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Editors

Stroke Revisited:
Vascular Cognitive Impairment

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ISSN 2522-5588 ISSN 2522-5596 (electronic)
Stroke Revisited
ISBN 978-981-10-1432-1 ISBN 978-981-10-1433-8 (eBook)
https://doi.org/10.1007/978-981-10-1433-8

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

Dementia is one of the biggest challenges facing the aging society. However, clinical trials related to the development of therapeutic agents for Alzheimer's disease have failed in succession and have frustrated not only researchers but also major pharmaceutical companies and patient groups. Lessons from the failure of Alzheimer's drug trials have redirected attention to other therapeutic targets besides the amyloid cascade. One of these targets is "vascular contributions to cognitive impairment and dementia."

The Framingham heart study reported a reduction in the incidence of dementia at each study epoch, mainly due to a reduction in the incidence of vascular dementia rather than Alzheimer's disease. In addition, the population attributable risk of common modifiable risk factors was reported to be comparable to that caused by APOE genotypes, which is the most well-known risk factor for Alzheimer's disease.

We can reach a deeper understanding of the functional localization of human cognition by understanding various vascular disorders accompanied by focal lesions, just as we have accumulated knowledge of localization of brain functions through discovery of "lesion-symptom" mapping in the late nineteenth to early twentieth century.

Thus, vascular cognitive impairment has attracted attention as a disease that can be prevented through comprehensive cardiovascular risk factor control, and as a disease model that can explain the pathogenesis of cognitive dysfunction through interaction between vascular lesions and neurodegenerative changes.

This book presents the recent developments as clearly as possible for beginners in this field. It also looks at the changes in the diagnostic criteria that have been made recently and their conceptual background. This book discusses the clinical characteristics of post-stroke dementia and subcortical vascular dementia, two major axes of vascular cognitive impairment. It also deals with gait disturbances and behavioral and psychological symptoms of dementia that are relatively unrecognized. The interactions of neurodegenerative changes and vascular factors are now being investigated due to recent advances in imaging technology, and the results of recent studies are summarized. In addition, recent updates involving brain imaging studies, including the STRIVE protocol for unified research, are reviewed. Finally, the results of previous studies on therapeutic agents are summarized.

Vascular cognitive impairment is an area where its pathophysiology is not clearly defined yet. We hope that this book will give you a chance to keep up with the accumulated knowledge and to learn the latest concepts. We would like to thank all the authors for their willingness to contribute to this book.

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1 Definition and Concept of Vascular Cognitive Impairment

Fernando D. Testai and Philip B. Gorelick

1.1 Epidemiology and Global Impact of Dementia

Dementias constitute one of the largest public health challenges. A systematic review including 147 epidemiological studies showed that approximately 35.6 million people worldwide carried the diagnosis of dementia in 2010. The highest prevalence was noted in Western Europe (7.0 million) followed by East Asia (5.5 million), South Asia (4.5 million), and North America (4.4 million). When organized by country, the largest prevalence of dementia was in China (5.4 million) followed by the United States (3.9 million) and India (3.7 million). The number of people with dementia is projected to double every 20 years resulting in a total number of cases of 65.7 million in 2030 and 115.4 million in 2050 [1]. Current trends indicate that the increase in prevalence will be particularly steeper in low- and middle-income countries (LMIC). It was determined that 58% of the dementia cases in 2010 occurred in LMIC; however, this proportion is expected to increase to 63% in 2030 and 68% in 2050 [2].

Every year, 7.7 million new cases of dementia are diagnosed worldwide which results in a new case every 4 s. The incidence of dementia doubles every 5.9 years of age and increases exponentially from 3.1 per 1000 person-years for subjects aged 60–64 to 175 person-years for older than 95 years [1]. Interestingly, the incidence of dementia is lower in LMIC than in high-income countries. Methodological factors, exposure to environmental and acquired risk factors, and region-specific patterns of survival may account, at least in part, for the apparent lack of correlation between prevalence and incidence.

