatment of cerebral small-vessel disease. Furthermore, regarding the progression of WMLs and small deep infarcts, and the morbidity due to vascular parkinsonism, the search for a specific therapeutical option in cerebral small-vessel disease is also an important issue. More knowledge on various aspects of hypertension in relationship with end-organ (brain) damage could lead to such options, as hypertension is probably the most important risk factor in cerebral small-vessel disease. Such studies are currently being done.

Summary

Stroke is a general term for several types of vascular injuries to the brain. Risk factor profiles, symptoms and signs, pathogenesis, therapy, prognosis, and long-term sequelae differ among stroke subtypes. To arrive at effective prevention of stroke, knowledge of what causes a stroke in individual patients is needed. The risk reduction of stroke achieved by carotid surgery and anticoagulation-therapy in certain stroke subgroups, shows that effective intervention depends on the pathogenesis and vascular risk factor profile.

In this study we chose to investigate several aspects of lesions presumably caused by cerebral small-vessel disease, such as small deep (lacunar) infarcts, white matter lesions (WMLs), and primary deep intracerebral haemorrhage. We aimed firstly to investigate whether these heterogeneous lesions are homogeneous as to the type of underlying vascular disease (presumably cerebral small-vessel disease). The type of cerebral small-vessel disease probably differs among these lesions. Post-mortem studies showed that arteriolosclerosis of the deep penetrating arteries and arterioles is the underlying vasculopathy in primary deep intracerebral haemorrhage. In small deep (lacunar) infarcts pathological evidence points at two distinct small-vessel diseases: arteriolosclerosis in multiple, usually silent small deep infarcts, and microatheromatosis in the somewhat larger symptomatic ones. Although in WMLs sometimes a mixture of pathologic changes is found, many authors hold arteriolosclerosis as the underlying vasculopathy. Furthermore, possible long-term consequences of cerebral small-vessel disease were investigated, such as cerebral atrophy and vascular parkinsonism.

In *Chapter 2* the vascular risk factor profiles in patients with a primary deep intracerebral haemorrhage, a lacunar or territorial stroke were compared, assuming that such profiles may be indicative of the nature of the underlying vasculopathy. A history of ischaemic heart disease and diabetes mellitus were more strongly associated with ischaemic stroke of either type than with primary intracerebral haemorrhage. Hypertension did not emerge as an independent variable associated with stroke subtype. These differences in vascular risk factors do not support the idea of a similar nature of the underlying small-vessel disease in primary intracerebral haemorrhage and the majority of lacunar strokes.

In *Chapter 3* the progression over time of WMLs and the number of small deep and territorial infarcts in stroke patients was studied. Furthermore, the hypothesis was tested that WMLs are associated with small deep infarcts. We performed a computed tomogra-

phic (CT) follow-up study in a cohort of 107 ischaemic stroke patients (median follow-up 3.0 years). WMLs progressed in 26% of the patients. This progression was associated with symptomatic lacunar stroke at study entry, silent small deep infarcts at study entry, old age, and longer follow-up. We found progression of small deep infarcts in 38% of the patients. The progression was associated with symptomatic lacunar stroke at study entry and longer follow-up. Progression of both WMLs and small deep infarcts, which occurred in 16% of the patients, was related to symptomatic lacunar stroke at study entry, silent small deep infarcts at study entry, and longer follow-up. The number of territorial infarcts increased in 13% of the patients. This increase was associated with symptomatic territorial stroke at study entry and a history of ischaemic heart disease. We concluded that the marked progression of WMLs and small deep infarcts that occurred mainly in lacunar stroke patients suggests that both WMLs and small deep (lacunar) infarcts are caused by a small-vessel disease, which is progressive despite standard stroke treatment.

In *Chapter 4* the hypothesis was tested that WMLs are especially associated with multiple, usually silent small deep infarcts. We studied the incidence of WMLs in 960 first-ever ischaemic stroke patients: 332 patients with a lacunar stroke, 213 with a cardio-embolic territorial stroke, and 415 with a atherothrombotic territorial stroke. Furthermore, we determined the relationship of WMLs with vascular risk factors, symptomatic and silent infarcts. Of all stroke patients 24% had WMLs. WMLs were associated with higher age, lacunar stroke and, very strongly, with silent small deep infarcts. Furthermore, WMLs were related to silent territorial infarcts in the atherothrombotic stroke subgroup. We concluded that these findings support the hypothesis that WMLs and multiple, usually silent small deep infarcts have the same vascular cause, namely arteriolosclerosis.

