A Clinico-Pathological Study of Heart and Brain Lesions in Vascular Dementia

Ulla Andin^a Lars Gustafson^a Ulla Passant^a Arne Brun^b

Departments of ^aPsychogeriatrics and ^bPathology, Lund University Hospital, Lund, Sweden

Key Words

Vascular dementia · Neuropathology · Cerebrovascular · Cardiovascular

Abstract

All vascular dementia (VaD) cases, neuropathologically verified in a longitudinal prospective dementia project, were classified according to the vascular brain lesion type and related to the dementia type and cardiovascular pathology. From 1976 to 1995, there were 175 VaD cases, 49 of which were pure, without Alzheimer pathology and only one type of cerebrovascular lesion. Furthermore, it was found that 6 cases suffered hypoxic hypoperfusive disease, while 7 were found to have large vessel disease and 36 small vessel disease. In addition to Alzheimer pathology, more than one type of vascular brain pathology was found in the remaining 126 cases. In these cases, diagnosed in accordance with the predominant type of VaD, hypoxic-hypoperfusive lesions were found in 55, large vessel lesions in 50 and small vessel lesions in 110 cases. It should be stressed that 87% of all cases with hypoxic hypoperfusive lesions also had Alzheimer pathology. Cardiovascular and aortic pathologies were more prevalent in small vessel dementia than in the other VaD groups. Clinically diagnosed arterial hypertension was significantly associated with small vessel dementia, but not with hypoxic-hypoperfusive dementia. Cardiovascular symptoms varied considerably in frequency between different dementia groups. VaD is a heterogeneous group regarding lesions caused by different

pathophysiological mechanisms and with different combinations of brain pathologies. It is therefore necessary to identify the various types of vascular brain lesions for a correlation with clinical symptoms and for diagnostic purposes in the search for risk factors and therapeutic strategies.

Copyright © 2005 S. Karger AG, Basel

Introduction

Dementia, derived from the Latin *de mens*, ‘without mind’ is an acquired clinical syndrome, defined as such on account of its long duration as well as its progression. The classification of dementia has developed by accumulating evidence of clinicopathological entities in addition to presumed aetiological findings, including genetic factors.

At the end of the 19th century, Alzheimer and Binswanger studied the clinical and pathological heterogeneity of vascular dementia (VaD). Binswanger [1] pointed out the relationship between a slowly progressive, subcortical vascular encephalopathy (PSVE), also called Binswanger’s disease, with focal neurological deficits and vascular white matter lesions. Alzheimer further developed the subclassification of VaD into arteriosclerotic brain atrophy, PSVE, dementia apoplectica and perivascular gliosis [2]. In 1974, Hachinski et al. [3], introduced the term ‘multi-infarct dementia’ to emphasise the relationship between dementia and large multiple cerebral infarcts.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2005 S. Karger AG, Basel
1420–8008/05/0194–0222\$22.00/0

Accessible online at:
www.karger.com/dem

Ulla Andin
Department of Geriatrics
University Hospital
SE–701 85 Örebro (Sweden)
Tel. +46 19 602 26 43, Fax +46 19 602 26 45, E-Mail ulla.andin@orebroll.se

The classification of VaD may have different approaches and can be based on the primary vascular aetiology (large or small artery disease, haemorrhages, etc.), type of ischaemic brain lesion (complete, incomplete, lacunar infarcts, etc), location of brain lesions (cortical and/or subcortical, strategic) or clinical syndrome (cortical, subcortical, prefrontal-subcortical, etc.) [4]. The pathophysiologic classification of VaD diseases used here was developed in the Lund longitudinal dementia study [5, 6], and formed the basis of the Swedish consensus of dementia diseases [7]. Against that background, further neuropathological studies have contributed to subgroups, which are more often pure than mixed [8–10].

The aims of the study were to:

(1) Apply consensus criteria for the classification of VaD in deceased patients with predominant vascular pathology as well as study the prevalence of pure and mixed forms of brain pathology. The presence of Alzheimer pathology was also taken into consideration. (2) Study coronary, aortic and heart infarct pathology in different types of VaD. (3) Analyse the relationship between concomitant cardio/cerebrovascular disorders and the type of VaD.