Dementias shorten life expectancy and are associated with an approximately two-and-a-half-fold increased risk of death. The mortality attributable to dementias is 10% in men and 15% in women above the age of 65 years; these estimates increase steadily with age and reach 18% for men and 23% for women 85–89 years old. Life expectancy differs among different dementia subtypes. The median survival for individuals with Alzheimer disease (AD) is 7.1 years and for vascular dementia (VaD) 3.9 years. Dementias are the leading cause of dependency and disability in both LMIC and high-income countries. The economic burden of this condition at the personal

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S.-H. Lee, J.-S. Lim (eds.), *Stroke Revisited: Vascular Cognitive Impairment*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1433-8_1

and societal levels is considerable. Worldwide, the total costs of dementia were $604 billion in 2010. This was unevenly distributed with aggregated costs of approximately $29 billion in LMIC and US$ 537 in high-income countries [1]. Projections that incorporate variables such as aging population, increasing costs of medical care, and annual inflation estimated that the global cost of dementia will continue to increase steadily in the subsequent years and likely cross the threshold $1 trillion in 2018 [2].

The annual cost of care for an individual with dementia ranges from $868 in low-income countries to $56,218 in high-income countries [2]. An elevated proportion of dementia patients become physically, mentally, financially, and legally vulnerable requiring continuous supervision and assistance of a caregiver to perform their basic (e.g., eating, bathing, etc.) and/or instrumental activities of daily living (e.g., shopping, managing personal finances, etc.). It was estimated that in 2016, more than 15 million of unpaid Americans, including friends and family members, provided approximately 18 billion hours of care to patients with dementia resulting in an estimated monetary cost of $221 billion [3]. Finally, dementias have a relentless and progressive course. The increasing disability and dependence take a toll on the resilience and productivity of family members, friends, and other unpaid caregivers. Observational studies have shown that caregivers of dementia patients have higher rates of psychologic stress, represented by anxiety and depression, and poorer health, including higher inflammatory burden, than noncaregivers [4].

1.2 Current Diagnostic Criteria and Consensus of Vascular Cognitive Impairment (NINDS-AIREN, DSM-V, AHA-ASA Statement, VasCog Statement, VICCCS)

Historically, terms such as “hardening of the arteries” and “arteriosclerotic psychosis” have been used to denote underlying vascular causes of cognitive impairment and failure of cerebral function in patients with vascular cognitive impairment (VCI) [5]. In the 1950s, Roth described arteriosclerotic psychosis in those with focal signs and symptoms of cerebral vascular disease, fluctuating or remitting course which might include emotional incontinence, preservation of insight, and epileptiform seizures [6]. Later, the criteria were refined by Mayer-Gross, Slater, and Roth to portray a condition with age of onset in the 60–70 year range, presence of hypertension, conspicuous symptoms following a stroke such as memory disturbance, restlessness, wandering at night and emotionality, somatic complaints, maintenance of creative and intellectual powers, cooling of emotions, diminished drive and initiative, but preservation of judgment and personality [7]. The term was subsequently replaced by multi-infarct dementia (MID), a categorization coined by Hachinski and colleagues referring to progressive loss of cognitive function with impairment of social skills that appeared with abrupt onset, stepwise deterioration, fluctuating course, and focal neurological signs associated with cerebral infarcts [8]. This definition led to the Hachinski Ischemic Score, a tool used to differentiate dementia associated with cerebral infarcts from neurodegenerative dementia such as AD. It was C. Miller Fisher who remarked that cognitive impairment associated with stroke was a matter of strokes large and small [5].

Over time, the terminology used to refer to cognitive impairment associated with stroke has changed. In more recent epochs, the term VaD has evolved as a broader term than MID and one that takes into account any dementia related to underlying disease of the cerebral blood vessels [9]. Thus, VaD represents a heterogeneous entity that may be classified according to the location of stroke and underlying stroke subtype or mechanism [5]. For example, superficial or deep brain infarcts responsible for cognitive impairment might emanate from large or smaller brain blood vessels and any of many underlying stroke mechanisms. VaD included not only brain infarcts but also brain hemorrhage and the consequent vascular mechanism responsible for the hemorrhage. Therefore, use of VaD to define or categorize cognitive impairment associated with stroke led

to an emphasis on an understanding of the underlying vascular mechanism underlying cognitive impairment.

