REVIEW

The enigma of vascular cognitive disorder and vascular dementia

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Abstract The prevalence, morphology and pathogenesis of vascular dementia (VaD), recently termed vascular cognitive impairment, are a matter of discussion, and currently used clinical diagnostic criteria show moderate sensitivity (average 50%) and variable specificity (range 64–98%). In Western clinic-based series, VaD is suggested in 8–10% of cognitively impaired aged subjects. Its prevalence in autopsy series varies from 0.03 to 58%, with reasonable values of 8–15%, while in Japan it is seen in 22–35%. Neuropathologic changes associated with cognitive impairment include multifocal and/or diffuse disease and focal lesions: multi-infarct encephalopathy, white matter lesions or arteriosclerotic subcortical (leuko)encephalopathy, multilacunar state, mixed cortico-subcortical type, borderline/watershed lesions, rare granular cortical atrophy, post-ischemic encephalopathy and hippocampal sclerosis. They result from systemic, cardiac and local large or small vessel disease. Recent data indicate that cognitive decline is commonly associated with widespread small ischemic/vascular lesions (microinfarcts, lacunes) throughout the brain with predominant involvement of subcortical and functionally important brain areas. Their pathogenesis is multifactorial, and their pathophysiology affects neuronal networks involved in cognition, memory, behavior and executive functioning. Vascular lesions often coexist with Alzheimer disease (AD) and other pathologies. Minor cerebrovascular lesions, except for severe amyloid angiopathy, appear not essential for cognitive decline in full-blown AD, while both mild Alzheimer pathology and small vessel disease may interact synergistically. The lesion pattern of "pure" VaD, related to arteriosclerosis and microangiopathies, differs from that in mixed-type dementia (AD with vascular encephalopathy), more often showing large infarcts, which suggests different pathogenesis of both types of lesions. Due to the high variability of cerebrovascular pathology and its causative factors, no validated neuropathologic criteria for VaD are available, and a large variability across laboratories still exists in the procedures for morphologic examination and histology techniques.

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Addendum In a recent clinicopathological evaluation of 79 autopsy cases derived from a prospective longitudinal study of subcortical ischemic vascular disease (SIVD) and Alzheimer disease (AD), Chui et al. [555] found significant cerebrovascular lesions (CVL) in 30%, AD pathology in 54%, and hippocampal sclerosis (HS) in 18%. Statistical assessment showed that all three pathology variables contributed independently to cognitive status, but only the neuritic Braak scores contributed significantly to cognitive impairment, indicating that advancing AD pathology overwhelms the effects of the two other factors that, in the absence of considerable AD, contribute to mild cognitive impairment. A recent histologic-neuroimaging study in two patients with SIVD showed correspondence between subinsular T2 hyperintensive lesions and demyelination, gliosis, and dilated perivascular spaces [556].

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Historical background and synonyms

While Alzheimer disease (AD) has become accepted as the most common cause of dementia in advanced age [268], the role of cerebrovascular disease (CVD) and ischemic brain damage for cognitive decline remains controversial and confusing. Until the 1950s and 1960s, dementia in elderly subjects was usually labeled "arteriosclerotic dementia" [319], originally conceived as an arteriosclerotic disorder arising from diffuse low cerebral perfusion [35, 274], and in 1919, Mingazzini [334] stated that this was the result of cerebral infarction, similar to the concept stressed by Fisher [163], for rev. see [423]. Tomlinson et al. [486] described the relationship between the volume of infarcted tissue and cognitive impairment, suggesting that destruction of large volumes of cortex is necessarily followed by dementia, whereas subtle cerebrovascular lesions (CVL) may or may not contribute to dementia, probably depending on their location. Hachinski et al. [196] criticized this term as both misleading and inaccurate, and coined the term "multi-infarct dementia" (MID) due to the accumulation of cerebral infarct volumes in excess of a critical threshold. Because this phenotype constitutes only a small subdivision of dementias of suggested ischemic–vascular etiology, the term "vascular dementia" (VaD) [119, 142, 291, 311, 312, 326, 332, 345, 367] and others were chosen (Table 1). Later, they were replaced by "vascular cognitive impairment" (VCI) to acknowledge that the cognitive effects of CVD may be significant, but fall short of a true dementia syndrome as defined by impairment of activities of daily living (ADL) [19, 54–58, 194, 245–247, 313, 366, 418, 460]. Others proposed the term "vascular cognitive disorder" (VCD) as a global diagnostic category, ranging from VCI to VaD [426, 430]. VCD has been recently limited to cases without dementia, i.e., cognitive impairment-no dementia

Table 1 Cognitive dysfunctions caused by cerebral lesions due to vascular/ischemic pathology

Synonyms
Old: Arteriosclerotic dementia [319], inaccurate and misleading [196]
Multi-infarct dementia [196], only subtype
Dementia associated with stroke [527]
Post-stroke dementia [185, 394]
Vascular dementia [119, 143, 291, 311, 312, 332]
Cerebrovascular dementia [136]
Ischemic–vascular dementia [509]
Vascular–ischemic dementia [241, 248]
Vascular cognitive impairment [19, 56, 58, 194, 245–247, 417]
Vascular cognitive disorder [426, 430]
Dementia due to vascular disease [435]

(VCI-ND), but there are no universally accepted criteria for VCI [53, 56, 57, 365, 426]. Other subgroups include post-stroke dementia (PSD) [185], subcortical vascular dementia [138] and mixed AD plus CVD [326].

Although considerable progress has been made in understanding VaD, and clinical diagnostic criteria have been proposed, many questions remain open, particularly when pathologic lesions produce cognitive impairment and by what mechanisms.

Many authors consider VaD to be an ill-defined entity [118, 340]. Causal relationships between CVD and dementia are difficult to prove and morphologic substrates of cognitive impairment resulting from CVLs remain confusing, since they constitute a multifactorial disorder related to variable types, sizes and location sites of the lesions which are due to a large variety of causes [142, 143, 241, 242, 245, 246, 311, 312, 333]. A list of potential etiologies capable of producing VCD has been given [426]. Even when cerebrovascular pathology appears to be a main underlying process, the effect of damaged brain parenchyma is variable and forms a continuum of abnormalities that also can occur in the absence of dementia [154, 246, 248, 509]. Therefore, the clinical, neuroimaging and pathologic appearances may be heterogeneous; no single set of criteria proposed for the clinical diagnosis of VaD has been generally accepted (see [88]), and the phenotype remains elusive [304], making epidemiologic and treatment studies of VaD/VCI challenging. Complicating its diagnosis are other frequently co-existing pathologic entities, in particular Alzheimer-type lesions, in the aging brain [88, 97, 154, 225, 249, 255, 361, 390, 535]. This review will critically discuss current problems of the pathology and pathogenesis of acquired forms of VCD and VaD. The hereditary forms of VaD (see [257]) and the problems of mixed dementia (AD + vascular encephalopathy) have been reviewed recently (see [251]).

Clinical diagnostic criteria

Standard diagnostic criteria and assessment procedures for dementia have been published in a Practice Parameter by the American Academy of Neurology (AAN) [266], by the Clinical Practice Committee of the American Geriatrics Society [1]. While AD can today be diagnosed with a high degree of accuracy (see [44, 175, 214, 261, 262, 266, 344]), agreement on clinical definitions of VaD is incomplete. There is no singular or specific cognitive impairment that is characteristic of VaD, and clinical criteria for VCI or VaD in general do not specify a particular neuropsychological profile.

In the preimaging era, the Hachinski Ischemic Score relied on a number of vascular signs and symptoms to gauge the likelihood of VaD versus AD [197]. Subsequent studies have shown that this score has a rather poor correlation with neuropathologic diagnosis and can be regarded as only a rough indicator of underlying pathology [161, 343]. Even the addition of CT scanning to the Score does not greatly increase its sensitivity [549]. Currently used clinical diagnostic criteria for VaD/VCI use variable data and consider variable pathogenic mechanisms and causal relationships [13, 86, 87, 197, 420, 528, 536].

All these criteria based their definition of dementia on the fact that memory deficits must be present. However, cerebral infarcts can occur in any brain territory and do not always affect memory-related circuits [42] or cause impairments in social or occupational functioning. The problem of the memory-based definition of dementia is not exclusive of VaD, but it excludes the main possible cognitive sepueloe of stroke, which in the ICD-10 classification are properly categorized as VCI [376, 528]. Some attempts to correct this problem have been made. For instance, the Cardiovascular Health Study (CHS) [303] used a definition of dementia that did not necessarily include memory loss, but a progressive or static cognitive deficit of sufficient severity to affect the subject's ADL, and a history of normal intellectual function before the onset of cognitive abnormalities.

Modifications have been proposed to existing diagnostic criteria: VCI/VaD should be subdivided into those associated with focal neurological lesions, usually MID [196, 486], and a more diffuse disorder of "subcortical vascular dementia" (SVaD) as a clinically and pathologically homogenous syndrome, with only minimal or absent regional cerebral infarction and arising from small vessel disease (SVD) [138, 401, 424]. Integration of neuropsychological and neuroimaging data was suggested to be sufficient for the diagnosis of this more homogenous subtype [11, 401]. Regional cerebral blood flow (CBF) in subcortical and limbic areas is significantly decreased in SVaD compared to controls [449]. Further criteria have been suggested for Binswanger's syndrome [40, 300] and for early changes of VaD termed VCI [56, 57, 194].

The newer criteria share three components: (1) evidence of dementia or cognitive impairment; (2) evidence of CVD by history or neuroimaging (CT or MRI) and (3) evidence of a relationship between cognitive impairment and CVD, e.g., temporal relationship [176, 268]. Unfortunately, these criteria are not interchangeable and may result in up to threefold differences in the number of cases classified clinically as VaD [88, 395], and may exclude a number of subjects

with VaD [470]. A recent longitudinal study of VaD showed both clinical similarities and differences between pathologically defined subgroups [15]. VCI impairment harmonization standards have been published recently by the NINDS and the Canadian Stroke Network (CSN) [195].

Clinico-pathologic studies

Several class I and II studies that compared clinical diagnosis and neuropathologic findings in reference cohorts, similar to population-based studies, reported low sensitivity of clinical criteria (average 50%, range 20–89%), but high specificity (average 87%, range 64–98%), with variable interrater reliability [95, 169, 182, 183, 268, 291, 416]. A critical discrepancy among diagnostic criteria is the difference in estimating the severity of cognitive impairment necessary to make the diagnosis of dementia. Comparison of different clinical criteria for VaD showed 52% of stroke patients to meet the DSM-IV criteria for VaD, 33% of ICD-10, 27% of ADDTC and 14% of NINDS-AIREN criteria [528], while in Japan only 14% met the NINDCS-AIREN and 31% the ADDTC criteria [321]. In the CHS none of the clinical criteria for VaD identified the same group of subjects with incidental dementia—VaD classification by NINDS-AIREN, DSM-IV and ADDTC criteria was 9, 13 and 24%, respectively, and the majority of the VaD cases had AD clinical features [303]. In general, the NINDS-AIREN criteria were the most conservative ones. However, in an interobserver study, use of the operational definitions for these criteria improved agreement but only for already experienced observers [502]. Most of these figures do not take into account the more prevalent and subclinical type of cerebrovascular events, characterized by multiple or strategic lacunar infarcts and diffuse WMLs linked with small vessel dementia (SVD) [248, 383, 455]. The Mayo clinical criteria (temporal relationship between stroke and dementia or worsening of cognition, or bilateral infarction in specific regions) had 75% sensitivity and 81% specificity for autopsy-proven VaD [268]. Reclassification of 308 dementia cases from the population-based Kungsholmen Project, using vascular risk factors retrospectively, reclassified only 47% of the suggested AD cases as "pure" AD. About 26% of pure AD subjects developed a vascular disorder in the following 3 years, and among subjects with AD and a vascular component, CVD was the most common (40%) [2]. Evaluation of 3.375 participants of the CHS using MRI classified 44% of 480 incident dementia cases as possible or probable VaD by ADDTC, but there was a substantial overlap between cases classified as AD and

VaD suggesting a high prevalence of mixed dementia [279]. CVD is a coincident finding in 30 to 40% of patients with autopsy-proven AD and is associated with a significantly greater likelihood of dementia for a given level of AD pathology [251, 404, 443, 444], but pathologic evidence of microvascular injury may be as frequent as Alzheimer pathology in select postmortem samples [529, 549, 550].

Accuracy of clinical diagnosis of VaD has been reported in 89 autopsy cases, in which VaD was defined pathologically by the presence of cortical infarcts in at least three areas but without subcortical lesions [183]. Using these criteria as reference standard, the clinical criteria for VaD tended to be specific but insensitive, suggesting that they underestimate the extent of ischemic brain injury. Among 110 autopsy cases, 32.8% were confirmed VaD, 42% of which had not presented with stroke, while 30% of morphologic mixed dementia cases had been clinically diagnosed as VaD by both NINDS-AIREN and ADDTC criteria [25].

In a retrospective study of consecutive autopsies of 1,050 demented patients (aged over 55 years) in Vienna, Austria, post-mortem confirmation of the clinical diagnosis of possible/probable AD was achieved in 93%, of mixed dementia in 60%, and of VaD in 52.3% [250]. Among 180 long-term followed patients in the Vienna Prospective Dementia study [30], the clinical diagnosis of AD was confirmed at autopsy in 90% (one-third each associated with vascular or Lewy pathologies) and that of VaD in only 53.3% (Jellinger, unpublished), while in other autopsy series the sensitivity for VaD ranged from 25 to 44% [513, 531].