Materials and Methods

Thirty-five years ago, a prospective and longitudinal study of dementia started at Lund University Hospital in southern Sweden. The project, still in progress, is based on a close co-operation between departments with a common interest in clinical brain research.

From this longitudinal study [11], all cases with neuropathologically verified VaD were selected consecutively during the 1976–1995 period. There were a total of 201 patients with VaD. In 15 cases, the cerebral pathology records could not be recovered, while another 9 cases were excluded because of insufficient pathological documentation. Two cases were excluded because of insufficient clinical documentation. The remaining 175 cases comprised 88 men and 87 women.

The medical records showed that most patients had undergone extensive investigation with neuropsychiatric evaluation. The evaluation included neurological status examination, neuropsychological testing and measurement of blood pressure and regional cerebral blood flow, EEG, neuroradiology and laboratory screening. Finally, post-mortem examination, including extensive brain pathology and heart pathology, was carried out.

Neuropathology

All cases were diagnosed in accordance with the earlier classification [8], slightly modified by Brun [12] (table 1). The whole brain was immersion-fixed in 4% formaline; in addition, an intraventricular injection of formaline was administered for more rapid central white matter fixation which took 2–3 weeks. The entire brain was then cut in 0.5- to 1-cm-thick coronal slices, which were paraffin-embedded and cut in 5 µm-thick sections.

Table 1. Pathophysiological classification of VaD

1. LVD

MID:

Multiple large infarcts, cortical and subcortical, with perifocal incomplete infarcts, especially in white matter.

SID:

Restricted, few infarcts in functionally important regions, often subcortical brain regions, e.g. striate body or thalamus, white matter key areas, basal forebrain, but also cortical, e.g. ACA and MCA territories including angular gyrus.

2. SVD

Subcortical infarct dementia:

Multiple small lacunar infarct with large perifocal incomplete infarcts especially in white matter.

Lacunar state

Binswanger's disease

Hereditary angiopathies

Cortical plus subcortical infarct dementia:

Multiple, restricted small infarcts due to:

Hypertensive and arteriolosclerotic angiopathy

Amyloid angiopathy, sometimes with haemorrhages

Collagen or inflammatory vascular disease

Hereditary forms

3. HHD

Incomplete white matter infarcts

Border zone infarcts

Diffuse hypoxic-ischemic encephalopathy

or restricted according to regional selective vulnerability

4. Venous infarct dementia

Large haemorrhagic, congestive symmetric infarcts due to thrombosis of the sagittal sinus or the great vein of Galen

5. Haemorrhagic dementia

Subdural haemorrhage

Subarachnoid haemorrhage

Intracerebral haemorrhage

VaD: Vascular dementia; LVD: large vessel dementia; MID: multi-infarct dementia; SID: strategic infarct dementia; SVD: small vessel dementia; HHD: hypoperfusive, hypoxic-ischaemic dementia.

This whole brain semi-serial sectioning with subsequent extensive microscopical analysis is a prerequisite for a safe neuropathological mapping of type, severity and distribution of changes as well as for the exclusion or verification of other types of brain pathology.

Staining routines included hematoxylin-eosin for overall structural assessment and Luxol fast blue with cresyl violet counterstaining for myelin and appreciation of cell density. Congo red was used in selected sections for amyloid and van Gieson-elastica staining was applied for meningeal and vascular fibrosis and degeneration. In addition, Campbell's silver and Gallyas stainings were used for the detection of neuritic plaques, dystrophic neurites and neurofibrillary tangles. The regional distribution and severity of white matter changes were mapped and quantified in accordance with a grading

system consisting of three main degrees used previously for correlation with quantitative neurochemical measures [9].