Cerebral small vessel disease responsible for subcortical brain changes (e.g., white matter disease, small subcortical infarcts, and cerebral micro-hemorrhages) is considered to be the most common type of cognitive impairment associated with stroke [10]. There seems to be a common mechanistic theme underlying cognitive impairment associated with cerebral small vessel disease that includes hypoxic hypoperfusion, lacunar infarction, oxidative stress, and inflammation with disruption of the blood-brain barrier resulting in damage to deep brain myelin [10]. The neurovascular unit (NVU) comes under attack by oxidative stress and inflammation with resultant neurovascular dysfunction, brain injury, and VCI. An upstream mechanistic approach to reduce vascular risks has been advocated to identify and prevent the cascade of events in the at-risk brain stage before subcortical brain injury progresses [11].

Contemporarily, we now use terms such as VCI and vascular cognitive disorder (VCD) to refer to cognitive impairment associated with stroke. We now review diagnostic criteria for cognitive impairment associated with stroke that has evolved since the 1990s.

1.2.1 National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement in Neurosciences (NINDS-AIREN) Research Diagnostic Criteria

NINDS-AIREN diagnostic criteria for VaD included acknowledgment of the heterogeneity of vascular dementia syndromes and underlying neuropathologic subtypes, the importance of linking a temporal relationship between stroke and occurrence of dementia, clinical features, and variability of clinical course (e.g., the classic stepwise cognitive deterioration expected with stroke might not be the case, and a static, remitting, or progressive time course could occur) [12]. Specific clinical features early in the course of the disorder might include gait dysfunction, urinary incontinence, and mood or personality changes. The criteria also emphasized the value of neuroimaging, formal neuropsychological testing of multiple cognitive domains, and correlative neuropathologic-clinical-neuropsychologic evaluation to establish a proper diagnosis. NINDS-AIREN criteria were devised to classify cases according to the following probabilistic categories: possible, probable, and definite.

NINDS-AIREN VaD research diagnostic criteria may be simply broken down into the following components: (1) presence of dementia; (2) cerebral vascular disease according to neurological history, clinical exam, or brain imaging; and (3) a reasonable linkage between the temporal occurrence of stroke and dementia [12]. A diagnosis of dementia was met if there was impairment of memory, loss of cognitive abilities sufficient to cause impairment of activities of daily living (ADLs), and deficits in at least two other major cognitive domains. Whereas NINDS-AIREN criteria have been the most widely used ones in clinical trials of VaD, the inclusion of memory loss as a necessary criterion to establish a diagnosis of VaD has been a point of contention. Controversy exists as memory impairment could serve as a criterion whereby AD cases or mixed vascular and neurodegenerative cases could be present as opposed to the occurrence of pure VaD [13].

1.2.2 State of California Alzheimer Disease Diagnostic and Treatment Centers (ADDTC) Criteria for Ischemic Vascular Dementia (IVD)

ADDTC research diagnostic criteria draw a distinction between IVD and VaD [14]. The ADDTC criteria also served to emphasize a broader concept of VaD, the value of neuroimaging to help establish a diagnosis, the need for validation of the criteria, and research gaps in the field of study. Dementia was operationalized as deterioration in

cognition from a prior known level of intellectual function sufficient to result in loss of one's ability to carry out customary affairs of life independent of level of consciousness and verified by bedside mental status assessment or, preferably, formal neuropsychological testing.

Diagnostic criteria were scored according to a probabilistic scheme, whereby there was probable, possible, and definite IVD [14]. Probable IVD was characterized by the presence of dementia, evidence of one or more strokes by neurological history, examination, and/or neuroimaging, or the occurrence of a single stroke with a clear temporal association with dementia. According to this criterion, at least one brain infarct was required to be outside the cerebellum. Suggestive features to establish a diagnosis of IVD were multiple brain infarcts in brain regions known to be associated with cognitive impairment, history of transient ischemic attack (TIA), and other features [14]. There were also supportive features (e.g., abnormal gait early in the course of the disorder) and "neutral" features (e.g., slowly progressive time course). The key characteristics of possible IVD were presence of dementia and single stroke or Binswanger's disease. Definite IVD included the presence of dementia and multiple brain infarcts on neuropathologic exam with some infarcts being found outside the cerebellum [14]. ADDTC criteria included the possibility of mixed dementia if AD neuropathology was present.