Admittedly, the presence of CVLs found by neuroimaging techniques or autopsy does not prove that they definitely cause dementia [136, 291, 311, 374], and no VCI subtype was associated with a specific neuro-imaging abnormality [418]. Therefore, the clinical diagnosis of VCI/VaD remains subjective and problematic. Controversies concerning the validity and reliability of diagnostic criteria for VaD/VCI continue, and the lack of neuropathologic criteria undermines the attempts to improve clinical and imaging criteria, and the importance of further clinico-pathologic correlations has been emphasized [136, 248, 250, 268, 291, 366].

Post-stroke dementia

Román [422] recently suggested that VaD may be the most underdiagnosed and underestimated form of dementia in the elderly. This is important because "silent" cerebral infarcts increase with advancing age and are considered major contributors to the increasing incidence of cognitive impairment [267, 506], occur-

ring in 25–30% of patients after stroke [120, 185, 212], associated with a twofold increase in odds of dementia [293, 443]. Other recent studies confirmed that incident stroke significantly increased risk of dementia, but did not find an effect of CVD risk factors on dementia risk [170, 409]. While not all stroke patients with VCI develop dementia according to standard diagnostic criteria, such patients are at risk of a dementia syndrome in the next 3 years after stroke [212, 473], and 20–41% of them progress to cognitive impairment or dementia [101, 233, 339, 461, 527, 554]. Cognitive impairment can develop after a single ischemic lesion, after recurrent transient ischemic attacks [26] or after multiple insults, while some patients may manifest progressive cognitive decline associated with multiple "silent" ischemic lesions [143, 220, 296], and the presence of an *APOE* ε4 and ε2 allele is associated with greater progression of cognitive decline [28]. It is also associated with asymptomatic high-grade stenosis of the left internal carotid artery without clinically evident CVD [252]. The role of diffuse PSD has been proposed [379], although many patients with dementia identified after stroke already had cognitive impairment before [170, 212, 292]. During a 4-year follow-up the incidence of PSD increased gradually [10], but many patients with lacunar infarcts have a good functional outcome after 5 years. For older patients and those with an initial severe stroke or with additional vascular risk factors, however, the prognosis is more severe, with an increased risk for mortality, stroke recurrence and physical and cognitive decline [16, 17, 293, 307]. Dementia showed a correlation with widespread small ischemic lesions throughout the CNS [111], mainly lacunes, microinfarcts and hippocampal injury, and much less with larger infarcts; many brains showed more than one type of CVLs, although in cognitively normal aged controls similar lesions were present [102, 108, 241, 242, 509].

Because the criteria chosen to diagnose VaD will influence estimates on its incidence and prevalence, as well as its recognition and treatment, new research criteria have been proposed [136–138, 248, 250, 291, 366, 368], and the need for prospective, multi-institutional, population-based studies evaluated thoroughly and longitudinally by clinical, neuropsychological and imaging studies, with autopsy follow-up has been emphasized [193, 266, 268].

Pathologic diagnostic criteria of VaD

In contrast to recently refined morphologic criteria for AD and other neurodegenerative dementias (see [129,

221, 222, 250, 260, 318, 335, 347, 352, 363, 490]), no generally accepted neuropathologic criteria for VaD/VCI have been established up to date and no definite morphologic substrates have been included in the currently used clinical diagnostic criteria for VaD. Two important challenges exist. First, there is no accepted neuropathologic scheme for quantitating CVD in cognitive disturbances, and second, agreement on clinical definitions of VaD is limited. The ADDTC criteria did not suggest specific details for the post-mortem diagnosis of VaD but indicated that histopathologic examination of the brain with clinical evidence of dementia was necessary to confirm the presence of multiple infarcts [86]. The NINDS-AIREN criteria emphasized the heterogeneity of the VaD syndrome and its pathologic subtypes [420]. The diagnosis of "definite" VaD criteria required that the clinical probability be completed by histopathologic evidence of CVD and absence of Alzheimer-type lesions exceeding those expected for age and other conditions causing dementia. Several investigators have emphasized the inverse relation between Braak stage of neuritic Alzheimer lesions and cerebrovascular pathology [186, 239] or have used variable criteria [134, 137, 236, 268, 495].

VaD is related to a variety of pathologic lesions, the clinical significance of which and their relation to AD and other age-related changes of the brain, e.g. subcortical WMLs, remain controversial [130, 131, 136, 137, 142–144, 234, 241, 242, 246, 248, 291, 311, 312, 332, 382, 394, 454, 509]. On the other side, many elderly patients exhibit morphologic changes similar to AD, VaD or mixed dementia (MD), but do not meet the clinical criteria of dementia [179]. We are not aware of any validation study of the currently used criteria for neuropathologic diagnosis of VaD/VCI or published neuropathology data about the substrates of PSD.

The task of neuropathology is to describe the nature and severity of vascular pathology using harmonized morphologic procedures and criteria—as recently published for the assessment of AD-related lesions [8]—addressing the question, whether the CVLs present in a particular brain are of sufficient magnitude to likely contribute or are even the sole substrate of the profile which was demonstrated clinically. A proposal for the assessment of key variable to define the pathology of VaD has been made by the Newcastle group (Table 2), but the existing concepts of VaD present difficulties in generalizing clinico-pathologic correlations from patient to patient [226]. In addition, the appreciation of the presence and extent of morphologically verified vascular lesions in cognitively impaired patients may be influenced by the heterogeneity of the criteria for commonly found brain lesions and their interpretation

Table 2 Key variables to define the pathology of VaD (modified from [255])

Identify as ischemic or hemorrhagic infarct(s)
Presence of lacunes and lacunar infarcts: état lacunaire (gray matter) and état criblé (WM)
Location of infarcts: cortex, WM, basal ganglia, brainstem, cerebellum
Circulation involved: arterial territories—anterior, middle or posterior
Laterality: right or left anterior and posterior
Size and number of infarcts: 0–4, 5–15, 16–30, 31–50 and >50 mm; if size <5 mm, determine as small or microinfarcts
Presence and location of small vessel disease: lipohyalinosis, fibrinoid necrosis, CAA
Presence of white matter disease: rarefaction or incomplete infarction
Degree of gliosis: mild, moderate or severe
Presence of Alzheimer pathology (including NFT and neuritic plaque staging). If degree > stage III, the case is mixed AD and VaD
Presence of hippocampal sclerosis

Each of the above features can be scored numerically to provide a summary. For example, 0 absent and 1 present or using a grading system. Less frequent lesions including watershed infarcts and laminar necrosis may be scored similarly. Increasing numerical value may also be assigned to the infarcts

CAA cerebral amyloid angiopathy; *NFT* neurofibrillary tangles; *WM* white matter

applied in different centers, as recently shown by the large variability of answers in a semistructured questionnaire among 13 neuropathologic centers around the world [384]. The difficulty of accurately undertaking this task is formidable.

In contrast to inter-observer validation associated with pathology protocols for AD [8, 128, 201, 335–357, 389] there are no criteria, validated across different laboratories of cerebral vascular pathologies, nor for synthesizing a global "vascular pathology score" where multiple pathologies are present. The frequency of specific morphologic features of VCI depends largely on study inclusion criteria [447], and neuropathologic confirmation of a clinical diagnosis of VaD/VCI therefore remains largely subjective. It must be kept in mind that VCI/VaD has a broad spectrum of CVLs of heterogeneous pathophysiology that may result in cognitive decline, developing consensus neuropathologic criteria will be difficult.

Prevalence and epidemiology

Estimates of incidence and prevalence of VaD are affected by three major factors: choice of diagnostic criteria, availability of brain imaging and confirmation by autopsy. There is considerable lack of agreement about

VaD epidemiology and prevalence. Given the difficulties in diagnosing this disorder, considerable methodologic and geographic differences, epidemiologic studies must be interpreted cautiously. Although VaD was previously considered the second most common type of dementia after AD [142, 168, 208, 253, 328, 408, 415], and is the second leading cause of death worldwide [422], in the Western world it follows AD (60–70%), dementia with Lewy bodies (DLB) (10–25%) and other non-Alzheimer dementias (8–10%) at place 3 or 4 [242, 248, 406]. A review of clinical studies showed a frequency of VaD ranging from 4.5 to 39% [258], but in most Western memory clinic-based series, it is diagnosed in about 8–10% [136, 248], with age-standardized incidence ratios (SIR), varying from 0.42 to 2.68.

Evaluation of 11 pooled European population-based studies of subjects over age 65 revealed an age-standardized prevalence of 6.4% for all dementias, 4.4% for AD and 2.6% for VaD [299]; VaD accounted for 15.8% of all dementia cases. In Canadian clinical studies, 12.1% had VaD and 12.8% mixed AD/VaD [417]. The incidence of VaD varies between 6 and 15/year/1,000 persons aged 70 and older, and increases with advancing age [209]. Among US Medicare beneficiaries VaD rose form 1991 to 1999 from 43 to 144/1000 among whites compared to 52 to 161/1000 among African Americans (3.1 to 3.3 times increase) [477]. Studies from Japan revealed that the prevalence of VaD was more than double that of AD [205, 223, 293, 494, 544], while in others, AD was two times more frequent than VaD [83], from 12 to 23% compared to 47% for AD and 22% for dementia with Lewy bodies [406].

A review of pathologic studies on the prevalence of VaD is difficult because most studies may contain referral biases because they are weighted with patients from clinical centers, where AD predominates, e.g., the CERAD group [220, 451]. The divergences in estimates of prevalence [33, 53, 299, 506] and incidence of VaD [120, 223] suggests that the concept of VaD needs further validation.

A review of autopsy studies of 2,784 patients with dementia between 1962 and 1990 revealed an overall mean risk of VaD (range 2.0–85.2%); between 1962 and 1995 the overall risk was 11.3% [311], while others classified 15–19% as "pure" VaD [337] or showed even a wider range between 9.0 and 85.2%, with a mean of 17.9% [258]. Other reports showed a prevalence of 2–9%, while in the CERAD, the Nun Study and the Florida Brain Bank series, pure VaD without other pathologies was seen in only 0.03 and 2.5%, respectively [33, 220, 455, 456]. Among 3,438 autopsy cases between 1991 and 2003, the prevalence of VaD ranged from

0.03 to 35% with a mean of 11.6%, and in a smaller community-based autopsy sample of dementia "pure" VaD was seen in 7% [414] (Table 3). For comparison, in recent autopsy series of subjects with dementia from Japanese geriatric hospitals, the incidence rates for AD, VaD and mixed or other dementias were 34, 35, 11 and 20%, respectively, in one [448] and 42, 22, 6 and 26%, respectively, in the other series [3]. Of 650 demented patients diagnosed during life as having AD, at autopsy 505 (78%) had AD; only 390 (60%) of these had AD as the only neuropathologic condition. Of the remaining 22% with no evidence of AD, 39 had Parkinson disease (PD), 25 nonspecific degenerations, 15 Pick disease, 14 multiple infarcts and 11 lacked any neuropathologic abnormality [324]. Evaluation of 363 autopsy cases of the updated Honolulu-Asia Aging Study (HAAS) showed a low correspondence between clinical and neuropathologic diagnosis, with 56% diagnosed as probable or possible AD but only 19% having neuritic plaques or NFTs as the sole or predominant dementia-related morphologic lesions. Although 16% were attributed to mixed cases during life, almost 40% were found to have significant mixtures of dementia-related lesions at autopsy [390].

Among 180 autopsy cases of the Religious Order Study (60 not cognitive impaired, 37 MCI, 83 demented), almost all patients had at least some AD pathology; cerebral infarcts were present in 35.2%, and LBD in 15.6%. Persons with MCI had intermediate levels of both AD pathology and cerebral infarctions from those without cognitive impairment and those with dementia, suggesting that MCI is related to both pathologies [41]. Neuropathologic examination of 206 demented subjects revealed AD with Lewy bodies

Table 3 Autopsy series showing prevalence of VaD/VCI (modified from [248])

1962–1990	15 studies (Europe, USA, Canada) 2,784 cases Prevalence 2.0–85.2% (mean 24.5%)
1962–1995	Markesberry (1998) [311] Prevalence mean 11.3%
1991–2003	11 studies (USA, Scandinavia, Japan) 3,438 cases Prevalence 0.03–35% (mean 11.6%)
2004, Seattle, USA	20/170 cases Prevalence 7% [414]
2005 Austria	Jellinger: retrospective, dementia/AD 1,500/850 cases Prevalence 10.8/2.2%
Austria	Jellinger (unpublished): prospect. Dementias 180 cases Prevalence 7.8%
Japan	Seno et al 1999 [448], Akatsu et al 2002 [3] 122 / 270 cases prevalence 35.0 / 23.6 %

(LBs) in 38%, AD with vascular lesions in 25%, "pure" AD and AD with LBs (with or without vascular lesions) in 13% each and 8% for pure vascular lesions [491]. In centenarians, cerebral infarcts and lacunes are frequent and are responsible, at least in part, for the high proportion of cognitive dysfunctions in these patients [207].