This assessment was combined with a similar mapping of the grey matter encephalopathy, using a grading system combining a number of histopathological variables [13], such as neuronal atrophy, gliosis, microvacuolization, neurofibrillary tangles, senile plaques and dystrophic neuritis. In terms of severity, it ranges from a basal Alzheimer encephalopathy consistent with normal ageing (Alzheimer encephalopathy) to a level of severity recognised as Alzheimer's disease (AD), which is in turn divided into three main degrees (mild, moderate and severe) [13]. Intermediate stages were also used in a number of cases. The vascular pathology was mapped with regard to large vessel involvement, including carotid and main cerebral arteries (mainly arteriosclerosis), and small vessels (occluding or stenosing arteriolosclerosis, amyloid angiopathy as well as other vascular changes) [14].

Pathological Classification

Large vessel dementia (LVD) is usually caused by large infarcts due to occlusion of larger, extra-cerebral vessels. These infarcts are complete, leaving behind a cavity or a scar without neuronally functioning components. They are surrounded by an incomplete infarct within the perifocal penumbra zone, which is narrow in grey matter, but wide in white matter due to the lower vascular density here. This zone of hypoperfusion is a consequence of the infarct pathophysiology and not a primary pathogenetic feature, which is why it is not an example of primarily hypoperfusive infarction.

Strategic infarct dementia is caused by either a single or multiple grey or white matter infarcts in strategic positions. These may be small or large, usually caused by large vessel obstruction, but sometimes by small vessel occlusions [12].

Small vessel dementia (SVD) is caused by small, lacunar infarcts due to occlusions of multiple small, most often intracerebral, vessels. Complete infarcts are surrounded by incomplete infarcts in the perifocal penumbra zones, especially in the white matter. In the same way as in LVD, these zones are secondarily hypoperfused; as a result, they do not qualify for the primary hypoperfusive group.

The various types of VaD may occur together, especially SVD and LVD. These types, single or combined, are always accompanied by perifocal incomplete infarcts. These infarcts are 'secondary' associates of the complete infarct, a perifocal hypoperfusion caused by inadequate contribution from adjoining vessels, and cannot be recognised as a sign of primary hypoperfusive aetiology. In borderzone cases, there may also be concurring LVD or SVD in sites outside the borderzone region. Microembolic minimal infarcts, usually in the cortex, would represent an SVD which is, however, of minimal or no clinical relevance. As a result of this, in a few such cases these small infarcts are ignored in the case classification.

Hypoxic-hypoperfusive dementia (HHD) is caused by damage due to the critically reduced flow or delivery of nutrients.

Selective incomplete white matter infarct (SIWI) is an incomplete, often widespread, infarct of the white matter due to hypoperfusion, usually augmented by non-occlusive stenosis or sclerosis of the penetrating arterioli and capillaries. These vessels are thereby rendered insufficient, with a reduced autoregulatory capacity in a situation of reduced blood pressure.

Borderzone infarcts are caused by hypoperfusion of the borderzones between the main cerebral arteries. The hypoperfusion, in turn, is caused by carotid artery stenosis or occlusion. In addition, an insufficient blood flow in the collaterals causes a critical condition.

The hypoperfusion often becomes severe enough to cause complete infarcts of segments of or the whole borderzone. Anoxia, if severe enough, produces an apallic syndrome with more or less widespread anoxic neuronal damage.

Heart and Aortic Pathology

The heart and aorta were evaluated macroscopically and studied histopathologically with hematoxylin-eosin and Von Giesen. Of the 175 cases examined for brain pathology, coronary pathology was examined in 162 cases, and aorta pathology was examined in 152 cases. Heart infarct pathology was studied in 163 cases.

Clinical Evaluation

The clinical features associated with cardiac and cerebrovascular disorders derived from the medical records were angina, atrial fibrillation, transitory ischaemic attack (TIA), stroke, hypertension, hypotension, diabetes mellitus and heart infarct. Hypertension was defined as blood pressure >140/90 mm Hg for people aged <70 years, and >160/90 for people aged >70 years, recorded on three separate occasions [15, 16]. Hypotension was defined as a repeated supine systolic blood pressure in the same arm of <100 mm Hg [16]. The measurements recorded during the last month before death were excluded.

Statistical Analysis

The statistical work was conducted using SPSS 11.1.5 for Windows (SPSS Inc.).

The χ^2 or two-tailed Fisher's exact tests (when the expected cell counts were <5), were carried out for comparison of cardiac and cerebrovascular diagnoses and neuropathology (table 2).