Aiming to test whether cerebral atrophy in stroke patients is related to presence of WMLs and stroke, we first assessed and compared the interobserver variability of two cerebral atrophy measures on CT scans in *Chapter 5*. The bicaudate ratio (BCR) and the Sylvian fissure ratio (SFR) were measured on 20 CT scans of ischaemic stroke patients by 3 investigators. The intraclass correlation coefficient of BCR measurements was 0.82 (95% confidence interval (CI) 0.75–0.94), and of SFR measurements 0.69 (95% CI 0.57–0.89). The range of Pearson correlation coefficients calculated for all pairs of investigators was smaller in the measurements of the BCR (0.89 to 0.92), than in the SFR measurements (0.66 to 0.84). So, the interobserver agreement of the BCR measurements was excellent and that of the SFR measurements only moderate.

In *Chapter 6* the results are shown of the cerebral atrophy study. Cerebral atrophy was measured by the BCR, in 917 first-ever ischaemic stroke patients. The first aim of this study was to investigate whether in ischaemic stroke patients cerebral atrophy, as measured by the

degree of ventricular enlargement, is associated with presence of WMLs, stroke subtype, or silent brain infarcts. Ventricular enlargement was associated with higher age, male gender, use of diuretics, WMLs, and with silent small deep and territorial infarcts. As ventricular enlargement in ischaemic stroke patients was associated with WMLs and silent small deep and territorial infarcts, we concluded that ventricular enlargement is merely due to tissue loss and not specifically associated with either small- or large-vessel disease.

In the syndrome of normal pressure hydrocephalus, cerebral ventricular enlargement might be especially associated with periventricular hypodensities on CT. In this syndrome such hypodensities are thought to be the result of leakage of cerebrospinal fluid into the adjacent brain parenchyma. Therefore, we investigated whether periventricular and deep WMLs were both associated with ventricular enlargement, and compared vascular risk factor profiles of patients with deep or periventricular WMLs to gain indirect clues pointing at the alleged distinct pathogenesis in these two types of WMLs. We found that both deep and periventricular WMLs were associated with ventricular enlargement. Furthermore, both types of WMLs were associated with higher age, silent small deep infarcts, and with lacunar stroke compared with cardio-embolic stroke. So, in ischaemic stroke patients deep and periventricular WMLs had similar risk factor profiles and were both related to ventricular enlargement, pointing at a similar, presumably vascular, pathogenesis.

In *Chapter 7* parkinsonian signs were studied in ischaemic stroke patients 3 years after the first-ever stroke. Parkinsonian signs in ischaemic stroke patients might be a long-term consequence of cerebral (small-) vessel disease. However, the concept of vascular parkinsonism is still a matter of debate. Certain parkinsonian features are considered to indicate a vascular cause of the parkinsonian syndrome: lower body parkinsonism, lack of resting tremor, marked gait difficulty, and L-dopa unresponsiveness. We examined patients 3 (median, range 1.2–4.7) years after the first-ever ischaemic stroke for presence of parkinsonian signs (bradykinesia, rigidity, tremor, and gait disorder). All patients had a follow-up CT scan of the brain, to study whether the parkinsonian signs were associated with small deep (lacunar) infarcts, WMLs, and/or territorial infarcts. We found one or more parkinsonian signs in 36% of the patients; 11% had clinically had parkinsonism (i.e., 2 or more parkinsonian signs). Parkinsonian signs were more frequent in lacunar than in territorial stroke patients: bradykinesia in 45% and 7%, rigidity in 13% and 7%, tremor in 6% and 7%, gait disorder in 16% and 7%, respectively. Patients with WMLs at study entry (N=16) were compared with those without (N=87): 56% and 25% had bradykinesia, 25% and 8% rigidity, 25% and 3% tremor, 38% and 8% gait disorder, respectively. Multivariate regression analysis showed that WMLs at study entry were associated with bradykinesia, gait disorder, and tremor. Bradykinesia was related to lacunar stroke at study entry. We concluded that one third of our stroke patients had one or more parkinsonian signs. Ten percent clinically had a parkinsonian syndrome, that differed from Lewy-body parkinsonism: only a few

patients had a resting tremor, whereas gait disorder occurred frequently. The parkinsonian signs were associated with lesions caused by cerebral small-vessel disease. Therefore, this study favours a distinct vascular parkinsonian syndrome, which is related to cerebral lesions caused by small-vessel disease.