In a recent prospectively followed series of community-dwelling individuals involved in the Medical Research Council Cognitive Function and Ageing Study (MRC-CFAS), up to 78% of the participants presented with cerebrovascular pathology and 70% with AD-pathology upon autopsy, vascular lesions being as common in demented and nondemented individuals, although multiple CVLs were more frequent in the former group [154, 361]. An update of 456 autopsies in 41% of demented cases showed moderate or severe neurofibrillary tangles (NFTs) compared to 4% in nondemented people, 27% of whom had severe cortical neuritic plaque and 1/3 had some neocortical NFT pathologies. SVD was the most frequent lesion and mixed pathology was much more common than pure AD or vascular disease, and incidental WMLs were common in −67 to 90% [227].

A stronger correlation exists between memory impairment and NFTs [46, 322, 402] and vascular lesions [52] than with amyloid [228, 269, 479], with notable exceptions showing correlation of entorhinal Aβ42 with memory in both AD and VaD but not in DLB [481]. Circle of Willis atherosclerosis was found to be more severe in subjects with VaD and AD than in controls, while it was equivalent between elderly controls and subjects with non-AD dementia. Increasing atherosclerotic grade increased the Odds ratios (OR) for the diagnosis of both AD and VaD [39].

In a retrospective study of 1,500 consecutive autopsies of demented patients with a mean age of 83.3 ± 6.0 years in Vienna, Austria, "pure" VaD was seen in 10.8% but only in 2.2% of 850 patients with the clinical diagnosis of possible or probable AD. Alzheimer pathology was present in 40.0 and 50.7%, respectively, whereas 20–25% showed coexisting CVLs and 9% Lewy body pathology. Other disorders (Creutzfeld-Jakob disease/CJD, PD, etc.) were seen in 4.5 and 3.3%, respectively, while in 1% a morphologic basis for dementia was not found [250]. In a prospective clinico-pathologic study [30] of 180 demented patients, the prevalence of "pure" VaD was 8% compared to 46% AD, 24% AD plus minor CVD, 10% AD with Lewy pathology, 7% MD and 4% of other dementing disorders (Jellinger, unpublished data). These and other autopsy studies [143, 149, 178, 216, 338] have clearly shown the high frequency of mixed pathologies in eld-

erly subjects with and without cognitive impairment (see [251]).

Major morphologic lesions in VCD/VaD

Pathologic changes in the brain of patients with cognitive impairment are multifold and include multifocal and/or diffuse disease and focal lesions [171, 224, 245, 246, 248, 255, 427, 509] (see Tables 4–6):

1. Multifocal lesions with large territorial or borderline infarcts due to large vessels disease, distal field (watershed/borderzone) infarcts mainly related to hemodynamic events and carotid artery stenosis, microinfarcts throughout the brain, often due to embolic disease, small and medium-sized lesions mainly in functionally important brain areas, lacunes and lacunar infarcts or scars, WMLs, subcortical arteriosclerotic leukoencephalopathy (SAE) resulting from chronic ischemic hypoperfusion due to SMV and other mechanisms [132, 146, 224, 464, 517], incomplete ischemic injury, cortical pseudolaminar necrosis in cases of global ischemia and

Table 4 Major types of vascular lesions associated with cognitive impairments (modified from [171, 242, 250, 312, 420])

1. Classical multiinfarct encephalopathy (MIE)
 Multiple large (sub/territorial) infarcts in cortex
 and white matter/basal ganglia in territories of large
 cerebral arteries, MCA, MCA + PCA; involving left
 or both hemispheres
2. Strategic infarct dementia (SID)
 Small or medium-sized infarcts/ischemic scars in functionally
 important brain regions: thalamus, hippocampus (PCA),
 basal forebrain angular gyrus (ACA), bilaterally
 or dominant hemispheres
3. Microangiopathic (small vessel infarct) dementia (SMVA)
 (a) Multilacunar state
 Multiple cortico-subcortical microinfarctions
 (mixed encephalopathies)
 (b) Subcortical arteriosclerotic leukoencephalopathy
 Binswanger (SAE)
 Multiple small inf. in basal ganglia + white matter
 ("leukoaraiosis") with preservation of cortex
 (c) Granular cortical atrophy
 Multiple microinfarcts or small scars within
 border zones ACA/MCA in one/both hemispheres (rare)
4. Subcortical microvascular leukoencephalopathy/
 white matter lesions
 (acquired/genetically determined)
5. Pseudolaminar cortical necrosis, mainly in arterial
 border zones (post-ischemic lesions)
6. Hippocampal sclerosis or gliosis
7. Inflammatory angiopathy and other mechanisms
8. Combined cerebrovascular/ischemic lesions

ACA anterior cerebral artery; *MCA* medial cerebral artery; *PCA* posterior cerebral artery

Table 5 Pathophysiological classification of VaD (modified from [509])

A. Multifocal/diffuse disease
 1. Large vessel dementia (LVD)
 Multiple infarct dementia (MID): Multiple
 large artery/borderline infarcts, cortical and subcortical,
 with perifocal incomplete infarcts, especially in white matter.
 2. Small vessel dementia (SVD)
 Subcortical infarct dementia
  Multiple small lacunar infarcts with perifocal lesions
 in white matter.
  "Granular atrophy" of cortex (multifocal cortical
 microinfarcts, scars)
  Lacunar state
  Binswanger subcortical encephalopathy (SAE)
  Hereditary angiopathies: CADASIL (cerebral autosomal
 dominant arteriopathy with subcortical infarcts
 and leukoencephalopathy)
 Cortical plus subcortical infarct dementia
  Multiple, restricted small infarcts due to
   Hypertensive and arteriolosclerotic angiopathy
   Amyloid angiopathy, with/without hemorrhages
   Collagen or inflammatory vascular disease
 (angiitis, PCNSA, FMD)
   Hereditary forms
 3. Hypoperfusive, hypoxic-ischemic dementia (HHD)
 Incomplete white matter infarcts
 Anti-PL related ischemia
 Diffuse hypoxic-ischemic encephalopathy (cortical lacunar
 necrosis, post-cardiac arrest, hypotension)
 4. Venous infarct dementia
 Large hemorrhagic, congestive symmetric infarcts due
 to thrombosis of the sagittal sinus or the great vein of Galen
 5. Hemorrhagic dementia
 Subdural hemorrhage
 Subarachnoid hemorrhage
 Intracerebral hemorrhage
B. Focal disease/strategic infarct dementia (SID)
 Few infarcts restricted to functional important regions
 Mesial temporal (including hippocampal)
 infarcts/ischemia/sclerosis
 Caudate and thalamic infarcts (especially DM thalamic
 nucleus, bilateral damage)
 Fronto-cingulate infarcts (basal forebrain,
 ACA territory)
 Angular gyrus infarct (dominant cerebral
 hemisphere - ACA and MCA territories)
 White matter key areas

Anti-PL anti-phospholipid; *PCNSA* primary angiitis/arteritis of the central nervous system; *FMD* fibromuscular dysplasia; *ACA* anterior cerebral artery; *DM* dorsomedial

hypoperfusion, hippocampal sclerosis due to systemic and cardiovascular disease [122, 239] and multiple post-ischemic lesions.

2. Focal disease with circumscribed, often strategically placed lesions, i.e., in functionally important brain areas and neuronal circuits. They are caused by many vascular and ischemic mechanisms including large arterial and small vessel diseases, cardiac embolic events, hemodynamic mechanisms and

cerebral ischemia of various etiology. Complicated angiopathies such as fibromuscular dysplasia, arterial dissection, granulomatous angiitis, collagen vascular disease and other arteritides are rarer causes of VaD [142, 171, 224, 241, 242, 245, 246, 248, 255, 311, 312, 332, 351, 374, 426, 509].

Another classification distinguishes large and small vessel disease (Tables 5, 6):

1. Large vessel dementia (LVD): Classical multi-infarct encephalopathy (rather rare).
2. Small vessel disease (SVD): Microangiopathic (small vessel infarct) dementia (SVI), dementia with lacunes, strategic infarcts mainly in subcortical areas and WMLs [14, 101, 154, 346, 350, 520].
3. Other types of VaD.

Although cause-relationships between CVLs and cognitive impairment evade strict classification [139, 144, 171, 185, 241, 242, 245, 246, 248], the major CVLs associated with cognitive impairment are summarized in Table 7. The key variables to define the pathology of VaD are summarized in Tables 2 and 7.

Classical multi-infarct encephalopathy (MIE)/large vessel disease

Single or multiple infarctions involving the areas of major cerebral arteries commonly result from atherosclerosis affecting intra-oder extracranial vessels, giving rise to local thromboembolism or hypoperfusion. These infarcts may be large (sub)territorial lesions involving much of a cerebral hemisphere. Their size is determined by assessing the two largest diameters of such a lesion or may represent multiple small lesions in cortex and/or adjacent white matter and basal ganglia, mainly in the medial cerebral artery (MCA) territories and less frequently in other supply areas or in adjacent territories, involving the dominant or both hemispheres [143, 301, 332, 408, 443] (see Table 2). Occlusion of extracranial arteries, e.g., the internal carotid artery (ICA) and the main intracranial arteries including the MCA, can lead to MIE which forms approximately 15% of VAD [69]. Medium-sized arteries in the leptomeninges and proximal perforating arteries can be involved. The damage can be worse depending upon the presence of hypertension and related CVD. Artery-to-artery embolism involves breaking of thrombi from often ulcerated lesions in extracranial arteries or heart valves. Various types of cardiogenic emboli may also find their way to the anterior and posterior cerebral circulation to cause infarcts in the respective supply areas.

Table 6 Subtypes of vascular dementia

Major lesions			
Larger arteries		**Smaller vessels**	
Type of infarcts			
Multiple territorial infarcts	Strategic territorial infarcts	Strategic lacunar infarcts	Multiple lacunar infarcts
Pathogenesis			
Cardial Embolic	Arterial Emboli Embolic	Hyalinosis Amyloidosis	Binswanger CADASIL
Arterial emboli	Cardial	Vasculitis	
Carotid stenosis		Thrombosis	

The development of infarcts follows typical stages and the intensity of gliotic scars is an important consideration in judging the degree and age of infarction. Glial scarring may be seen after global ischemia, e.g., transient cardiac arrest causing lesions in vulnerable brain areas including hippocampus and neocortical (pseudo)laminar necrosis. Stroke patients with dementia had infarcts in the left hemisphere that were eight times larger than those in the right one, with a strong correlation between dementia and infarctions in the left posterior cerebral artery (PCA), anterior cerebral artery (ACA) and in parietal areas [298]. Cardiac sources, such as atrial fibrillation and myocardial infarction, provide a source for cerebral emboli, whereas most other causes, such as hematological conditions, inflammatory angiopathies/vasculitides, Sneddon's disease [112] and familial CVD, e.g., autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) related to *NOTCH*3 mutations [389, 488] or cerebral amyloid angiopathy (CAA), both sporadic (see [20]) and hereditary (see [257]), usually cause multiple subcortical and/or cortical vascular lesions.

Microangiopathic small vessel lesions: lacunes and lacunar infarcts

Small vessels, including intracerebral end-arteries and arterioles, undergo progressive age-related changes [52, 283, 520], and may accelerate microvascular changes due to aging [445], which may result in lacunar or microinfarcts. The declining cerebral blood flow (CBF) and energy metabolism of the aging brain have been mainly attributed to ultrastructural alterations of the capillary walls. In aging rats, the vascular anomalies included perivascular collagen deposits, also referred to as microvascular fibrosis and basement membrane thickening [145]. Recently, age-related vessel changes in the human putamen have been demonstrated [496]. Due to the accumulation of collagen type IV, microvessels thicken and show a reduction in their lumen. Those changes likely promote occlusion or progressive

stenosis with consequent acute or chronic ischemia in the dependent tissue. Alternatively, arteriosclerotic changes in small vessels in deep gray and white matter cause vessels to loose their elasticity to dilate and constrict in response to variations in systemic blood pressure or loss of autoregulation which, in turn, causes changes in cerebral perfusion. The deep cerebral structures are most vulnerable because their vessels are end arteries almost devoid of anastomoses. Small vessel pathology and acidosis acting on brain capillary endothelial cells could also lead to damage of the blood–brain barrier (BBB) with leak of fluid and macromolecules into cerebral microenvironment [392]. The presence of heavy deposits of serum proteins exclusively around the capillaries of the gray matter in cases with vascular dementia may indicate a defect of the cortical capillary system which might play a role in the clinical symptoms seen in VaD [7].