Results

Age at Death

The group of 175 patients included 88 males (m) and 87 females (f). The mean age at death was 80 ± 8.5 (SD) years (range 54–100), and almost identical in the SVD, LVD and HHD groups. The mean age at death was 78 years for men and 82 for women. Twenty-four (13%) patients died before the age of 70, 46 (26%) between the ages of 70 and 79, while 107 (61%) patients were 80 years or older.

Brain Pathology

Table 3 shows the distribution of the three types of vascular pathology and Alzheimer pathology in the material.

The majority of cases ($n = 126$) showed more than one type of brain pathology, (but usually one type of vascular lesion was clearly dominant). The remaining 49 cases were pure, with only one type of brain pathology, of which 7 had LVD, 36 had SVD and the remaining 6 cases had HHD.

Among all 175 patients, LVD pathology was found in 50 cases (25 m/25 f), SVD was diagnosed in 110 cases (57 m/53 f), being the most common type of VaD, while

Table 2. The relationship between LVD, SVD, HHD and clinical cardiac and cardiovascular characteristics analysed by χ^2 test or Fisher's exact test

Clinical characteristics	LVD			SVD			HHD		
	total (n = 50)	males (n = 25)	females (n = 25)	total (n = 110)	males (n = 57)	females (n = 53)	total (n = 55)	males (n = 25)	females (n = 30)
<i>Atrial fibrillation</i>									
+	0.006**	0.07	0.042*		0.58				
–				0.85		0.41	0.23	0.13	0.86
<i>TIA</i>									
+	0.037*	0.10	0.24 ¹			0.73			
–				0.74	0.41		0.023*	0.28	0.035*
<i>CVL</i>									
+	0.031*	0.17	0.10	0.20	0.13	0.80			
–							0.004**	0.008*	0.14
<i>Angina</i>									
+	0.017*	0.46 ¹	0.034 ^{1,*}	0.58	0.49 ¹				
–						1.0 ¹	0.06	0.72 ¹	0.06 ¹
<i>Heart infarct</i>									
+	0.83	0.93	0.84			0.33	0.85	0.026*	
–				0.21	0.005**				0.06
<i>Hypertension</i>									
+	0.20	0.92	0.09	0.001**	0.001**	0.16			
–							0.000***	0.001**	0.009**
<i>Diabetes</i>									
+	0.17			0.57	1.00 ¹	0.38			
–		1.00 ¹	0.10 ¹				0.20	1.00 ¹	0.13 ¹

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
TIA: Transitory ischaemic attack; CVL: cerebrovascular lesion.
¹ Fisher's exact test.

HHD was found in 55 cases (25 m/30 f). Brain haemorrhage was found in four cases only, a group too small to allow any conclusion to be drawn.

LVD coexisted with Alzheimer pathology in 31 cases (62%) and with SVD in 27 cases (54%). SVD coexisted with Alzheimer pathology and with LVD in 61 cases (56%) and 27 cases (25%), respectively. HHD coexisted with Alzheimer pathology in 46 cases (87%), but concurred with SVD or LVD in only a few percent. Only minor differences between males and females were seen within the groups.

Heart Pathology

In table 4, the distribution of coronary, aortic and heart infarct pathology is shown for the different VaD groups.

The coronary arteries were studied in 162 (83 m/79 f) of the 175 cases. Coronary arteriosclerosis was diagnosed in 152 cases (80 m/72 f). The aorta was studied in 152 cases, and aorta arteriosclerosis was diagnosed in 149 (75 m/74 f) cases. Three cases were normal. Heart infarct was found in 81 (49 m/32 f) cases.

Arteriosclerosis in the coronary arteries and aorta, and heart infarct were significantly more common in the SVD group than in the LVD and HHD group.

Clinical Cardiac and Cerebrovascular Features

The relationship between the type of VaD and clinical cardiac and cerebrovascular diagnoses is shown in table 2.

Angina and atrial fibrillation were significantly associated with the LVD diagnosis, but not SVD and HHD.