In *Chapter 8* we evaluated the results of this study. The aim of the studies described in this thesis was to investigate clinically whether heterogeneity of cerebral vascular lesions (intracerebral haemorrhage, different types of small deep infarcts, and WMLs) coincided with homogeneity as to the underlying type of cerebral vascular disease. It may be concluded that this is largely the case; except for single, symptomatic lacunar infarcts (due to small-vessel atheromatosis) the remaining lesions are caused by arteriolosclerosis. Further study of factors determining the heterogeneity in cerebral lesions remains of utmost importance in aiming to arrive at a better treatment of patients with cerebral small-vessel disease. Furthermore, regarding the progression of WMLs and small deep infarcts, and the morbidity due to vascular parkinsonism, the search for a specific therapeutical option in cerebral small-vessel disease is also an important issue. More knowledge on various aspects of hypertension (e.g., its degree and duration, and the possible influence of genetic factors) in relationship with end-organ (brain) damage could lead to such options, as hypertension is probably the most important risk factor in cerebral small-vessel disease.

Samenvatting

CVA (cerebro-vasculair accident) is een verzamelnaam voor verschillende soorten hersenbeschadigingen met een vasculaire oorzaak. Elk type CVA wordt gekenmerkt door een specifiek klachtenpatroon, risicofactoren-profiel, pathogenese, therapie, prognose en eventuele gevolgen op de lange termijn. Alvorens men kan komen tot een effectievere preventie van het CVA, is allereerst meer kennis vereist m.b.t. de oorzaken van de verschillende CVA-subtypen. Het feit dat carotis-endarteriëctomie en antistollingstherapie bij bepaalde CVA-subtypen een duidelijke vermindering geven van de kans op een CVA, toont aan dat effectieve interventie afhankelijk is van kennis m.b.t. de pathogenese en vasculaire risicofactoren-profielen.

Het doel van dit onderzoek was het bestuderen van diverse aspecten van lesies veroorzaakt door pathologie van de kleine hersenarteriën, zoals kleine diepe herseninfarcten, afwijkingen aan de cerebrale witte stof en primaire hersenbloedingen. Ons eerste doel was te bepalen of al deze verschillende lesies veroorzaakt worden door een gelijksoortige beschadiging van de kleine hersenarteriën. Voorheen zijn er reeds aanwijzingen gevonden dat dit waarschijnlijk niet zo is. Bij autopsie-studies van patiënten met een primaire hersenbloeding is een specifieke afwijking aan de kleine hersenarteriën, genaamd arteriolosclerose, gevonden. Bij kleine diepe herseninfarcten zijn er twee verschillende vaatafwijkingen gevonden: arteriolosclerose bij multiple, meestal asymptomatische kleine diepe herseninfarcten en microatheromatose bij de wat grotere symptomatische herseninfarcten. Ofschoon er bij afwijkingen aan de cerebrale witte stof diverse pathologische veranderingen zijn gevonden, wordt arteriolosclerose als de onderliggende vaatpathologie beschouwd. Een ander doel van deze studie was het bestuderen van mogelijke gevolgen op de lange termijn van pathologie van de kleine hersenarteriën, zoals hersenatrofie en vasculair parkinsonisme.

In *Hoofdstuk 2* werden de risicofactoren-profielen vergeleken van patiënten met een primaire hersenbloeding, een klein diep herseninfarct of een territoriaal herseninfarct. Hierbij werd aangenomen dat de profielen van de risicofactoren een aanduiding kunnen zijn van de onderliggende vaatpathologie. Zowel een voorgeschiedenis van ischemische hartziekte als diabetes mellitus bleken vaker bij beide typen herseninfarcten voor te komen dan bij primaire hersenbloedingen. Hoge bloeddruk was niet specifiek geassocieerd met een bepaald type CVA. Deze verschillen in vasculaire risicofactoren vormen een extra aanwijzing dat het type pathologie van de kleine hersenarteriën bij primaire hersenbloedingen niet overeenkomt met dat bij de meerderheid van de kleine diepe herseninfarcten.