Lacunar infarcts or microinfarcts appear central to the most common cause of VCD/VaD [27, 142, 245, 246, 248, 255, 256, 509]. The term *lacune* appeared in the French literature in the early 1900s to describe small capsular [310] and pontine [157] infarcts with specific symptoms. Lacunar infarcts are small miliary softenings from 3 to 15 mm in diameter or small cavitations that may have more than one pathologic substrate, the most significant representing small infarcts and, less frequently, healed or reabsorbed tiny hemorrhages [162–164, 166, 171]. Seen radiologically and upon gross examination at autopsy, these lesions most frequently involve the periventricular white matter and subcortical structures, including thalamus, basal ganglia, internal capsule, pons and cerebellar white matter [166, 172]. Lacunes were classified into three types [117, 397, 398]. Type I lacunes are irregular cavities containing lipid-laden macrophages and blood vessels surrounded by a rim of gliotic, rarified brain; they are arising from small infarcts. This most significant type, resulting from narrowing or occlusion of small penetrating arteries branching directly from larger cerebral arteries [29] has been reported in 6–11% of selected

Table 7 Major cerebrovascular lesions associated with cognitive impairment (modified from [255])

Vascular dementia subtypes related to	Newcastle subtype
Large infarct or several infarcts (>50 ml loss of tissue); multi-infarct dementia	I
Multiple small or microinfarcts (>3 with minimum diameter 5 mm); small vessel disease (involving greater than three coronal levels; hyalinization, CAA, lacunar infarcts, perivascular changes, microhemorrhages)[a]	II
White matter lesions/leukaraiosis / Binswanger disease	
"Strategic" infarcts (e.g., thalamus, hippocampus, basal forebrain)	III
Cerebral hypoperfusion (hippocampal sclerosis, ischemic–anoxic damage, cortical laminar necrosis, borderzone infarcts involving three different coronal levels)	IV
Cerebral hemorrhages (lobar, ICH or SAH)	V
Cerebrovascular changes with AD pathology (> Braak III); mixed dementia	VI
Combined cerebrovascular lesions	

The age of the vascular lesion(s) should correspond with the time when disease began. The proposed Newcastle categorization includes six subtypes. Post-stroke cases are usually included in subtypes I–III. While these may not be much different from other published subtypes, they are practical and simple to use

AD Alzheimer's disease; *CAA* cerebral amyloid angiopathy; *ICH* intracerebral hemorrhage; *SAH* subarachnoid hemorrhage

[a] Subtype I may result from large vessel occlusion (athero-thromboembolism), artery-to-artery embolism or cardioembolism. Subtype II usually involves descriptions of arteriosclerosis, lipohyalinosis, hypertensive, arteriosclerotic, amyloid or collagen angiopathy. Subtypes I, II and V may result from aneurysms, arterial dissections, arteriovenous malformations and various forms of arteritis (vasculitis)

brain autopsy series [162, 493]. A variant type—incomplete lacunar infarct—characterized by loss of only selectively vulnerable cellular elements without cavitation, suggests a common underlying cause, i.e., arterial obstruction, but perhaps of shorter duration or lesser severity [284], or may represent the squeal of edema-related gliosis [306]. Type II lacunes are smaller in size and distribution and contain numerous hemosiderin-laden macrophages, representing old, small hemorrhages or old hemorrhagic microinfarcts, resulting from fibrinoid vascular necrosis (Fig. 1), but are rare [282, 283]. Type III are dilatations of perivascular spaces, surrounded by a single layer of epithelial-like cells or more segments of a normal artery, and have been ascribed to small vessels permeability, interstitial fluid drainage disorders [116, 399], cerebral atrophy, mechanical stress from pulsating arterioles [219], distortion or elongation of small arteries, perivascular
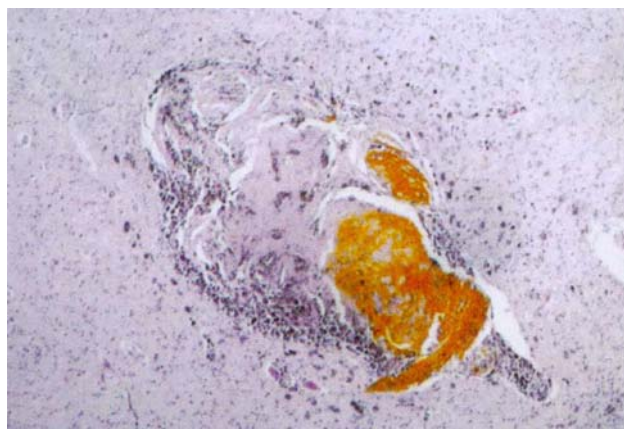
Fig. 1 Hypertensive microangiopathy with fibrohyalinosis and microaneurysm with perivascular hemosiderin in putamen. H&E, ×250

inflammation or other nonspecific factors. Misclassification between lacunar infarcts and enlarged perivascular spaces (EVPS) may occur, but most of these measure <2 mm, and normally surround perforating arteries entering the striatum at the anterior perforated substance [51, 61]. Their appearance in large numbers reflects focal brain atrophy around blood vessels and may lead to the so called *état criblé*, especially in the basal ganglia [23, 397]. EPVS are only rarely observed in the brains of young healthy adults, while they are increasingly common with aging [210]. Their presence has been associated with hypertension [90, 503], cerebral arteriosclerosis [504], PD [281], CADASIL [96] and diabetes [153].

Lacunes were found in 36–42% of patients studied, representing the most frequent type of CVLs [419, 544]. Among 750 autopsy-proven AD brains and 562 age-matched controls, lacunar lesions were found in 32 versus 27% [237].

Hypertension has been regarded as the principal determinant of these lesions which occur in locations supplied by penetrating arterioles measuring 40–200 μm in diameter [50, 164, 166]. A classic post-mortem study of remote necroses in brains of hypertensive patients noted segmental arterial disorganization in association with 40–50 lacunes [164], caused by intracranial atherosclerosis, lipohyalinosis or segmental fibrinoid necrosis affecting small arteries with subsequent occlusion of single deep perforating vessels, whereas in one-fifth of the patients no thrombosis was found. However, most perforating branches have multiple stenoses and post-stenotic dilatation, suggesting that hemodynamic events might also play a role in the pathogenesis of lacunar state [110]. The pathogenesis

of lacunar infarcts in the white matter and lenticular nucleus seems to be different, stenosis in the former and probably hemodynamic disturbances in the latter [330]. Other mechanisms are cerebral microembolism of vascular or cardiac origin, such as atrial fibrillation [142, 171].

Some recognize two distinct forms of lacunes: (1) patients with a single, symptomatic lacune having a vascular risk profile who presumably have microatheromatosis or embolism and (2) patients with multiple, usually asymptomatic, lacunes, with a higher frequency of hypertension and hypertensive SMV [50]. The pathogenesis of tissue damage in hypertension based on experimental studies has been reviewed recently [354].

Microscopic vascular pathology represents a heterogeneous group which includes two types of lesions: (1) those visualized by currently available neuroimaging methods, i.e., lacunes and WMLs [519] and (2) those that cannot be detected in vivo such as cortical microinfarcts and focal gliosis, but the increasing use of MRI to assess these lesions led to contradictory data. While some studies suggested that many lacunes identified neuropathologically or by MRI may be essentially silent from a cognitive point of view [244, 493, 506], and lacunar infarcts may be an incidental finding at neuroimaging and/or autopsy, a recent MRI-based study of 633 elderly subjects reported a significant association between lacunar scars and both the MMSE and ADAS scores, but only in cases with no or minimal disability, and therefore no or only minimal cognitive impairment were evaluated [501]. The importance of evaluation in defining the strategic importance of lacunes has been discussed recently [180].

Brain lesions associated with cognitive decline due to SMV, mainly subcortical vascular dementia [137], comprise of a tetrad of cerebral lacunes, microinfarcts, arteriosclerosis and WMLs. They are most reliable to a dementia syndrome when situated in the basal ganglia and cerebral white matter, either being single or multiple on neuroimaging or at autopsy. A cribriform pattern of multiple perivascular dilatations affecting the corpus striatum and other deep structures is referred to as "*état lacunaire*" or "lacunar state".

According to the type and predominant location of SMVA, the following types of SMV-related VaD can be distinguished (Table 4):

1. (Multi)lacunar state
2. "Strategic" infarct dementia (SID) with borderline infarcts and other lesion
3. White matter lesions and subcortical arteriosclerotic (leuko)encephalopathy (SAE)

Multilacunar state

The pathologic changes of lacunar state in basal ganglia, thalamus, hemispheral white matter and brainstem have been repeatedly reviewed [165, 282, 283, 405, 519, 520]. People with dementia are more likely to have such lesions than those without dementia, but the impact of microvascular lesions on cognitive impairment is under discussion [180].

"Strategic" infarct dementia syndrome

Focal infarctions or ischemic scars, often involving isolated functionally important brain regions, despite relatively small losses of cerebral parenchyma, may cause cognitive impairment, culminating in a dementia syndrome. Several studies have correlated cognitive impairment with the presence and emergence of lacunes, particularly in functionally important locations [476, 534]. These infarcts may be solitary but the clinico-pathologic picture is not infrequently complicated by, or dependent on, the occurrence of bilateral or multiple infarcts among which one or more may affect brain regions associated with a SID syndrome. They can be subdivided into those arising from the classical mechanisms associated with cerebral infarction (thromboembolism, atheromatous embolism, arteriosclerosis, atheromas, lipohyalinosis of small vessels) and those that manifest as focal ischemic lesions related to hypoperfusion, e.g., bilateral watershed infarcts in the cerebral hemispheres. Such strategic areas include [171, 245, 246, 248, 311, 332, 509]:

(a) Watershed or borderzone infarcts: Typical infarctions in cerebral convexities may occur symmetrically or unilaterally, in circulatory borderzones between the deep and superficial branches of ACA, MCA and PCA, caused by hypotension with "misery perfusion", i.e., diminished flow or stagnation of flow in distal vessels, or showers of microemboli. These infarcts usually occur in patients with severe atherosclerosis and extracranial carotid stenosis or occlusion and are often associated with prolonged episodes of hypotension [290]. They result in laminar necrosis of the cortex, multiple cortical and subcortical microinfarcts, often with small wedge-shaped lesions with their base to the pial surface and often extending into the white matter. They occur in the end-field territories between small superficial branches of large cerebral arteries or between deep and superficial vessel systems causing bilateral hippocampal or thalamic softening. Size and extent of these watershed infarcts depend

on the amount of leptomeningeal anastomoses between the main cerebral arteries [499], and the degree of arteriosclerosis stenosis of meningeal arterial branches. The superior frontal area, between the distal supply of the ACA and MCA, and the posterior parieto-occipital junction, among ACA, MCA and PCA, are involved more often. Hypoxia also causes alterations in the hippocampal subareas CA-1 and CA-4, the outer half of the caudate nucleus and putamen and the anterior and dorsomedial nucleus of the thalamus. Bilateral ICA occlusive disease causing such lesions is frequently associated with impaired intellectual function [386].

(b) Granular cortical atrophy, characterized by multiple small cortical microinfarcts and scars most often in the boundary zone between ACA and MCA in one or both hemispheres, is usually caused by hypoperfusion due to stenosis of the ICAs, cerebral microembolism to the cortex [487] or CAA, but they are a rare cause of dementia.

Other lesion patterns are:

(c) Angular gyrus: Lesions involving the angular gyrus in the supply areas of ACA and MCA may occur in the dominant hemisphere or bilaterally [42].

(d) Frontocingular infarcts: They involve the orbital and medial frontal cortex, in particular the territory of frontopolar and callosal marginal branches of the ACA [551].

(e) Dorsal-paramedian, dorsomedial and polar areas of the thalamus are involved by unilateral and more often bilateral lesions resulting from occlusion of the thalamo-perforating artery (Fig. 2), a branch of PCA [78, 89, 103, 468] or capsular genu infarction [473], and paramedian thalamopeduncular infarcts [474].

(f) Mesial temporal area of the hippocampus: Bilateral infarcts a result from circulation disorders in the supply area of the PCA [63, 140, 181, 241, 242, 245–247, 311, 551].

(g) Caudate nucleus: Such lesions result from obstruction of the lateral lenticulostriate arteries of the MCA and may include the anterior portion of putamen and anterior limb of internal capsule [75] or the head of the caudate [323] (Fig. 2).

White matter lesions

Neuroimaging data and clinical relevance

Recent studies have placed emphasis on deep WML that have been increasingly detected by modern neuroimaging methods [5, 18, 34, 36, 104, 106, 150, 160,
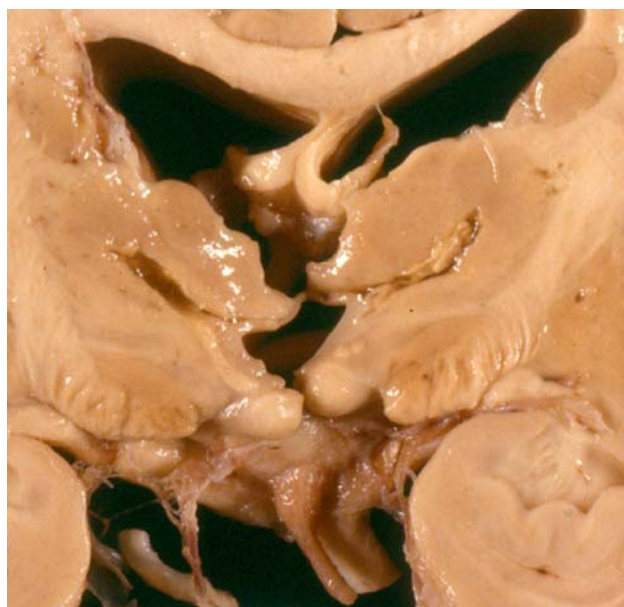
Fig. 2 Bilateral old infarcts in medial thalamus and old lacunar infarct in left caudate nucleus in 60-year-old hypertensive male with dementia after several TIAs

213, 271, 302, 403, 408, 424, 436, 463, 501, 514, 518], and their relation to CVD and VAD. Synonyms include SAE or Binswanger disease [24, 47, 48, 75], diffuse white matter disease, WMLs, leukoaraiosis [198], periventricular arteriosclerotic (leuko)encephalopathy or leukomalacia, (progressive) subcortical vascular encephalopathy [424] and periventricular lucency [518]. WMLs are anatomically divided into those in a periventricular distribution and those which affect deep white matter, referred to as "deep subcortical WMLs". Punctate and early confluent to confluent WMLs show distinguishable differences in their spatial distribution within a normal elderly population [133, 438–440].