Table 3. LVD, SVD and HHD pathologies, isolated and in combination with the other dementia diagnoses

Pathology	Total	Males	Females
LVD	50	25	25
Pure	7 (4)	4 (5)	3 (3)
+HHD	5 (10)	1 (4)	4 (16)
+SVD	27 (54)	13 (52)	14 (56)
+AD	31 (62)	15 (60)	16 (64)
SVD	110	57	53
Pure	36 (21)	22 (25)	14 (16)
+HHD	11 (10)	7 (12)	4 (8)
+LVD	27 (25)	13 (23)	14 (27)
+AD	61 (56)	27 (49)	34 (64)
HHD	55	25	30
Pure	6 (4)	4 (5)	2 (2)
+SVD	11 (20)	7 (28)	4 (13)
+LVD	5 (9)	1 (4)	4 (13)
+AD	46 (87)	19 (76)	27 (90)

Figures in parentheses indicate percentages.

Table 4. Coronary, aortic and heart infarct pathologies and types of VaD

VaD type	Pathology		
	coronary (n = 152)	aorta (n = 149)	heart infarct (n = 81)
LVD			
Total	43 (28.3%)	43 (28.9%)	28 (34.6%)
Males	22	20	12
Females	21	23	16
SVD			
Total	98 (64.5%)	92 (61.7%)	49 (60.5%)
Males	52	48	30
Females	45	43	19
HHD			
Total	46 (30.3%)	47 (31.5%)	22 (27.2%)
Males	23	22	16
Females	23	25	6

This correlation was significant for females, but not for males.

While heart infarct was significantly more common in males with HHD, a considerable negative correlation was seen in males in the SVD group.

LVD cases had significantly more TIA and stroke than the other groups in the total material. By contrast, TIA and stroke were distinctly less common in HHD.

Hypertension showed highly positive correlations to the diagnosis of SVD in the total material as well as males. However, the most consistent highly negative correlation was found between hypertension and HHD.

Hypotension, as defined here, was diagnosed in only 4 cases. There were no differences between the three diagnostic groups.

Diabetes mellitus was diagnosed in 25 (11 m/14 f) cases, with no marked differences between the three diagnostic groups.

Discussion

This study places the focus on the complexity of cerebrovascular pathology and its relationship to coexistent heart and vascular disorders, since angina, atrial fibrillation, heart infarct, TIA, stroke and hypertension are recognised as tentative risk factors for VaD [17, 18]. While the total number of 175 cases does not place this among the larger studies, it has, as its main merit, a thorough neuropathological investigation combined with a correlated long-term clinical follow-up study. The mean age at death was almost identical to that of the Swedish population in general [4, 19]. In our catchment area during the recruitment period (1976–1995), most patients with dementia were referred to the psychiatric and psychogeriatric departments [11]. Consequently, it can be concluded that this is representative of the general population.

When dividing VaD into pathological subgroups, the most striking findings are that SVD is twice as common as LVD and HHD and that pure SVD is five times more common than pure HHD or LVD in the respective groups. Furthermore, AD pathology coexists with the VaD pathology in all subgroups, most often in HHD. From table 4, it appears that coronary pathology, aortic pathology and heart infarct pathology are much more common in SVD than in the others. With regard to the clinical parameters, hypertension interestingly and unexpectedly has a strong positive correlation with SVD, but a negative correlation with HHD.

A major difficulty for any clinical study on VaD is the lack of a strict and reliable definition [20] anchored in neuropathology [2]. Several clinical criteria for VaD have been developed. The most commonly used are the DSM-IV, which do not, however, specify any neuropathological subtypes [21], the ICD-10, which presents six subtypes

(acute onset, multi infarct, subcortical, mixed cortical and subcortical, other and unspecified [22], and the NINCDS-ARIEN criteria, which include cortical VaD, subcortical VaD, Binswanger's disease and thalamic dementia [23]. The DSM-IV criteria for VaD are less restrictive compared with the others [24]. The strength of our study is that all cases are pathologically examined with whole semi-serial brain sections, and that the diagnoses are based on the classification of VaD on a pathophysiological basis [6, 8, 12].