1.2.3 Consensus Statement for Diagnosis of Subcortical Small Vessel Disease (SSVD)

This statement is an expert consensus piece to establish diagnostic criteria for SSVD that emphasizes a mechanistic approach [15]. SSVD was defined as subcortical gray and white matter lesions appearing as lacunar infarcts and white matter hyperintensities on MRI brain study. Neuropathologic or mechanistic linkages included lipohyalinosis and fibrinoid change for lacunar infarcts and, for example, blood-brain barrier leakage of substances toxic to myelin as a possible explanation for damage to the white matter, respectively [15]. Subtypes of SSVD were defined such as Binswanger's disease (gait and executive dysfunction, active deep tendon reflexes, apathy, and depression) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) secondary to the notch 3 gene mutation with white matter changes and lacunar infarcts. Mixed dementias were also defined. The work of this group is being used to help develop clinical trials for SSVD based on biomarker-enabled studies.

1.2.4 American Heart Association/ American Stroke Association (AHA/ASA) Diagnostic Criteria for VCI

As part of an initiative to characterize vascular contributions to cognitive impairment, AHA/ASA convened an expert panel that included addressing the definition of VCI [16]. VCI, distinct from VaD, represents a continuum of cognitive impairment associated with stroke taking into account the at-risk brain stage to slight to moderate to severe cognitive impairment or VaD. Thus, VCI not only takes into consideration the severity of cognitive impairment and the continuum of such, but it also emphasizes the importance of mechanism and prevention or delay in cognitive impairment.

Basic to the definition of VCI is a linkage between cognitive impairment and vascular disease, cognitive dysfunction according to neuropsychological test criteria, and a history of stroke or evidence of cerebral brain injury or disease associated with some form of stroke [16]. In contradistinction to the definition of VaD [12], VCI criteria do not require a diagnosis of memory loss and specify that the occurrence of white matter lesions in the elderly may be of less diagnostic value than in younger patients. In addition, dementia is specifically defined as a decline in cognitive function from a prior higher level involving two or more cognitive domains

sufficient to impair one's ability to successfully carry out ADLs when taking into account primary sensory and motor neurologic deficits associated with stroke [16]. In addition, probabilistic categories possibly and probably apply to VaD and other subtypes including vascular mild cognitive impairment (VaMCI) and unstable MCI. The latter categories are defined in the AHA/ASA publication [16]. Finally, VaMCI may be subdivided to include an amnestic form, amnestic plus other domain forms, non-amnestic single domain form, and non-amnestic multiple domain forms [16].

1.2.5 International Society of Vascular Behavioral and Cognitive Disorders Criteria (ISVBCDC)

These criteria were developed by a workgroup emanating from the Vas-Cog Society who carried out a critical reexamination of the term VaD given the background context of new criteria to define AD including biomarkers, the existence of pre-dementia phases in the continuum of cognitive impairment, and the opportunity to harmonize with Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) [17]. The workgroup elected to use the term VCD in light of knowledge of the heterogeneity of vascular disorders underlying cognitive impairment and different neuropathologies and clinical manifestations associated with stroke and cognitive impairment. Similar to VCI criteria, fundamental to the definition of VCD was the presence of cognitive impairment and the occurrence of vascular disease as the dominant or exclusive underlying cause of cognitive dysfunction [17].

Mild cognitive disorder and dementia were distinguished from one another based on the presence or absence of interference with one's ability to function independently [17]. This authoritative work provided detailed information about neuroimaging results, the role of vascular risks, probabilistic classification, psychiatric and behavioral symptoms, subtypes of VCD, and biomarkers in association with VCD, plus other information reviewed in detail elsewhere [17]. Of interest, the authors provided a definition of VCD in the absence of stroke or TIA: decline in speed of processing, complex attentional or frontal executive dysfunction, and occurrence of gait, urinary, or personality/mood change [17].

1.2.6 DSM-5 Criteria

These criteria, like others discussed in this section, link cognitive dysfunction of different severity temporally to stroke or the occurrence of decline in complex attention and fronto-executive function in the presence of stroke according to neurologic history, physical exam, or brain imaging [18]. Genetic disease causing cognitive impairment, such as the monogenetic notch 3 gene mutation disorder CADASIL, is defined by the DSM-5 criteria in relation to clinical phenotypic and genetic manifestations.