Using CT and MRI, WMLs have been found in 22% of subjects under age 40 and in 27–60% of those over age 65 years [104], whereas in patients with AD and VaD, they are detected by MRI in almost 100% of patients [106], and enable the diagnosis of VaD with a sensitivity of 88% and a specificity of approximately 95% [213]. Their frequency is increased in patients with CVD and those at risk for vascular disease, including arterial hypertension, ischemic stroke, cardiovascular disease and diabetes mellitus [62, 295, 365, 381, 516]. The relevance of these lesions is controversial, since WMLs can be found in aged individuals with normal cognitive function with or without depression, age being the strongest predictor of their presence and severity [85, 297, 302, 404, 440, 540], as well as in patients with AD, VaD, multiple sclerosis and many other disorders [32, 518]. WMLs are more common in

patients with VaD than in those with AD or healthy volunteers [385]. Longitudinal studies in white matter following ischemic stroke demonstrated improvement of the changes that continues at least into the second year following the insult [516]. WMLs and lacunes often coexist and the differential clinical significance of each of these types of lesions has been difficult to establish [180, 302, 422, 455, 540]. The relationship between *APOE* ε4 and WMLs in elderly subjects with lacunar infarcts is still controversial [31, 124, 277, 526].

Several cross-sectional studies support the view that WMLs have clinical implications even in healthy elderly people [105, 114, 173, 191, 272, 285]; their association with decline in essential cognitive abilities suggests that they should be regarded as a risk factor for cognitive impairment based on the site and volume of the lesions [91, 104, 157, 174, 308, 439, 457]. Others have only been able to confirm the association between WMLs and previous [173] or subsequent decline in cognitive function [105, 114, 278, 537]. Although longitudinal studies with serial MRI described progression of WML volumes, no association with cognitive decline was reported [59, 91, 439, 529], others observed an association with deficits of executive control [364, 401, 421, 462, 505], probably due to disruption of intra- and inter-hemispheric communications and prefrontal subcortical circuits that underlie behavior, cognitive and executive cortical functions [177, 396, 401, 421, 442]. In a long-term prospective study of 68 healthy nondemented individuals the association between both periventricular and subcortical WMLs on MRI and cognitive impairment was only significant in ages 70+ [173]. While the perivascular WMLs had a relationship with cognitive deficits [80], subcortical WMLs corresponded with depressive symptoms [104, 106, 297]. Other studies showed correlations between WMLs and worse visuospatial ability and verbal memory [308]. The Rotterdam Scan Study of 1,077 elderly revealed relations between the periventricular but not the subcortical WMLs with global cortical function [60]. In patients with both WMLs and lacunes, WMLs were related only to a subscore of dementia rating scale [525], while in the LADIS study, WMLs and lacunes were both independently associated with ADAS scores, the effect of lacunes being less prominent [501]. The latter data were not confirmed by others [184, 273]. Although quantitative analysis of WMLs showed no strong association with severity of cognitive decline, it may provide a neuroimaging parameter for dementia development [81]. Posterior periventricular and corpus callosum extension of WMLs associated with MCI and AD indicate involvement of strategic white matter bundles that may contribute to the cognitive deficits seen in these syndromes [544].

Impaired cognitive domains of the speed of mental processes and memory in elderly diabetic patients were associated with WMLs and subcortical atrophy. Degenerative changes in the cerebral small vessels may constitute predictive factors for the rate of cognitive decline in these patients [5].

Neuropathologic substrates of WMLs

The morphologic lesions underlying radiologically observed WMLs include several morphologic alterations [104, 106, 150, 158, 213, 255, 482]. In general, a morphologic triad of demyelination, axonal loss and lacunar infarcts are found mainly in the frontal, parietal and occipital white matter and in the periventricular areas. Myelin degeneration usually has a patchy confluent form sparing the subcortical U-fibers (Fig. 3). Lacunes are often scattered in the hemispheric white matter at the centers of areas of pallor (Fig. 4). There

Fig. 3 Periventricular and deep white matter lesion in cerebrum semiovale and dilated lateral ventricles in 65-year-old woman with VCI. Klüver-Barrera
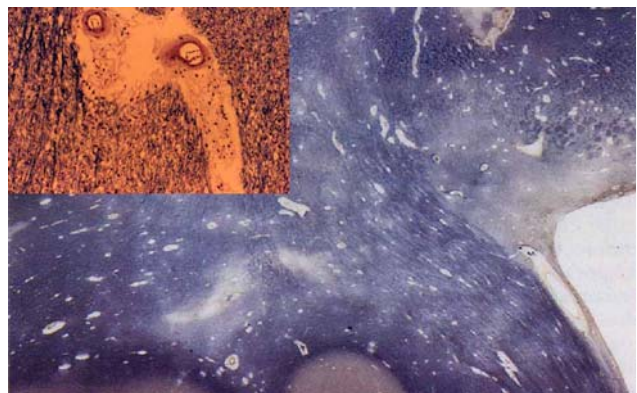
Fig. 4 Focal myelin pallor in periventricular frontal white matter in patient with dysexecutive syndrome. *Insert* Perivascular lacunes around fibrotic arterioles in frontal white matter. Klüver-Barrera, ×200

may be multiple, often asymmetrical, cavitary and non-cavitary infarctions (Fig. 5) or areas of vacuolation, loss or pallor of myelin, loss of axons and oligoden-droglia, areas of reactive astrocytosis, with or without macrophage reaction. Silver stains demonstrate that myelin pallor is secondary to fiber loss. Microinfarcts are generally smaller than 5 mm in diameter, and may present as a linear profile in the plane of section reflect-ing the course of an occluded microvessel. They are associated with astrocytic gliosis and presence of enlarged CD68-positive microglial cells. Dilated peri-vascular spaces may contain an insignificant and dis-persed population of lipid rich or iron pigment loaden macrophages. Dilatation of the Virchow–Robin spaces (VRS) is common in disorders associated with micro-vascular diseases, and VRS scores were similar to scores for periventricular hyperintensity [385]. When the lesions are large and confluent there may be focal areas of incipient cavitation for which the term "incom-plete white matter infarction" has been proposed [67], but a pathophysiological mechanism has not been accepted, and the term probably arose because of the lack of acceptance of a "misery perfusion" state of ischemic white matter leading to axonal and myelin loss. Vascular abnormalities include atherosclerosis of major cerebral arteries and several types of microangi-opathy of the penetrating arteries, with tortuosity of thickened fibrotic or hyalinized arterioles, focal fibri-noid necrosis of vessel walls in deep gray and white matter with or without occlusions [68, 76, 150, 167, 224,

234, 235, 255, 378, 497, 509], associated with small inf-arcts, microaneurysms, fibrotic or thrombotic vessel occlusion [59, 539]. Collagenous thickening and occlu-sion of venules has been observed [66, 342]. Other lesions include small arteriovenous (AV) malforma-tions, isolated central white matter infarcts, small foci of gliosis, vascular ectasia [518] or microvascular con-volute formations [497]. Punctate hyperintensive lesions on MRI corresponding to dilated perivascular spaces are to be distinguished from extensive WMLs, the histologic correlates of which are confluent patches of white matter pallor without cavitation (Fig. 4). Under high-power histology, these areas show vacuola-tion and decreased numbers of oligodendroglia. Peri-vascular vacuolation may represent an early stage of these changes. Comparative studies of post-mortem MRI and histology showed that periventricular lesions on MRI correlated well with the severity of demyelina-tion and astrogliosis, which were often associated with small lacunar infarcts in both the white matter and basal ganglia, suggesting a common pathophysiology, particularly arteriosclerosis of the penetrating arterer-ies [24, 68, 150, 155, 188, 224, 355, 437, 503, 504].

Attenuation of the cerebral white matter has been described into four clinical contexts: (1) SAE of Binsw-anger type that has been the subject of much contro-versy and reassessment, and some authors concluded that it should not be considered a distinct entity [76, 204, 300, 378, 471], (2) as a component of Alzheimer pathology and CAA [380], (3) as incidental finding of variable severity and debatable clinical relevance in the elderly and (4) as a feature of inherited cerebrovascu-lar SVD syndromes [121, 257].

Selective infarction in periventricular border zones in patients with carotid stenosis and superimposed hemo-dynamic failure [113] and ischemic leukoencephalopa-thies, irrespective of the cause, e.g., carbon monoxide (CO) intoxication, acute hypoxia, AV malformations, delayed radiation encephalopathy, CAA and CADA-SIL [79, 159, 189, 256], share widespread demyelination of the deep white matter and periventricular necrosis, sparing the cerebral cortex and   U-fibers. In AD, WMLs do not always parallel the severity of gray mat-ter pathology and, thus, may be caused by various fac-tors [131]. In contrast to meningeal and cortical arteries, CAA in white matter is rare, whereas fibrohyalinosis in this area is closely related with WMLs in AD, indicating their etiologic heterogeneity [485].

Cognitive impact of WMLs

The exact pathologic substrate of dementia to be associated with WMLs remains uncertain. Although

Fig. 5 Diffuse white matter lesions and old cystic subcortical infarction in 68-year-old hypertensive female with aphasia and subcortical dementia of Binswanger type

WMLs and lacunes may be independently associated with cognitive dysfunction, in AD they are significantly correlated with cortical atrophy [74], and medial temporal atrophy [107, 500], and, thus, contribute to cognitive decline [441]. Together with cortical microinfarcts, WMLs may contribute to progression of dementia, but do not essentially interact with AD pathology to increase the likelihood of dementia beyond their additive effects [444]. Although the neuropathologic evaluation of focal and white matter gliosis had no clinical validity [273], regional VML volumetry may be helpful in correlating subcortical pathology and cognitive impairment [329, 498]. Periventricular WMLs predict the rate of cognitive decline [102], and they are often associated with decline in executive functioning and visual memory, even in patients without dementia [275]. Recent clinico-pathologic studies showed that even severe WMLs may be an independent risk factor for dementia [154], outlining the uncertainty about the cognitive impact of WMLs on brain aging. Synaptophysin immunoreactivity as a measure of synapse density in the cortex of SAE was almost as severely reduced as in AD, suggesting that the loss of synapses is a factor of dementia [497, 552]. Some authors have suggested that cognitive impairment associated with subcortical ischemic vascular disease is particularly the result of associated hippocampal and cortical changes [152, 349], preventing adaptive response to local changes in metabolic elements. Others showed significant correlation between WMLs scores of the right frontal regions and dementia [213].

Pathogenesis of WMLs

Several studies provided evidence that WMLs are related primarily to small vessel disease [533]. The suggestion that their pathogenesis is a chronic ischemic disorder of heterogenous pathophysiology, with hypoperfusion of the penetrating arteries supplying the white matter resulting from hypotension and reduced blood flow due to narrowing rather than occlusion of arterioles [69], was recently confirmed by experimental studies, in particular bilateral common carotid artery occlusion in the rat [84, 146, 287, 353, 381, 515] (see [148, 354]).

Structural changes of small intraparenchymal cerebral arteries and arterioles related to hypertension, altered cerebral blood flow (CBF) autoregulation and the conditions created by the unique arterial blood supply of the hemispheral white matter contribute to WML development [378]. Age-related microvascular degeneration in the periventricular white matter, mainly in the frontal and occipital areas, was recently

described: Ultrastructural analysis identified the microvascular thickening as collagen deposits affecting the basement membrane. The vascular density did not correlate with the age. The basement membrane pathology significantly increased, while the number of intact microvessels gradually decreased, with advancing age in the frontal and occipital white matter [147].

MRI and PET studies showed decreased white matter CBF [271, 320, 377], which was even reduced in normal-appearing white matter [377], although their severity correlated better with the reduction in regional CBF in the cortex [271]. Others reported impaired vasodilatatory capacity in the deep white matter [64, 229]. Deep white matter hyperintensities and lacunar infarcts in basal ganglia and thalamus correlated with both a decline in mean global cortical metabolism and lowered cognitive function [465] and in patients without cortical infarctions, anterior periventricular hyperintensities reduced ipsilateral metabolic function [138]. The cortical global metabolic rates were lower in patients with subcortical strokes and cognitive impairment than in those without dementia [280], whereas others stressed the heterogeneity of CBF in subcortical VaD [541, 542].

A striking feature of WMLs is the sparing of the subcortical U-fibers, which may be related to the specific pattern of vascular supply. The periventricular regions and central white matter are fed by long penetrating arteries coming from the pial vessels on the surface of the cortex, whereas the peripheral parts of the centrum semiovale are supplied from penetrating vessels from the cortical surface. Periventricular border/watershed zones between the long ventriculoseptal and ventriculofugal branches of the choroid and lateral striatal arteries [109] are particularly vulnerable to hypotensive episodes with lowered perfusion pressure [341]. This concept has been rejected by those who believe that the centrifugal branches are veins rather than arteries [317]. The pattern of punctate WMLs is probably the consequence of mixed etiologies. Preferred localization of the more confluent WMLs with arterial watershed areas implies a stronger ischemic component in their development [133]. Atherosclerosis in large, peripheral vessels is considered to be a predictive marker of microvascular pathology in the white matter [147, 531]. It coincides with massive microvascular fibrosis, particularly in the frontal white matter, demonstrating an age-related microvascular degeneration in the periventricular white matter with loss of medial smooth muscle cells caused by hypertension [370], which may contribute to the development of WMLs by hindering a sufficient supply of the affected sites. In SAE the frontal lobe is the site at which WM

vulnerability is most pronounced, followed by parietal, occipital, and temporal lobes, and damaged nerve fibers are much more frequent than in age-matched control brains [4].