Frequency of VaD and Its Subgroups

In this study, SVD was the most prevalent type of VaD, diagnosed in 110 (63%) of the total 175 cases. This is in accordance with other pathologic studies, which report that SVD is the major aetiological component in VaD [8, 25–30]. Furthermore, 36 of the SVD cases were pure, viz. without any other pathology. This unexpectedly high number of pure cases will be further analysed in a forthcoming publication. The most common additional pathology was LVD (27 cases) and Alzheimer pathology (61 cases), which influenced the clinical picture during life. This may explain the difficulties in making correct clinical diagnoses [31, 32].

In contrast to SVD, LVD was pure, viz. without additional brain pathology in only seven cases (4%) [8, 33, 34], while the combination with Alzheimer pathology was seen in 31 cases (62%). This suggests that AD is a disorder independent of VaD.

In our material, HHD was found in as many as 55 cases, being pure in only 6 cases. In spite of the considerable size of this group, it is rarely reported in the literature. This might be explained by its common coexistence with Alzheimer pathology, which obscures the clinical and neuropathological picture. The dominant type of vascular pathology, SIWI, was already shown to be a common accompaniment of AD as early as in 1986 [35]. A major risk factor in HHD is probably hypotension, especially ortostatic hypotension, as shown in other studies [36–38]. Moreover, HHD often coexisted with other vascular pathologies, and very often with Alzheimer pathology. A further study will compare AD-SIWI cases with pure AD.

Coronary, Aortic and Heart Infarct Pathology and Type of VaD

Coronary vessel pathology, aorta pathology and heart infarct pathology were twice as common in SVD as in LVD and HHD (table 4). As expected, coronary and aortic pathology was found in almost all cases. Thus, SVD seems to be part of generalised vascular disorder, often complicated by hypertension, as seen in table 2.

There was an interesting difference concerning heart infarct pathology between the two sexes. Heart infarcts were more prevalent among men with HHD (16 m/6 f), and SVD (30 m/19 f).

Clinical Characteristics

As expected, atrial fibrillation, TIA and cerebrovascular lesions were more common in the LVD group than in the SVD group, but very uncommon in the HHD group. The opposite has been found in other studies [39]. Perhaps this divergence is due to lack of focus upon the distinction between SVD and HHD in other studies.

Angina was, unexpectedly, more common in the LVD group (11/50; 22%) than in the SVD group (15/110; 14%). It is difficult to make a comparison of literature in this field as the symptom angina is often included in the term cardiac disease [40].

In this study, clinical heart infarcts were strikingly unusual among males, but not among females, especially in the SVD group. However, as seen in table 4, pathology often revealed heart infarcts, which indicates that clinical heart symptomatology does not always correspond to the pathological findings. Angina and heart infarcts in VaD cases and in the different sexes are seldom reported.

Hypertension was significantly common in the whole group of SVD, particularly in males, a fact which concurs with other studies [41–44]. Although hypertension is the main risk factor for cerebrovascular disease, retrospective studies have not provided any indication of the role of hypertension in VaD [45]. It would not have been possible to show this difference without the pathological distinction between the SVD and the HHD group.

Conclusion

The findings in this study underscore the neuropathological and clinical heterogeneity in VaD. Such knowledge is of great importance, since some risk factors may not only be treatable but even preventable. An adequate clinical intervention thus has to be based on the recognition of different forms of pure and mixed types of vascular brain pathology and the aetiological factors for each of them.

Acknowledgement

This study was supported by the Swedish Alzheimer foundation, Stiftelsen Ellen och Henrik Sjöbrings minnesfond, and the Swedish Research Council (project no 3950).