1.2.7 Vascular Impairment of Cognitive Classification Consensus Study Criteria (VICCCS)

The VICCCS criteria were crafted by a group of international experts to establish a broad consensus on the concept of cognitive impairment associated with vascular pathology and to develop standard nomenclature and abbreviations applicable to practice [19]. The VICCCS categories included poststroke dementia, mixed dementia, subcortical ischemic vascular dementia, and multi-infarct dementia. The hallmark of poststroke dementia was acute presentation and cognitive decline within 6 months after a stroke. Mixed dementia referred to persons with AD plus VCI or VCI-AD and VCI-dementia with Lewy bodies with the order of the disorder signifying the relative contribution by underlying mechanism of cognitive impairment. Subcortical ischemic vascular dementia was related to small vessel ischemic processes, whereas multi-infarct dementia was cognitive impairment related to multiple large cortical infarcts [19].

1.2.8 Evolution of Criteria to Define Vascular Cognitive Impairment

Early modern criteria for defining cognitive impairment associated with stroke such as arteriosclerotic psychosis were largely descriptive in origin [5]. As the criteria evolved, there began to be an interest in focusing on stroke subtype or mechanism, albeit a narrow focus, and differentiating neurodegenerative from vascular causes of cognitive impairment. The term MID coined and defined by Hachinski was such an example though was limited to brain infarction [8]. As the concept became further refined, the heterogeneity of cognitive impairment associated with stroke was acknowledged (use of the term VaD) [12] as was the severity of cognitive impairment, multiple potential mechanisms, mixed pathologies, and prospects for prevention (e.g., VCI, VCD) [17, 19]. A current focus of research is the identification of upstream biomarkers in the at-risk brain stage in the hopes of prevention of cognitive impairment associated with stroke. Thus, we now have hope to prevent or delay the dementias of later life [20].

1.3 The Role of Vascular Risk Factors in the Spectrum of Dementias

At the pathological level, the spectrum of VCI is represented by different processes. Microvascular white matter lesions are commonly seen in the elderly, particularly in those with cognitive impairment. These lesions may become confluent in brain imaging, a radiological finding referred to as leukoaraiosis. Lacunes are <1.5 cm infarcts that classically localize to the basal ganglia or periventricular area and are related to the occlusion of small lentriculostriatal branches [21]. Lacunar infarction is caused by lipohyalinosis, arteriolosclerosis, and/or fibrinoid necrosis. Artery-to-artery embolism, cardioembolism, and border zone cerebral infarction, as can be seen in large artery occlusive disease with hemodynamic compromise, are additional established causes of VCI. Specific characteristics of the stroke such as anterior and posterior circulation stroke, left hemispheric stroke, and multiple infarcts increase the risk of VaD. In addition, a single cerebrovascular insult in a "strategic" area, this includes the left angular gyrus, inferomesial temporal, mesial frontal, anterior and dorsomedial thalamus, left capsular genu, and caudate nuclei, may be sufficient to cause VaD [16].

More recently, several advanced brain imaging modalities have been added to our armamentarium for the study of neurocognitive impairment. Critical information, including microarchitectural parenchymal integrity, functional connectivity, and neurovascular crosstalk, can now be obtained noninvasively by diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) [22]. In addition, positron emission tomography (PET) has allowed the quantification of biochemical abnormalities, such as amyloid-beta (Aβ) and tau (τ) burden, in the preclinical state of patients with pure neurodegenerative and mixed AD-VCI dementias [23]. Interesting observations have been made with these imaging modalities. As an illustration, DTI studies done in young cohorts provided compelling evidence that demonstrate that vascular risk factor-associated microstructural parenchymal disarrangements may start as early as the third or fourth decade of life and constitute a continuum with white matter lesions that eventually lead to VCI and possibly AD [24]. These observations suggest that earlier interventions may be necessary to preserve cognition in vulnerable individuals.

1.4 Links Between Vascular Risk Factors and Neurodegeneration

AD is a progressive neurodegenerative disorder associated with histopathological findings that include neurofibrillary tangles (NFT), hyperphosphorylated tau protein (p-τ), Aβ deposition in the brain parenchyma, and cerebral amyloid angiopathy (CAA). A bulk of evidence supports the notion that VCI and AD coexist and even share pathogenic mechanisms. An autopsy study including 1050 consecutive dementia cases

showed that approximately 86% of the patients had histopathological findings consistent with AD but only 43% had "pure" AD-related pathology and 28% had mixed AD- and vascular-related findings [25]. Also, large longitudinal observational studies provided conclusive evidence linking individual vascular risk factors, including midlife hypertension, diabetes mellitus (DM), smoking, and hypercholesterolemia, with both AD and VCI (Table 1.1) [26, 31].