The distribution of WMLs with sparing of the subcortical U-fibers points to the pattern of cerebral edema [151]. The histological findings—spongiosis and loss of oligodendrocytes—which are also comparable to edema induced by ischemia and other mechanisms, were confirmed by experimental studies [264]. Diffuse extravasation of serum proteins throughout the white matter owing to enhanced pinocytotic activity by endothelial cells is observed without accompanying infarction in the stroke-prone spontaneously hypertensive rat; even a brief opening of the BBB may result in persistent presence of serum proteins in the white matter, including fibronectin and fibrinogen, which are capable of exerting biologic effects [432]. Breakdown of the BBB in white matter in chronic hypertension may result in focal edema with destruction of perivascular myelin [380, 452]. The edema hypothesis is consistent with the clinical observation that patients with SAE deteriorate during periods of sustained hypertension [235], while disruption of the BBB in experimental chronic cerebral hypoperfusion has not been clearly proven [148].

The molecular mechanisms of subcortical vascular WMLs concern a higher susceptibility of white matter axons to the effects of abnormal influxes of calcium that travel through various routes, including reverse Na^+–Ca^{2+} exchange triggered by persistent Na^+ channels and a parallel pathway involving Ca^{2+} channel causing increased endothelial permeability. Oligodendrocytes and/or myelin sheaths are more vulnerable to glutamate-triggered injury, resulting from reverse Na^+-dependent glutamate transport. Some of the steps involved in these destructive events are subject to modifications by neurotransmitters, such as γ-aminobutyric acid (GABA), and by neuromodulators such as adenosine [522]. Excitotoxicity, once thought the unfortunate preserve of neurons, also contributes to white matter damage via both *N*-methyl-D-aspartate (NMDA) and nonNMDA glutamate receptors. However, important physiological differences are apparent in these receptors when compared to those present at the synapse [9]. Activated microglia is three times more immunoreactive for major histocompatibiity complex (MHC) class II antigen [484, 553]. The number of oligodendrocytes in the deep white matter is reduced by approximately 50% [538], and increased apoptosis of oligodendrocytes has been a major histologic correlate of WMLs [65, 287], indicating that loss of oligodendrocytes is involved in the reduction of nerve fibers. White matter reactive

and fibrillary astrogliosis are common, but the number of astrocytes with light metallothionin (MT) I–II immunoreactivity in the deep white matter are reduced in contrast to normal numbers of astrocytes with strong reactivity for glial fibrillary acidic protein (GFAP) and MT I–II in subcortical white matter and cortex, suggesting topographic and biochemical differences in their dynamic plasticity. MT expression is related to regeneration, repair and/or reaction to neuronal lesions, with metal ion metabolic processing, buffering and detoxification or neuroprotection against free radicals [547]. The accumulation of APP and chromogranin A in tortuous axon indicated disturbed or blocked axonal transport [515].

In conclusion, recent evidence suggests that WMLs result from chronic ischemia due to hypoperfusion and disturbance of CBF, and, alternatively, recurrent edema resulting from severe disturbance of the BBB [68, 156, 245, 246, 381], but its exact etiology is unclear.

Post-ischemic encephalopathy

The sequelae of local or diffuse hypoxia and ischemia resulting from different causes can be separated into three major groups according to their predominant distribution pattern:

1. Cortical laminar necrosis: Damage to cerebral cortex with laminar necroses and their sequelae may arise from cardiac or respiratory arrest (hypotension, anesthesia accidents, cardiac an/or respiratory failure, shock). They appear frequently at the arterial border zones [69, 256] and are often associated with diffuse white matter damage and cerebellar atrophy.

2. Multiple post-ischemic lesions occur in case of dramatic systemic blood flow failure, combined with focal narrowing of large and small brain-feeding vessels, leading to disseminated or systemic post-ischemic lesions in cerebral cortex, subcortical white matter and basal ganglia. Combined cortico-cortical encephalopathies with multiple cortical and subcortical (micro)infarcts, resulting from various causes, may be associated with VaD.

3. Hippocampal sclerosis (HS): This specific type of lesion defined as severe gliosis and neuronal loss in the CA1 region of the hippocampus and in the subiculum is a rare cause of cognitive impairment mimicking AD, and cognitive decline is often featured by marked memory impairment, but often without frank dementia [6]. Its prevalence in autopsy series of very old subjects with dementia ranged from 0.4 to 26% [22, 122, 123, 238, 289]. It

predominantly co-occurs with AD [94], but is associated with a variety of disorders [38], in particular frontotemporal lobar degeneration (FTLD) and tauopathies [206, 314] and is extremely rare in oldest–old nondemented patients [314]. Hippocampal damage/necrosis, ranging from selective neuronal loss and gliosis to frank infarction, is often accompanied by multiple small infarcts in other brain regions, leukoencephalopathy or both. Current data showed that patients with HS are significantly older than those without HS and had more coronary artery disease, suggesting that related occult hypoxic–ischemic episodes may represent pathogenic factors [22, 314]. It has been occasionally observed in elderly individuals after receiving general anesthesia. Age-associated and other disease-related processes, such as atherosclerosis and cardiac failure, explain why the elderly cannot tolerate hypoperfusion of these vulnerable diseases like younger, healthy adults [425]. The morphologic differences between HS of hypoxic–ischemic etiology and HS associated with FTLD have recently been discussed, the former showing more marked neuronal and synaptic loss and greater reactive gliosis than HS associated with neurodegeneration [12].

Factors involved in VaD

Volume of brain destruction

Although it is understandable that subjects with large brain infarcts might experience intellectual decline, the idea that the diagnosis of VaD requires a brain tissue loss exceeding 100 ml is a persistent component of neuromythology. Tomlinson et al. [486] showed that although all patients with brain tissue losses of more than 100 ml suffered from dementia and that infarct volumes between 50 and 100 ml produced dementia less consistently, they observed several cases of dementia with infarcts of lesser volumes. Those totaling over 20 ml were significantly more frequent in subjects with dementia than in controls, and a marked difference between the two groups was present at 50 ml tissue loss cut-off. According to their study, which has never been replicated, a relatively small aggregate volume of brain infarct may or may not contribute to dementia, probably depending on its location, whereas destruction of a larger volume of cortex is usually followed by dementia. Therefore, these authors proposed the concept of strategic sites of infarcts. A quantitative MRI study demonstrated that total cerebral infarct area and corti-

cal involvement were significantly larger in stroke patients than those without dementia [298]. PET studies also showed a correlation between metabolic impairment of frontal and temporomedial cortex and the total volume of hypometabolic regions to dementia severity in both VaD and AD, whereas VaD cases also showed metabolic impairment of subcortical regions not present in AD, suggesting some distinction with FDG PET between these two types of dementia [325, 331]. Studies measuring macroscopic infarcts in VaD brains revealed mean volumes of infarcted brain of 39 ml (range 1–229 ml) in one study [550] and 40.7 ml with a range of 6.9–220 ml in another [135], whereas patients with AD and AD plus VaD had infarct volumes of less than 10 ml. In patients who showed only vascular lesions on histologic examination with senile plaques below the level necessary for diagnosis of AD, the total volume of infarcted brain was more than twofold greater in subjects with than without dementia; only 3 patients had brain lesions larger than 100 g, and 17 had smaller volumes within the range of patients without dementia, suggesting that dementia is not directly and consistently related to the volume of infarction [115]. These data were confirmed by recent studies that found only a nonsignificant trend for lobar infarcts to occupy more cerebral hemispheral volume in VaD than in patients without overt dementia [143, 241, 242, 509].

Location of cerebrovascular lesions

The location of CVLs is probably more important than the volume of tissue destruction. Multiple brain regions have been implicated in VaD. Infarction in the left hemisphere and bilateral necroses with more involvement of the dominant hemisphere increase the risk of dementia after stroke [115, 134, 298]. Vascular lesions in the angular gyrus of the dominant hemisphere showed clinical similarities with AD [37, 99]. Cognitive impairment after stroke was more frequently associated with lesions in the left ACA and PCA territories [298, 475], and after left or bilateral PCA occlusion [99]. Bilateral (paramedian) thalamic infarction (Fig. 3) is often associated with memory deficit and "subcortical dementia" [78, 103, 468], as are lacunar infarcts in basal ganglia, especially in the head of the caudate [45, 79] and in the inferior genu of the anterior capsule, interrupting corticothalamic and thalamocortical pathways [474, 476]. However, whether selective lesions of the thalamus constitute a distinct dementia entity remains uncertain [336]. In patients with VaD, infarcts in hippocampus have been observed in 48%, in temporal lobe in 91% and in basal ganglia in 83%

[374], and both hippocampal infarcts and sclerosis, either alone or in combination with other vascular lesions, have been related to dementia [122, 311]. Although the entorhinal cortex and hippocampus are less affected by subcortical CVLs than by AD [125], VaD resulting from microvascular pathology showed significant hippocampal neuronal loss [276] related to impaired microcirculation due to decreased microvessel diameters [52], and hippocampal atrophy may increase the development of PSD [93].

Number of CVLs

Only few studies addressed the important problem of the number of lesions in VaD and whether severe large infarcts are more likely to cause dementia than multiple small lesions. Erkinjuntti et al. [134] found that the mean number of infarcts in VaD was 5.8, compared with 0.2 in mixed AD plus VaD, whereas others reported a mean number of 6.7 CVLs in patients with dementia compared with 3.2 in those without cognitive impairment [115]. This significance reached statistical significance in the ACA and MCA territory. Although infarct location, size and numbers are important, other factors, such as age, systemic disease, other brain lesions, the degree of aging changes, the extent of WMLs, medial temporal lobe atrophy and level of education, etc. are involved in determining intellectual decline [394].

Importance of small vascular lesions

Comparing the neuropathologic findings in elderly subjects without considerable Alzheimer pathology and nondemented controls, Esiri et al. [143] saw correlations of microvascular brain damage with dementia. Severe lacunar state, microinfarcts and CAA had a greater prevalence in the dementia group which had less frequent macroscopic infarcts than the nondemented. There was a nonsignificant trend for the ratio

of infarcted versus noninfarcted tissue in one cerebral hemisphere to be higher in the dementia group. Without differences in severity of extracerebral atheroma, the dementia group more often revealed arteriosclerosis and hypertensive microangiopathy. Examination of 19 different regions from 52 human brains showed that the expansion of CAA and arteriosclerosis/lipohyalinosis of small cerebral vessels was correlated with an increase of dementia, with amyloid β phases and neurofibrillary stages, suggesting that widespread small vessel changes are an important component of AD [480]. There was a correlation of dementia with widespread small ischemic lesions throughout the CNS, lacunes, microinfarcts and hippocampal injury being much more frequent than cystic infarcts greater than 1 cm in diameter [509]. Many brains showed more than one type of CVLs, most associated with severe atherosclerosis and arteriosclerosis. However, in two cognitively normal controls, similar multiple CVLs were seen. These data indicating that lacunes and microinfarcts are the most common neuropathologic features of VaD were confirmed in a study of 130 elderly subjects (age 80–92 years) [248]. Among demented subjects, 29% had large old infarcts, 57% multiple subcortical lacunes, 9.5% cortical and subcortical microinfarcts and 4.5% hippocampal sclerosis. Of the patients with MCI, 65% had cystic infarcts, 30% lacunar and 5% microinfarcts, while of the cognitively normal age-matched controls, 2/3 had cystic infarcts, 30% multiple subcortical lacunes with preserved thalamus and 1 multiple old microinfarcts (Table 8).

The impact of small CVLs has been examined in several autopsy series with vascular pathology confined to microinfarcts [273] and lacunes [184]. Among 45 patients (age 62–100 years, 13 with no dementia), there was a strong association between the extent of cerebral microinfarcts and cognitive findings. In the second study including 72 patients (mean age 83.4 years) with lacunes, deep white matter and periventricular demyelination contributed equally to cognitive dysfunction,

Table 8 Types of brain injury in ischemic–vascular encephalopathy

Category	MMSE (mean)	N patients (female/male)	Mean age (years)	Cystic infarcts (mean age)	Lacunes (mean age)	Microinfarcts (mean age)	Hippocampal sclerosis
Dementia 10 ± 4	0–20, mean 18.7	91 (37/54)	81.3	27 (80.3)	52 (80.5)[a]	8 (82.1)[b]	4 (84.5)[c]
Cognitively impaired	Approx. 20	19 (7/12)	79.6	6 (86.0)[d]	11 (77.0)	2 (76.5)	–
Cognitively normal	>20	20 (11/9)	83.0	13 (79.4)	6 (81.6)	1 (88.0)	–
Total		130 (55/75)		46	69	11	4

[a] Two cases associated with hippocampal sclerosis, one with subcortical microinfarcts

[b] One combined with multiple subcortical lacunes, one with cystic infarcts in left PCA area

[c] Two combined with lacunes in striatum and thalamus

[d] One with incidental Lewy body disease

and, contrary to earlier neuroimaging studies, the relationship between CDR scores and deep and periventricular WMLs was no longer significant after controlling for lacunes in a multivariant model [184]. In both univariant and multivariant models, thalamic and basal ganglia, but not deep white matter lacunes, significantly predicted cognitive impairment [180].