In *Hoofdstuk 3* werd de progressie in de tijd bestudeerd van cerebrale witte stof afwijkingen en van het aantal kleine diepe en territoriale herseninfarcten bij CVA-patiënten. Tevens werd de hypothese getest dat witte stof afwijkingen geassocieerd zijn met kleine diepe infarcten. We hebben een vervolgstudie gedaan bij een groep van 107 patiënten met een herseninfarct. Bij deze patiënten werd 3 jaar (mediaan) na het eerste herseninfarct opnieuw een computed tomographic (CT) scan gemaakt. De witte stof afwijkingen bleken bij 26% van de patiënten te zijn toegenomen. Deze progressie hing significant samen met symptomatische kleine diepe herseninfarcten, asymptomatische kleine diepe herseninfarcten bij het begin van deze studie, een hogere leeftijd en met een langere vervolgduur. We vonden bij 38% van de patiënten een toegenomen aantal kleine diepe herseninfarcten. Deze progressie was geassocieerd met symptomatische kleine diepe infarcten bij het begin van de studie en met een langere vervolgduur. Progressie van zowel witte stof afwijkingen als kleine diepe infarcten, kwam bij 16% van de patiënten voor, en hing samen met zowel symptomatische als asymptomatische kleine diepe herseninfarcten bij het begin van de studie en met een langere vervolgduur. Het aantal territoriale herseninfarcten steeg bij 13% van de patiënten. Deze toename was geassocieerd met symptomatische territoriale infarcten bij het begin van de studie en met een voorgeschiedenis van ischemische hartziekte.

De aanzienlijke progressie van witte stof afwijkingen en kleine diepe herseninfarcten die vooral voorkwam bij patiënten met een symptomatisch klein diep infarct toont aan dat zowel witte stof afwijkingen als kleine diepe herseninfarcten veroorzaakt worden door een aandoening van de kleine hersenarteriën, die progressief is ondanks de standaardbehandeling voor het herseninfarct.

In *Hoofdstuk 4* werd de hypothese getest dat witte stof afwijkingen vooral geassocieerd zijn met multiple, meestal asymptomatische kleine diepe herseninfarcten. We hebben bij 960 patiënten met een eerste herseninfarct de incidentie van witte stof afwijkingen bestudeerd. Dit betrof 332 patiënten met een klein diep herseninfarct, 213 met een cardio-embolisch territoriaal infarct en 415 met een atherothrombotisch territoriaal infarct. Tevens werd de relatie van witte stof afwijkingen met vasculaire risicofactoren, en met symptomatische en asymptomatische infarcten onderzocht. Van alle CVA-patiënten had 24% witte stof afwijkingen. Deze witte stof afwijkingen waren geassocieerd met hogere leeftijd en met zowel symptomatische als (vooral) asymptomatische kleine diepe herseninfarcten. Verder hingen de witte stof afwijkingen samen met asymptomatische territoriale infarcten bij patiënten met een atherothrombotisch territoriaal infarct. We concludeerden hieruit dat deze bevindingen de hypothese ondersteunen dat witte stof afwijkingen en multiple, meestal asymptomatische kleine diepe infarcten door dezelfde vaatafwijking veroorzaakt worden, namelijk door arteriële sclerose.

Omdat we ons tot doel hadden gesteld te onderzoeken of hersenatrofie bij CVA-patiënten samenhangt met witte stof afwijkingen en herseninfarcten, hebben we eerst de betrouwbaarheid van twee atrofie-metingen op CT scans bestudeerd in *Hoofdstuk 5*. Zowel de bicaudate ratio (BCR) als de ratio van de fissura Sylvii (SFR) werden bij 20 CT scans van patiënten met een herseninfarct gemeten door 3 onderzoekers. De "intraclass correlation coefficient" van de BCR-metingen bedroeg 0.82 (95% betrouwbaarheidsinterval 0.75–0.94), terwijl deze bij de SFR-metingen 0.69 (95% betrouwbaarheidsinterval 0.57–0.89) bedroeg. De spreiding van de "Pearson correlation coefficients" berekend voor alle paren van onderzoekers was kleiner bij de metingen van de BCR (0.89–0.92), dan bij die van de SFR (0.66–0.84). Concluderend kunnen we stellen dat de overeenkomst tussen de onderzoekers bij de BCR-metingen uitstekend was en bij de SFR-metingen matig.