Table 1.1 Epidemiologic studies investigating the association of hypertension and diabetes with cognitive impairment

Study	*N* and age	Design	Assessment	Outcome[a]
Hypertension				
Honolulu Heart Program	*N* = 3,735 Average age 78 years	Longitudinal	Cognitive Abilities Screening Instrument	For every 10 mmHg increase in SBP there was an increase in risk for poor cognition of 9%
Framingham Study	*N* = 1,702 55–88 years	Longitudinal	Neuropsychological tests (attention and memory)	For every 10 mmHg increment in blood pressure, cognition declined from −0.04 to −0.07 standard score units (z)
Uppsala Study	*N* = 999 men 65–84 years of age	Population study	Mini-Mental State Examination and the Trail-Making Test	Diastolic hypertension at midlife predicts late development of cognitive decline
Atherosclerosis Risk in Communities	*N* = 10,963 Average age 50 years at baseline	Longitudinal	Delayed word recall test, a ten-word delayed free recall task, digit symbol subtest of the Wechsler Adult Intelligence Scale-Revised and first-letter word fluency test	Both hypertension and diabetes at baseline were associated with late cognitive impairment
National Heart, Lung, and Blood Institute Twin Study	*N* = 514 pairs of male twins 42–56 years at baseline	Longitudinal	Delayed free-recall performance on the California Verbal Learning Test and MRI findings	Elevated midlife blood pressures increased white matter hyperintensities and the risk for MCI
Maine-Syracuse Study	*N* = 1,563 Average age 49 years at baseline	Longitudinal	Wechsler Adult Intelligence Scale subtests	Elevations in blood pressure were associated with poorer cognitive function
Diabetes				
Israeli Ischemic Heart Disease	*N* = 1,892 Mean age 82 years	Longitudinal	Telephone screening followed by formal face-to-face interview	Rate of dementia is 17% higher in individuals with midlife DM
Swedish Twin Registry	*N* = 13,693 Age > 65 years	Registry	DSM-IV	OR dementia 1.89 (1.51–2.38) OR AD 1.66 (1.16–2.36) OR VD 2.17 (1.36–3.47)
Kungshomen Project	*N* = 1,301 Age > 75 years	Longitudinal	DSM-III-R	HR dementia 1.5 (1.0–2.1) HR AD 1.3 (0.9–2.1) HR VD 1.7 (1.0–2.8)
Columbia Aging Project	*N* = 1,262 Mean age: 75 years	Longitudinal	DSM-IV and NINCDS-ADRDA criteria	RR AD 1.6 (1.2–2.1) RR stroke-associated dementia 3.4 (1.7–6.9)
Uppsala Longitudinal Study of Adult Men	*N* = 2,322 Age > 50 years	Longitudinal	DSM-IV and NINCDS-ADRDA criteria	HR AD 1.31 (1.10–1.56) per SD of insulin response at baseline HR VaD 1.45 (1.05–2.00) for SD of glucose intolerance

(continued)

Table 1.1 (continued)

Study	*N* and age	Design	Assessment	Outcome[a]
Kaiser Permanente Medical Care Program	*N* = 8,845 Age: 40–44 year at baseline	Retrospective	International Statistical Classification-9 (ICD-9) codes for dementia, memory impairment, AD, vascular dementia, and dementia not otherwise specified	HR of dementia was 1.46 (95% CI 1.19–1.79) for DM
DESIGN Study	*N* = 3,069 Mean age: 74 years	Prospective	Modified MMSE and Digit Symbol Substitution Test	DM and poor glycemic control among those with DM are associated with worse cognitive function and greater decline
Framingham Study	*N* = 3,535 Mean age: 70 years	Longitudinal	Based on NINCDS-ADRDA criteria	RR of AD 1.15 (0.65–2.05)

AD Alzheimer disease, *DM* diabetes mellitus, *HR* hazard ratio, *NINCDS-ADRDA* National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association, *MCI* mild cognitive impairment, *MMSE* Mini-Mental State Examination, *OR* odds ratio, *RR* relative risk, *VaD* vascular dementia
[a]Unless otherwise specified, numbers represent HR, OR, or RR (95% confidence interval)