References

- 1 Binswanger O: Die Abgrenzung der allgemeinen progressiven Paralyse. *Berl Klin Wochenschr* 1894;31:1103–1105, 1137–1139, 1180–1186.
- 2 Gustafson L: Historical overview; in Chiu E, Gustafson L, Ames D, Folstein M (eds): *Cerebrovascular Disease and Dementia-Pathology, Neuropsychology and Management*. London, Dunitz, 2000, pp 3–14.
- 3 Hachinski VC, Lassen NA, Marshall J: Multi-infarct dementia. A cause of mental deterioration in the elderly. *Lancet* 1974;ii:207–210.
- 4 Erkinjuntti T: Classification and criteria; in Chiu E, Gustafson L, Ames D, Folstein MF (eds): *Cerebrovascular Disease and Dementia-Pathology, Neuropsychology and Management*. London, Dunitz, 2000, pp 99–113.
- 5 Brun A, Gustafson L: Zerebrovaskuläre Erkrankungen; in Disker DP, Lander A, Meyer JE, Muller C, Strömgen E (eds): *Psychiatrie der Gegenwart, Band 6; Organische Psychosen*. Berlin, Springer, 1988, pp 253–294.
- 6 Brun A: Vascular dementia: Pathological findings; in Burns A, Levy R (eds): *Dementia*. London, Chapman & Hall, 1994, pp 653–663.
- 7 Wallin A, Brun A, Gustafson L: Swedish consensus on dementia diseases. *Acta Neurol Scand* 1994;90:7–31.
- 8 Brun A: Pathology and pathophysiology of cerebrovascular dementia: Pure subgroups of obstructive and hypoperfusive etiology. *Dementia* 1994;5:145–147.
- 9 Englund E, Brun A, Alling C: White matter changes in dementia of Alzheimer's type. Biochemical and neuropathological correlates. *Brain* 1988;111(Pt 6):1425–1439.
- 10 Fredriksson K, Brun A, Gustafson L: Pure subcortical arteriosclerotic encephalopathy (Binswanger's disease): A clinicopathologic study. *Cerebrovasc Dis* 1992;8:82–86.
- 11 Brun A, Gustafson L: The Lund Longitudinal Dementia Study: A 25-year perspective on neuropathology, differential diagnoses and treatment; in Corain B, Iqbal Q, Nicolini M, Winblad B, Wisniewski H, Zatta P (eds): *Alzheimer's Disease: Advances in Clinical and Basic Research*. New York, Wiley & Sons Ltd., 1993, pp 3–18.
- 12 Brun A: Vascular dementia and its overlap with Alzheimer's disease; in Chiu E, Gustafson L, Ames D, Folstein ME (eds): *Cerebrovascular Disease, Cognitive Impairments and Dementia*, ed 2. London, Dunitz, 2003.
- 13 Brun A, Englund E: Regional pattern of degeneration in Alzheimer's disease: Neuronal loss and histopathological grading. *Histopathology* 1981;5:549–564.
- 14 Brun A: Vascular dementia: Pathological findings; in O'Brien J, Ames D, Burns A (eds): *Dementia*, ed 2. London, Edward Arnold, 2000, pp 655–665.
- 15 Chalmers J, MacMahon S, Mancia G, Whitworth J, Beilin L, Hansson L, Neal B, Rodgers A, Ni Mhurchu C, Clark T: 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension. Guidelines sub-committee of the World Health Organization. *Clin Exp Hypertens* 1999;21:1009–1060.
- 16 Thulin T, Liedholm H: *Hypertoni*. Stockholm, Almqvist & Wiksell, 1993.
- 17 Skoog I: Risk factors for vascular dementia: A review. *Dementia* 1994;5:137–144.
- 18 Johansson BB: Vascular mechanisms in hypertensive cerebrovascular disease. *J Cardiovasc Pharmacol* 1992;19(suppl 3):S11–S15.
- 19 Socialstyrelsen: *Hälsa och sjukvårdsstatistisk årsbok*, 2000.
- 20 Leys D, Pasquier F, Parnetti L: Epidemiology of vascular dementia. *Haemostasis* 1998;28:134–150.
- 21 Statistics APACoNa: *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. Washington, 1994.
- 22 World Health Organization: *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva, World Health Organization, 1992.
- 23 Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A, et al: Vascular dementia: Diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993;43:250–260.