In *Hoofdstuk 6* worden de resultaten weergegeven van de hersenatrofie-studie. Bij 917 patiënten met een eerste herseninfarct werd hersenatrofie gemeten m.b.v. de BCR als maat voor de ventrikelgrootte. Het eerste doel van deze studie was te onderzoeken of hersenatrofie bij patiënten met een herseninfarct samenhangt met de aanwezigheid van witte stof afwijkingen, een bepaald type herseninfarct, en/of asymptomatische herseninfarcten. Toename van de ventrikelgrootte was geassocieerd met hogere leeftijd, mannelijk geslacht, gebruik van diuretica, witte stof afwijkingen en met asymptomatische kleine diepe en territoriale herseninfarcten. Gezien de associatie van toename van de ventrikelgrootte met witte stof afwijkingen en asymptomatische kleine diepe en territoriale herseninfarcten, hebben we geconcludeerd dat toename van de ventrikelgrootte puur te wijten is aan weefselverlies en niet specifiek samenhangt met pathologie van de grote of kleine hersenarteriën.

Bij het syndroom van de normale druk hydrocephalus, worden zowel toename van de ventrikelgrootte als periventriculaire hypodensiteiten gevonden op CT. Men neemt aan dat bij de normale druk hydrocephalus deze periventriculaire hypodensiteiten het gevolg zijn van lekkage van liquor cerebrospinalis in het aangrenzende hersenparenchym. Wij hebben onderzocht of zowel periventriculaire als diepe witte stof afwijkingen bij herseninfarct-patiënten samenhangen met toename van de ventrikelgrootte. Daarnaast werden de vasculaire risicofactoren vergeleken van patiënten met diepe of periventriculaire witte stof afwijkingen om indirecte aanwijzingen te vinden voor de mogelijk verschillende pathogenese bij deze twee localisaties van witte stof afwijkingen. Zowel diepe als periventriculaire witte stof afwijkingen bleken samen te hangen met toename van de ventrikelgrootte. Verder waren beide localisaties van witte stof afwijkingen geassocieerd met hogere leeftijd, asymptomatische kleine diepe herseninfarcten en met symptomatische kleine diepe infarcten vergeleken met cardio-embolische territoriale herseninfarcten. We mogen hieruit concluderen dat diepe en periventriculaire witte stof afwijkingen vergelijkbare risicofactorenprofielen hebben bij patiënten met een herseninfarct en tevens dat beiden gerelateerd zijn aan een toename van de ventrikelgrootte. Dit laatste maakt het waarschijnlijker dat aan

beiden een gelijksoortige, vasculaire pathogenese ten grondslag ligt.

In *Hoofdstuk 7* zijn de resultaten beschreven van een onderzoek naar het vóórkomen van symptomen van parkinsonisme bij patiënten 3 jaar na een eerste herseninfarct. Parkinson-symptomen bij CVA-patiënten zijn mogelijk een laat gevolg van pathologie van de (kleine) hersenarteriën. Het concept van vasculair parkinsonisme is echter nog omstreden. Bepaalde parkinson-symptomen zouden vaker voorkomen als het parkinsonisme een vasculaire oorzaak heeft: loopstoornissen, het ontbreken van een rusttremor, het overwegen van symptomen aan de benen en niet aan de armen, en het ontbreken van een gunstig effect van L-dopa. Wij hebben patiënten 3 (mediaan, spreiding 1.2–4.7) jaar na het eerste herseninfarct onderzocht op het vóórkomen van parkinson-symptomen (bradykinesie, rigiditeit, tremor, en loopstoornissen). Alle patiënten ondergingen een vervolg CT scan van de hersenen, om te bestuderen of de parkinson-symptomen geassocieerd waren met kleine diepe herseninfarcten, witte stof afwijkingen en/of territoriale herseninfarcten. Parkinson-symptomen bleken bij 36% van de patiënten voor te komen; 11% had klinisch een parkinson-syndroom (d.w.z. 2 of meer parkinson-symptomen). Parkinson-symptomen kwamen meer voor bij patiënten met een klein diep, dan met een territoriaal infarct: bradykinesie bij respectievelijk 45% en 7%, rigiditeit bij 13% en 7%, tremor bij 6% en 7%, een loopstoornis bij 16% en 7%. Patiënten met witte stof afwijkingen bij het begin van de studie (N=16) werden vervolgens vergeleken met die zonder (N=87): respectievelijk 56% en 25% had bradykinesie, 25% en 8% rigiditeit, 25% en 3% tremor, en 38% en 8% had een loopstoornis. Bij multivariate regressie analyse bleek dat witte stof afwijkingen bij het begin van de studie geassocieerd waren met bradykinesie, loopstoornissen en tremor. Bradykinesie hing tevens samen met kleine diepe herseninfarcten bij het begin van de studie. Concluderend kunnen we stellen dat een derde van de patiënten met een herseninfarct een of meer parkinson-symptomen had. Tien procent had klinisch een parkinson-syndroom, dat verschilde t.o.v. Lewy-body parkinsonisme: slechts weinig patiënten hadden een rusttremor, terwijl een loopstoornis frequent voorkwam. De parkinson-symptomen waren geassocieerd met lesies veroorzaakt door pathologie aan de kleine hersenarteriën. Al met al ondersteunt deze studie het bestaan van een parkinson-syndroom van vasculaire origine, samenhangend met lesies veroorzaakt door pathologie van de kleine hersenarteriën.