Data obtained in in vitro and in vivo models confirm that vascular risk factors not only participate in the pathogenesis of both VCI and AD but also potentiate the neurotoxic and vasculodegenerative effects of Aβ. At the histological level, neurons, astrocytes, and vascular cells—represented by endothelial cells, vascular smooth muscle cells (VSMC), and pericytes—comprise the *neurovascular unit* (NVU). Astrocytes regulate inflammation, provide synaptic support to neurons, and, along with the endothelium, are key components of the blood-brain barrier (BBB). Pericytes and VSMC, on the other hand, have contractile proteins and regulate vascular tone and tissue perfusion. This multicellular functional unit is regulated by a network of intertwined biochemical pathways that ensure cerebral blood flow meets neuronal metabolic demands. This process, called *neurovascular coupling*, results in microvascular dilation in response to neuronal and synaptic activation [27].

The function of each of the cells of the NVU is affected in different stages of AD. Aβ accelerates age-dependent pericyte loss, facilitates the development of CAA, and contributes to neurovascular uncoupling. Studies done in AD models showed that, in the presence of Aβ, VSMCs develop a hypercontractile phenotype with aberrant neurovascular coupling and decreased CBF. In the same model, Aβ induced the expression of proinflammatory cytokines and the secretion of the endogenous vasoconstrictor endothelin-1 by endothelial cells leading to a reduction in CBF [27]. Animal models of HTN have enhanced β-secretase activity which increases the production of Aβ and potentiates Aβ-mediated neurovascular dysfunction. Similarly, animal models of DM demonstrated that abnormal glucose metabolism enhances amyloid precursor protein (AAP) processing, Aβ deposition in astrocytes, and vascular inflammation. Aβ is a substrate of different proteases, including insulin-degrading enzyme; thus, hyperinsulinemia can reduce the clearance of Aβ, which might explain, at least in part, the association observed between type 2 DM and AD [26].

Endothelial cells are connected by tight and adherens junctions forming a continuous barrier (also known as BBB) that regulates the entry of nutrients to the brain and the removal of unnecessary molecules. A particular aspect of the BBB is related to its participation in the clearance of Aβ which is summarized in Fig. 1.1 [28]. Vascular risk factors can contribute to BBB dysfunction and influence the metabolism of Aβ [26]. Conversely, increased BBB permeability leading to vasogenic edema and parenchymal hypoperfusion has been observed in AD. BBB dysfunction also facilitates the extravasation of RBCs to