A similar preponderance of cortical and subcortical microinfarcts was observed in a cohort of longitudinally followed autopsy cases of AD, 36 with concomitant small cerebral infarcts with volumes less than 10 ml, which had no impact on cognitive decline [286]. These data, which were at variance to others suggesting a contribution to cognitive decline of CBLs with volumes of even less than 1 ml [92], were confirmed by studies in a larger sample showing that in AD with minor CVLs, the majority of lesions were lacunes in basal ganglia and/or white matter, and multiple microinfarcts [240, 248].

Evaluation of the type and topographic pattern of CVLs in a large autopsy series of demented subjects, in cases with "pure" VaD, i.e., those without essential concomitant Alzheimer-type or other pathologies, showed a significantly higher frequency of small subcortical lesions (lacunes and microinfarcts representing 71%) than of large infarcts involving one or both cerebral hemispheres (29%) (Table 9). This pattern differed considerably from that in cases of mixed dementia (combination of definite AD with vascular encephalopathy), where 64% revealed large, often lobar infarcts or multiple cortical and subcortical infarcts larger than 10 ml in diameter involving one or both hemispheres, whereas lacunes and small subcortical microinfarcts

were seen in only 36% (Table 10), which suggests different pathogenic mechanisms between both types of disorders [248].

These and other data indicate that subcortical lacunes and multiple disseminated infarcts are the most common morphologic features of VAD, while large cystic infarcts are less common [224, 241, 242, 245, 246, 248, 255]. Recent studies comparing CBF, cerebral metabolic rate of oxygen ($CMRO_2$) and vascular reactivity (VR) in VaD showed significant reduction as compared to AD, mainly in frontal lobes, suggesting that patchy reduction of CBF and $CMRO_2$ seem to be distinct features of VaD [356]. The vicious circle of factors causing VaD is summarized in Figs. 6 and 7.

Hemorrhagic dementia

Primary intracerebral hemorrhages are uncommon causes of dementia. Most occur in basal ganglia and thalamus, although a few are located in cerebral cortex and white matter. These hemorrhages may vary in size. Massive basal ganglia bleeds with rupture into the ventricles or brainstem compression are often fatal. Multiple small or slit-like hemorrhages in cortex and white mater may lead to cognitive impairment [311, 332]. In addition to hypertension and atherosclerosis, the majority of dementing disorders related to cerebral hemorrhages and/or hemorrhagic infarcts occur in sporadic and familial conditions associated with CAA [411–413], and other hereditary forms of VaD [257].

Table 9 Types and location of cerebrovascular lesions in *vascular dementia* (total 131)

1. Multiple infarcts (38)	
ACM bilateral	5
ACM left/right	6/2
ACM bilat. + ACPS/ACPD	2/1
ACMS + ACPS	2
ACMD + ACPD	1
ACP bilateral	2
ACP left/right	3/1
ACAS + ACMS	1
Multiple bilateral	10
Multiple left hem.	2
2. SAE (subcortical) (72)	
Basal ganglia	41
Basal ganglia + white matter	24
Basal ganglia + thalamus	7
3. SID/strategic infarcts (21)	
Thalamus bilateral	9
Thalamus left	2
Thalamus + hippocampus	10

Table 10 Types and location of cerebrovascular lesions in *mixed dementia* (*n* = 64; personal series)

1. AD + multiple infarcts (41)	
ACM bilateral	5
ACM left	8
ACM right	3
ACM + ACA bilat	1
ACM + ACP left	2
ACM + ACP right	1
ACM + ACP left/right	3/3
ACM bilat. + ACPD	1
ACP bilateral	1
Multiple cortical and subcortical bilateral	9
Multiple left hemisphere	4
2. AD + SAE (subcortical) (19)	
Lacunes basal ganglia	8
Lacunes + white matter	6
Lacunes + thalamus	5
3. AD + SID/strategic infarcts (4)	
Thalamus bilateral	2
Thalamus + hippocampus	2
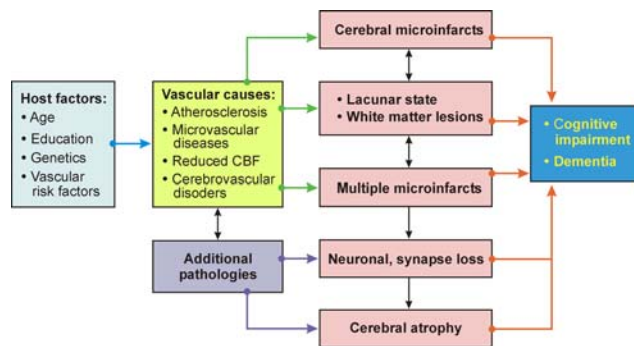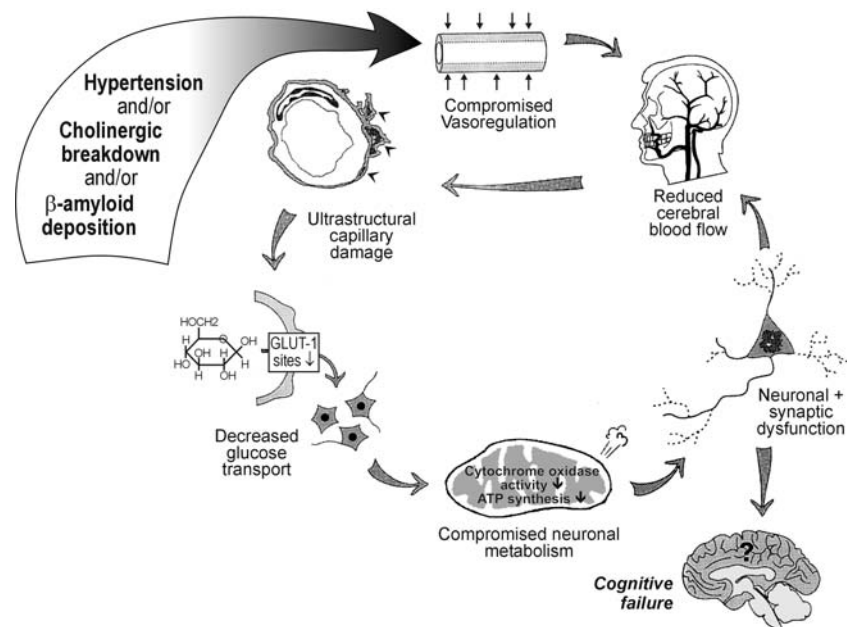
Fig. 7 Schematic interplay of pathogenic factors causing vascular cognitive impairment/dementia

Sporadic cerebral amyloid angiopathy

CAA is defined as deposition of amyloid β peptide (Aβ) in the walls of meningeal and intracortical (parenchymal) arteries, arterioles, capillaries and rarely veins, with thickening of their walls and degeneration of smooth muscle cells (SMC), sometimes with additional spread into the surrounding neuropil or depositions in the glia limitans or capillary wall, referred to as capillary CAA (capCAA) [20]. The origin of Aβ in blood vessel walls is poorly understood, and several mechanisms have been proposed: (1) systemic hypothesis suggesting that Aβ, at least partially, originates from circulation [410–412]; (2) vascular hypothesis suggesting production of Aβ by SMCs within the vessel walls and/or pericytes [410, 532]; (3) drainage hypothesis,

suggesting that Aβ produced by neurons is transported in the course of perivascular drainage, is strongly supported by transgenic animal models [20, 215, 523, 524]; (4) other pathogenetic mechanisms (see [413]). Although hereditary forms of CAA caused by mutations of different genesis are known, CAA is most commonly sporadic. Its incidence increases with age to almost 100% after 80 years, and ranges from 70 to 97.6% in AD [20]. Infiltration of vessel layers by Aβ and loss of SMCs, fibrinoid necrosis and formation of microaneurysms are the mechanisms by which CAA progresses and becomes symptomatic [411–413, 510]; two types of sporadic CAA have been described [477].

Many different approaches have been used to evaluate the severity of CAA (see [20]). In routine neuropathology two grading systems are commonly used. Olichney et al. [371] proposed the scale: 0—no Aβ-positive vessels; 1—scattered Aβ positivity in either leptomeningeal or intracortical vessels; 2—strong, circumferential Aβ positivity in either some meningeal or intracortical vessels; 3—widespread, strong, circumferential Aβ deposition in both; 4—same as 3 with additional dyshoric changes. This system has a rather quantitative approach, whereas Vonsattel et al. [512] graded CAA with respect to the severity of pathologic changes in a given blood vessel: mild—Aβ restricted to the tunica media without significant destruction of SMCs; moderate—tunica media replaced by amyloid and is thicker than normal; severe—extensive amyloid deposition with focal wall fragmentation or double barreling of the vessel wall, microaneurysm formation, fibrinoid necrosis and leakage of blood through the vessel wall. Despite the practical value of these systems,

they have some limitations. The first links meningeal and intracortical involvement, and does not allow scoring cases with strong positivity in parenchymal vessels but without involvement of meningeal vessels, the other does not distinguish between meningeal and intracortical involvement. Another system distinguishes between meningeal and parenchymal involvement and also allows screening CAA in different regions. Meningeal and intracortical vessels are scored separately: 0—no Aβ positive vessels; 1—mild (scattered positivity in a few vessels); 2—moderate (scattered positivity in many vessels or strong positivity in a few ones); 3—severe (strong positivity in many vessels), 4—severe with dysoric changes in intracortical vessels. For each region, both the meningeal and intracortical score is assessed separately, and the overall severity of CAA is calculated as mean values of all scores [20, 21]. A similar protocol has been suggested recently by an international working group (Table 11). To date, however, no validated and generally accepted neuropathologic criteria for rating CAA are available, and "this lack makes it difficult to compare results across different populations and studies, and clearly outlines an obstacle to be addressed by the investigators in this field" [190].

CAA, now recognized as a major cause of nonhypertensive, nonatherosclerotic CVLs including lobar or multiple cortical hemorrhages and multiple infarcts in the elderly [20, 230, 232, 508], has a pathogenic role in dementia and can be associated with vasculitic process, usually a granulomatous, giant cell arteritis [411–413, 510]. CAA-related intracerebral hemorrhages are seen in 5–20% of all spontaneous (nontraumatic) bleeds in elderly subjects [243, 512]. Both acute and recurrent CAA-related cerebral hemorrhages are mainly located in the frontoparietal (35%), parietal (11–26%), temporal and occipital regions (5–18%), in basal ganglia (5–10%), with multiple bleeds in about 10%, and multiple simultaneous hemorrhages may occur [217, 413]. Microbleeds in AD, detectable in vivo by MRI [71]

may be associated with CAA, but not with hypertension or CVD [358]. The co-localization of hem, a marker of cerebral bleeding, and amyloid as a marker of plaques, has suggested that senile plaques are sites of microhemorrhages, both lesions being more frequent in demented than in non-demented subjects [98]. CAA is also associated with ischemic infarctions, the frequency of which increases with its severity, and the combination of CAA and hypertension is highly associated with cerebral infarcts, suggesting an additive injury to blood vessels [72, 372, 373].

CAA may also be a cause of WMLs [469]. The severity of WMLs is significantly correlated with fibrohyalinosis of deep vessels, but neither with the age at onset nor the scores of CAA, suggesting that although CAA is an independent risk factor for WMLs in AD, its role is limited in comparison to that of fibrohyalinosis of white matter microvessels, which may or may not be associated with CAA, thus indicating the pathogenetic heterogeneity of WMLs [485]. There is progressive increase in WMLs in subjects with CAA, and the association of WMLs with incident lobar hemorrhages suggests that the white matter damage may reflect a progressive microangiopathy due to CAA [82]. In any case, coexistent pathology is a much more common cause of dementia in sporadic CAA, which is explained by the closely related pathobiologies of both conditions [141]. Several studies suggested severe CAA to be an independent risk for cognitive decline [154, 190, 361, 543, 551], whereas others did not confirm a higher prevalence of CAA in demented subjects [391]. Advanced CAA causes clinically important vascular dysfunction [190]. Since it frequently occurs in subjects with cortical infarcts but only mild Alzheimer pathology, it has been suggested that CAA represents an underestimated variant of VaD [199]. Microinfarcts in cerebral cortex associated with severe CAA could be a primary pathologic substrate of VaD [200]. Studies in a 95+ cohort, showing a strong association between CAA and *APOE* ε4 as well as dementia,

Table 11 Suggested protocol for the assessment of cerebral amyloid angiopathy and concomitant vasculopathy

Score	Parenchymal CAA	Meningeal CAA	Capillary CAA	Vasculopathic score	Examined region	Vasculopathy description
0	Absent	Absent	Absent	Absent	Frontal	FN, hemorrhage
1	Scant deposition	Scant deposition	Present	Occasional vessel	Temporal	FN
2	Some circumferential amyloid	Some circumferential amyloid		Many vessels	Parietal	FN
3	Widespread circumferential amyloid	Widespread circumferential amyloid			Occipital	FN
					Median	

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suggest that the contribution of CAA to dementia is largely dependent of *APOE* ε4 [472], and long term studies showed that plasma Aβ-40 concentration is independently associated with WMLs in subjects with AD, mild cognitive impairment (MCI) or CAA [192], but the relations between these factors and the potential contribution of vascular dysfunction and CAA in cognitive decline remain debatable [288].

Although the role of CAA as an independent, primary cause of dementia is unclear, it is widely assumed that it has an aggravating effect on other pathologies and may lower the threshold for overt dementia, especially in AD, where subjects with only medium neuritic pathology, e.g., Braak stages III and IV, but considerable CAA were clinically demented [249, 391].