In *Hoofdstuk 8* hebben we de resultaten van deze studie nader beschouwd. Het doel van de studies die beschreven zijn in dit proefschrift was om met klinische parameters te onderzoeken of een aantal vasculaire lesies in de hersenen (primaire hersenbloedingen, verschillende typen kleine diepe herseninfarcten en witte stof afwijkingen) door dezelfde soort pathologie van de kleine hersenarteriën veroorzaakt worden. We mogen concluderen dat dit grotendeels het geval is; met uitzondering van de solitaire, symptomatische kleine diepe herseninfarcten (veroorzaakt door microatheromatose) worden de overige lesies veroorzaakt

door arteriolasclerose. Er zijn zeker nog meer studies nodig om te bepalen welke factoren van invloed zijn op het ontstaan van al deze verschillende lesies in de hersenen. Hopelijk zal dit leiden tot een betere therapie voor patiënten met pathologie van de kleine hersenarteriën. Dit is van belang met het oog op de progressie van witte stof afwijkingen en kleine diepe herseninfarcten en de morbiditeit die veroorzaakt wordt door het vasculaire parkinson-syndroom. Om betere therapeutische opties te verkrijgen is vooral meer kennis nodig van de verschillende aspecten van hypertensie (b.v. de ernst, duur en de mogelijke invloed van genetische factoren) in relatie tot eind-orgaan schade (b.v. aan de hersenen), aangezien hypertensie waarschijnlijk de belangrijkste risicofactor is bij pathologie van de kleine hersenarteriën.

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- en natuurlijk Maarten van wiens hand deze layout is: wat moeten we nu nog verder bereiken als koppel "doctors"? Gewoon heerlijk verder leven, denk ik.

Curriculum Vitae

Marian van Zagten werd geboren op 5 juni 1964 te Beek-Ubbergen. In 1982 deed ze eindexamen VWO aan het Canisius College-Mater Dei te Nijmegen. Hierna ging ze Geneeskunde studeren aan de Katholieke Universiteit Nijmegen. In 1984 combineerde ze dit, aanvankelijk zonder serieuze bedoelingen, met de bovenbouw-studie Wijsbegeerte, eveneens aan de KUN. In 1987 werd het Doctoraalexamen Geneeskunde behaald. De co-schappen werden nog even uitgesteld, zodat in 1989 het doctoraal Wijsbegeerte werd behaald in de richting Filosofie van de Geneeskunde met een afstudeerscriptie over de hersenanaatom/psychiater Theodor Meynert. De hierop volgende co-schappen werden afgesloten met het artsexamen in 1991. Ze ging meteen in de Neurologie aan de slag in Medisch Spectrum Twente, Enschede, bij (toen nog) Dr. J. Troost. In 1992 kwam ze in dienst van het Academisch Ziekenhuis Maastricht, alwaar met de opleiding Neurologie werd begonnen (opleider Prof.dr. J. Troost). Ze is nu met haar laatste stage bezig op de afdeling Klinische Neurofysiologie, bij Prof.dr. F. Spaans, en hoopt in augustus 1998 haar opleiding te voltooien.