- 24 Pohjasvaara T, Mantyla R, Ylikoski R, Kaste M, Erkinjuntti T: Comparison of different clinical criteria (DSM-III, ADDTC, ICD-10, NINDS-AIREN, DSM-IV) for the diagnosis of vascular dementia. *National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences*. *Stroke* 2000;31:2952–2957.
- 25 Esiri MM, Wilcock GK, Morris JH: Neuropathological assessment of the lesions of significance in vascular dementia. *J Neurol Neurosurg Psychiatry* 1997;63:749–753.
- 26 Morris J: *Vascular dementia*. Cambridge, Cambridge University Press, 1997.
- 27 Wallin A, Blennow K: Pathogenetic basis of vascular dementia. *Alzheimer Dis Assoc Disord* 1991;5:91–102.
- 28 Cervos-Navarro J: *Vascular dementia: The search for a correlate*. Berlin, Springer, 1991.
- 29 Roman GC: Senile dementia of the Binswanger type. A vascular form of dementia in the elderly. *JAMA* 1987;258:1782–1788.
- 30 Jellinger KA: The pathology of ischemic-vascular dementia: An update. *J Neurol Sci* 2002;203–204:153–157.
- 31 Lontos E, Passant U, Brun A, Gustafson L: Clinical Lewy body dementia and the impact of vascular components. *Int J Geriatr Psychiatry* 2000;15:40–49.
- 32 Gustafson L, Passant U: Clinical pathological correlates; in Chiu E, Gustafson L, Ames D, Folstein MF (eds): *Cerebrovascular Disease and Dementia-Pathology, Neuropsychology and Management*. London, Dunitz, 2000, pp 85–97.
- 33 Leys D, Erkinjuntti T, Desmond DW, Schmidt R, Englund E, Pasquier F, Parnetti L, Ghika J, Kalaria RN, Chabriet H, Scheltens P, Bogousslavsky J: Vascular dementia: The role of cerebral infarcts. *Alzheimer Dis Assoc Disord* 1999;13(suppl 3):S38–S48.
- 34 Leys D, Englund E, Del Ser T, Inzitari D, Fazekas F, Bornstein N, Erkinjuntti T, Bowler JV, Pantoni L, Parnetti L, De Reuck J, Ferro J, Bogousslavsky J: White matter changes in stroke patients. Relationship with stroke subtype and outcome. *Eur Neurol* 1999;42:67–75.
- 35 Brun A, Englund E: A white matter disorder in dementia of the Alzheimer type: A pathoanatomical study. *Ann Neurol* 1986;19:253–262.
- 36 Passant U: Posture and brain function in dementia. Lund, BTJ Tryck, 1996.
- 37 Passant U, Warkentin S, Gustafson L: Orthostatic hypotension and low blood pressure in organic dementia: A study of prevalence and related clinical characteristics. *Int J Geriatr Psychiatry* 1997;12:395–403.
- 38 Sulkava R, Erkinjuntti T: Vascular dementia due to cardiac arrhythmias and systemic hypotension. *Acta Neurol Scand* 1987;76:123–128.
- 39 de Leeuw FE de, Groot JC de, Breteler MMB: White matter changes: Frequency and risk factors; in Pantoni L, Inzitari D, Wallin A (eds): *The matter of white matter*. Utrecht, Academic Pharmaceutical Productions, 2000, pp 19–33.
- 40 Skoog I: Status of risk factors for vascular dementia. *Neuroepidemiology* 1998;17:2–9.
- 41 Puisieux F, Monaca P, Deplanque D, Delmaire C, di Pompeo C, Monaca C, Leys D, Pruvo JP, Dewailly P: Relationship between leuko-araiosis and blood pressure variability in the elderly. *Eur Neurol* 2001;46:115–120.
- 42 Kalaria RN: Small vessel disease and Alzheimer's dementia: Pathological considerations. *Cerebrovasc Dis* 2002;13(suppl 2):48–52.
- 43 Schmidt R, Schmidt H, Kapeller P, Lechner A, Fazekas F: Evolution of white matter lesions. *Cerebrovasc Dis* 2002;13(suppl 2):16–20.
- 44 Skoog I: A review on blood pressure and ischaemic white matter lesions. *Dement Geriatr Cogn Disord* 1998;9(suppl 1):13–19.
- 45 Johansson BB: Pathogenesis of vascular dementia: The possible role of hypertension. *Dementia* 1994;5:174–176.