Aβ-related hereditary CAAs (hereditary cerebral hemorrhage/HCH)

Most of these disorders that are associated with dementia combine CAA with multiple cerebral hemorrhages or infarcts, and are caused by mutations of various genes.

Familial CAA can be caused by deposition of Aβ due to mutations of the APP gene located on chromosome 20. They include the Flemish (A692G), Dutch (E693Q causing HCH-WA-d), Arctic (E693G), Italian (E693K) and Iowa (D694N) mutations. The Dutch form (HCHA-D), the Islandic type (HCHWA-I), the Flemish, Italian and Arctic mutations, all inherited as autosomal traits, show dementia and leukodystrophy with multiple recurrent hemorrhages or hemorrhagic infarcts mainly in the subcortical white matter, completed by diffuse plaques [187, 362, 521]. Neurofibrillary pathology is minimal in HCHWAD, dementia being largely independent from tangles and plaques but attributable to multiple CAA-related CVLs [360]. These hereditary forms are rare and include about a dozen pedigrees with 150 post-mortem cases [393]. APP locus duplication explained <2% of familial, nonautosomal dominant early onset AD with severe CAA [453].

Other mutated proteins such as variant transthyretin (ATTS), variant gelsolin (Agel), variant cystatin (Acys), amyloid-Bri (Abri), amyloid-Dan (Adan) or disease-associated prion protein (PrPsc) are also implicated in CNS amyloidosis with CAA [411–413]. In some familial forms, such as in familial British dementia (FBD) and familial Danish dementia (FDD), CAA is much more widespread and affects most CNS areas [218, 265, 270].

CAA due to deposition of ATTR (amyloid transthyrenin), resulting from more than 60 mutations of the TTR gene, located on chromosome 18, shows characteristic morphologic phenotypes with prominent amyloid deposition and CAA in leptomeninges, cerebral parenchyma and vitreous vessels [43, 49].

Gelsolin-related amyloidosis of the Finish type, due to mutations (D187N amino acid mutation and others) of the gelsolin gene on chromosome 9, in addition to MCI and other lesions show widespread CAA, with deposition of gelsolin-related amyloid in almost all organs and diffuse myelin loss in centrum semiovale [202, 410–412].

Familial British dementia (FBD) associated with point mutation in the BRI gene located on chromosome 13, dementia, ataxia and spastic tetraparesis, in addition to NFTs and neuroils threads in hippocampus shows widespread CAA and Binswanger type WMLs but only rare cerebral hemorrhages [411, 412, 507].

Familial Danish dementia (FDD), associated with duplication between codons 265 and 266 on the BR12 gene, with cataracts, deafness, ataxia and dementia shows CAA in almost all CNS regions and hippocampal and perivascular amyloid plaques and tangles, mimicking pathologic aspects of AD [411, 412].

Other types of hereditary VaD

A number of monogenic diseases is associated with hereditary forms of VAD. They include hereditary MID, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADA-SIL), cerebral autosomal recessive arteriopathy with subcortital infarcts and leukoencephalopathy (CARA-SIL, Maeda syndrome), cerebroretinal vasculopathy, hereditary endotheliopathy with retinopathy, nephropathy and stroke and hereditary vascular retinopathy (CRV and HERNS) and MELAS syndrome.

Hereditary MID in a Swedish family with onset between 29 and 38 years of age at autopsy revealed multiple cystic infarcts in gray and white mater and pons with cerebral cortical atrophy resulting from occlusion of small arteries and arterioles [458], but its genetics are unknown [256].

CADASIL with clinical onset in midadult life and a history of small strokes, migraine, progressive dementia and pseudobulbar palsy is caused by a defective *NOTCH*3 gene on chromosome 19q12. Neuropathology shows multiple small, deep infarcts, diffuse leukoencephalopathy [546] and widespread vasculopathy causing fibrotic thickening of the arteriolar walls with or without obliteration of small arteries (see [256, 257, 330]). The vascular lesions consisting of granular osmiophilic material (GOM) in SMCs are also seen (with electron microscopy) in other organs (vessels in spleen,

kidney, muscle, skin) allowing diagnosis by skin biopsies [316] or by a histochemical method to demonstrate the extracellular domain of *NOTCH*3 [254]. In CADASIL with white matter infarcts, cholinergic denervation was seen in parietal, frontal and occipital regions, and the entorhinal and temporal neocortex usually affected in AD were preserved [327], whereas a recent study reported prominent cholinergic deficits in the frontal and temporal cortex [259]. Cortical neuronal apoptosis involved in cortical atrophy appears related to the burden of subcortical ischemic lesions [511]. Transgenic animal models of CADASIL are available (see [257]).

CARASIL, another nonhypertensive, nonamyloid small vessel arteriopathy with similar lacunar infarcts as in CADASIL, but with different vascular pathology, recessive inheritance, pseudobulbar palsy and orthopedic problems, pathologically shows severe changes of small penetrating arteries of white matter and basal ganglia, less severe in brainstem and meninges. So far no genetic defect has been reported.

Two other very rare hereditary small vessel diseases are CRV and HERNS, showing progressive visual impairment, headache and strokes with neurologic deficits and cognitive decline to dementia, have been mapped to locus 3p21 [375]. Brain biopsies showed fibrosis of small cerebral arteries with fibrous thrombi but no vasculitis and infarction and gliosis of the surrounding brain (see [257].

A totally different disorder related to mitochondrial encephalopathies is MELAS syndrome (mitochondrial myopathy encephalopathy, lactic acidosis and stroke-like episodes), caused by a A-to-G mutation at nucleotide 3243 in the mitochondrial tRNA LEU(UUR) gene in approximately 80% of patients [400], which is clinically characterized by stroke-like episodes, seizures and dementia with onset before 40 years of age. Pathology shows generalized mitochondrial microangiopathy without paracrystalline aggregates [348]. The diffuse atrophic brain shows multifocal and asymmetric, occasionally "punched-out" or cystic infarct-like lesions in cortex and subcortical white matter. Cerebral lesions are distributed in pseudolaminar, pancortical and cortico-subcortical patterns; deep cortex with increased vascularity, spongy changes in white matter and rare small infarcts in basal ganglia. The meningeal and cortical arteries and arterioles are patent, whereas myocytes and small artery endothelium show degenerative changes with increased numbers of mitochondria. These data indicate that mitochondrial vasculopathy is responsible for the CVLs in MELAS [369], although others questioned the hypothesis that defective mitochondria are responsible for the infarct-like lesions [305].

Pathophysiology of VaD

VAD/VCI is thought to be caused by focal and multifocal vascular and/or ischemic lesions involving various, often strategically/functionally important brain areas with deafferentation of frontal and limbic cortical structures and interruption of thalamo-cortical, striato-cortical, cortico-cortical as well as ascending pathways caused by lesions in basal ganglia, thalamus, white matter and subfrontal areas. VaD may present with memory loss resulting from interruption by ischemic injury of segments of the Papez circuit comprising the hippocampus, fornix, mamillary body, mamillothalamic tract (fasciculus of Vicq d'Azyr), anterior thalamus and cingulate gyrus [127]. Memory loss also occurs with ischemic damage to the medio-basal forebrain, in particular cholinergic neurons in septal and basal nuclei and their projections, in the vicinity of septal gray and nucleus basalis Meynert and destruction of cholinergic loops in the deep white matter [428]. These lesions may sometimes be confused clinically with AD. The pattern of cognitive impairment is consistent with models of disturbed cortical and subcortical neuronal circuits [275]. Complex interactions between subcortical lesions and radiologically detected changes in cortex and hippocampus in producing cognitive decline have been shown [152], while others suggested significant correlations to cortical lesions and frontal atrophy [70, 213]. WMLs impair frontal functions regardless of their location [492], are associated with neocortical more than entorhinal and hippocampal atrophy [126], that is more severe in AD than in VaD [548], and increase the risk of dementia, particularly in patients with lacunar infarcts [409, 525]. Strategically situated small lesions that may represent a mixture of large and small vessel disease rather than an isolated entity may destruct thalamo-cortical, striatocortical and prefrontal-basal ganglia pathways, involving cognition, memory and behavior [42, 76, 103, 248, 290, 301, 332, 425, 468, 473, 550]. The suggestion that cognitive impairment associated with lacunes in basal gray and white matter may result from disruption of subcortical frontal circuits [100, 407] has been confirmed by recent studies on the impact of subcortical lacunes and microinfarcts on cognitive dysfunction [180, 184, 273] and by experimental models of ischemia [359].

The above findings indicate that damage in the subcortical gray matter may directly influence cognitive performance, whereas the frequent development of lacunes within the deep white matter in brain aging appears not sufficient to induce dementia. Frontal impairment in VaD is responsible for greater executive dysfunction in comparison with AD patients who show

more severe impairment of attentional shifting and working memory [73].

Neurochemical studies showed that VaD is associated with abnormalities in key neurotransmitter systems, in particular the basal forebrain cholinergic system, while earlier studies showed a significant reduction of substance P-like immunoreactivity, choline acetyltransferase (ChAT) activity and muscarinic receptors in the hippocampus of MID and AD/MID brains [431], but preserved nicotinic receptors in VaD [315]. There is emerging evidence that this system is affected in SVaD related to diffuse WMLs involving the central axonal radiation fields for this projection pathway [446, 467], such lesions may cause widespread disconnection of cholinergic projections to the center [467]. Since cholinergic mechanisms play a role in the regulation of regional blood flow in the brain [203, 433, 434], dysfunction of the cholinergic system caused by extensive WMLs and other vascular lesions may cause decreased CBF and hypoperfusion that are critical in the pathogenesis of VaD [425], and may cause cognitive impairment. Preclinical [263, 483] and clinical evidence [315, 466] suggested that cholinergic deficit may be associated with VaD [311, 428], and evidence of cholinergic changes from animal models of CVD/VaD have been reviewed recently (see [429]). AD and mixed dementia (AD + VaD) usually have greater deficits of ChAT activity in temporal cortex than age-matched controls and patients with "pure" VaD [388], but a recent study showed severe cholinergic deficits in frontal and temporal cortices in CADASIL cases [259]. There is paucity of data related to other specific neurotransmitter deficits in VaD. The involvement of the supraoptic and tuberomamillary nuclei [231] and the corresponding reduction in vasopressin and histamine may have clinical correlates (e.g., incontinence in VaD). An important neurotransmitter involved is the striatonigral dopaminergic system giving rise to vascular pseudoparkinsonism [449].

Conclusions and future aspects

Recent autopsy data confirm that (1) VaD is a nonfrequent entity, in the course of which multiple ischemia and/or vascular brain lesions of variable etiology, pathogenesis, extent and location result in progressive cognitive and memory impairment (Fig. 7). While most of the currently used clinical guidelines for diagnosis of VCI/VaD show variable sensitivity and specificity, and recent Mayo Clinic criteria [268] await further validation; at present, no generally accepted and validated

neuropathologic criteria are available. Further criteria should be more evidence-based, but how the VCD/VaD debate will evolve, remains unclear [266]. Cognitive impairment appears to correlate with widespread or even focally limited vascular lesions throughout the brain. "Pure" VaD that should only be diagnosed in the absence of Alzheimer-type lesions beyond age-related levels and other concomitant pathologies is rather rare, but ischemic/vascular brain lesions even of smaller volume, particularly in functionally important ("strategic") areas and neuronal loops, may aggravate the neuropsychologic deficit in aging brain and AD. (2) The concept that VaD is determined primarily by the volume of infarcted brain is oversimplistic and was not confirmed by a majority of neuroimaging and autopsy studies. (3) Although disputed as an isolated nosologic entity, VaD/VCI is correlated with multiple vascular/ischemic brain lesions, due to a multitude of causes including large and small vessel disease, cardiovascular and systemic disorders, that need to be determined more precisely. (4) Sporadic and genetic/familial CAA and other hereditary vascular disorders related to a multitude of gene defects frequently cause cerebral hemorrhages and other CVLs which may result in dementia. (5) MD resulting from combined AD and VaD (or other pathologies) is a diagnostic challenge for which neither validated clinical criteria, generally accepted and validated neuropathologic guidelines nor exact epidemiologic data are available. (6) The histologic pattern of vascular brain lesions in "pure" VaD, mainly related to multiple small CVLs in subcortical brain regions or multiple cortico-subcortical microinfarcts, differs considerably from that in MD that more often shows larger hemispheral infarcts, suggesting different pathogenic mechanisms. (7) Hippocampal sclerosis, often accompanied with AD lesions or multiple other CVLs, is a not infrequent form of VaD in very old subjects. (8) Neuropathologic examination of brains in which vascular pathologies are identified necessitates careful documentation of the nature, severity, anatomical extent and location of the vascular lesions.

Additional quantitative studies in larger series including not only the assessment of Alzheimer-type lesions but also estimates of numbers of both synapses and microvascular lesions as well as characterization of microvessel abnormalities are needed to give further insights into the structural substrates of cognitive impairment in the elderly and to develop standardized neuropathologic criteria for the diagnosis of both vascular and mixed dementia. Future development of homogenous and harmonized neuropathological definitions and procedures in classifying vascular lesions

and of methods to more accurately characterize the independent severity of vascular and neurodegenerative brain lesions remain an important priority for the future. Accurate diagnosis of both VCI/VaD and MD and further exploration of the structural substrates of cognitive impairment in order to get better insights into the impact of CVLs and their interrelationship to Alzheimer and other pathologies on cognitive function are among the most important challenges of modern neuroscience.

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