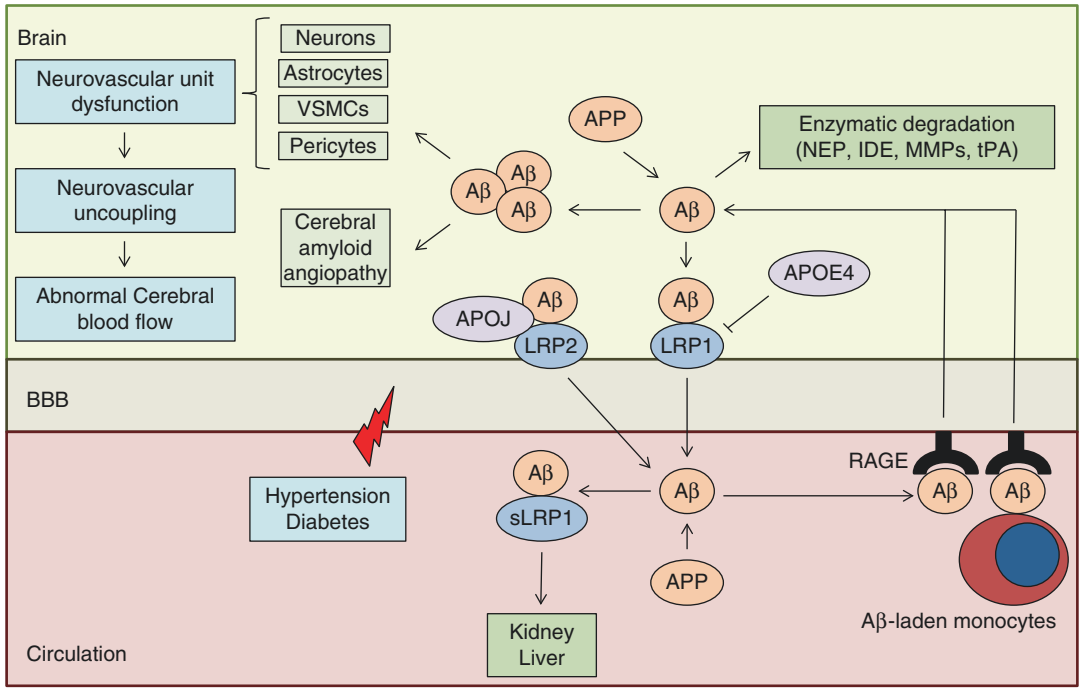

Fig. 1.1 Clearance of amyloid-beta through the blood-brain barrier. Amyloid beta (Aβ) precursor protein (APP) is metabolized to Aβ in the brain and in peripheral tissues by β-secretases and γ-secretases. Aβ in the brain is cleared across the blood-brain barrier (BBB) by the low-density lipoprotein receptor-related protein 1 (LRP1). APOE4 inhibits LRP1. Aβ bound to APOJ (also known as clusterin) is cleared from the brain by LRP2. In the brain, Aβ is degraded by different enzymes, including neprilysin (NEP), insulin-degrading enzyme (IDE), tissue plasminogen activator (tPA), and matrix metalloproteinases (MMPs). In the periphery, Aβ forms a complex with soluble LRP1 (sLRP1) which prevents its entry into the brain. Systemic Aβ is eliminated by the liver and kidneys. The receptor for advanced glycation end products (RAGE) facilitates the influx of Aβ into the brain across the BBB by binding either free Aβ or Aβ-laden monocytes. Traditional vascular risk factors, including hypertension and diabetes, cause endothelial dysfunction, vascular inflammation, and BBB dysregulation. Abnormal Aβ clearance facilitates Aβ accumulation in the brain which forms aggregates that induce cerebral amyloid angiopathy. In addition, Aβ has a toxic effect on each of the cells that form the neurovascular unit (neurons, astrocytes, vascular smooth muscle cells (VSMCs), and pericytes) that results in neurovascular uncoupling and abnormal cerebral blood flow

the parenchyma which release hemoglobin and iron leading to the formation of reactive oxygen species (ROS) which, together with thrombin, are neurotoxic and cause endothelial injury. By activating microglial cells and astrocytes, thrombin can also facilitate the development of a proinflammatory state characterized by an upregulation of NO, cytokines (TNF-a, interleukin-1b, etc.), chemokines (monocyte chemoattractant protein 1, interleukin-8, etc.), prostaglandins, matrix metalloproteinases, and leukocyte adherence proteins [27].

At the mechanistic level, the association between hypoxia and neurodegeneration is multifactorial. Hypoxia increases the levels of p-τ, downregulates neprilysin—an Aβ-degrading enzyme—and enhances the expression of β- and γ-secretases that facilitates the amyloidogenic processing of APP. In addition, both oxidative stress and APOE4, the most important genetic risk factor for AD, compromise the transport of the Aβ across the BBB and to the periphery [26, 28].

Collectively, these results suggest that Aβ has a detrimental effect on neurovascular coupling and CBF regulation. Additionally, vascular risk factors appear to have a synergistic effect on Aβ-associated vascular dysfunction. The association between

vascular risk factors and neurodegeneration has been summarized in the *two-hit hypothesis*. This postulates that environmental, genetic, and traditional vascular risk factors induce cerebrovascular damage (hit 1) which results in early BBB breakdown and resting neurovascular dysfunction. These processes lead to the accumulation of neurotoxic substances (thrombin, plasmin, ROS, etc.), neuroinflammation, and microvascular hypoperfusion. BBB dysfunction and tissue hypoxia, in addition, impair the clearance of Aβ and the amyloidogenic processing of APP leading to the accumulation of Aβ in the brain (hit 2). Increased levels of Aβ, p-τ, and other neurotoxic and vasculotoxic mediators lead to synaptic dysfunction and neuronal injury which manifest, clinically, with progressive neurocognitive decline (Fig. 1.2) [27].

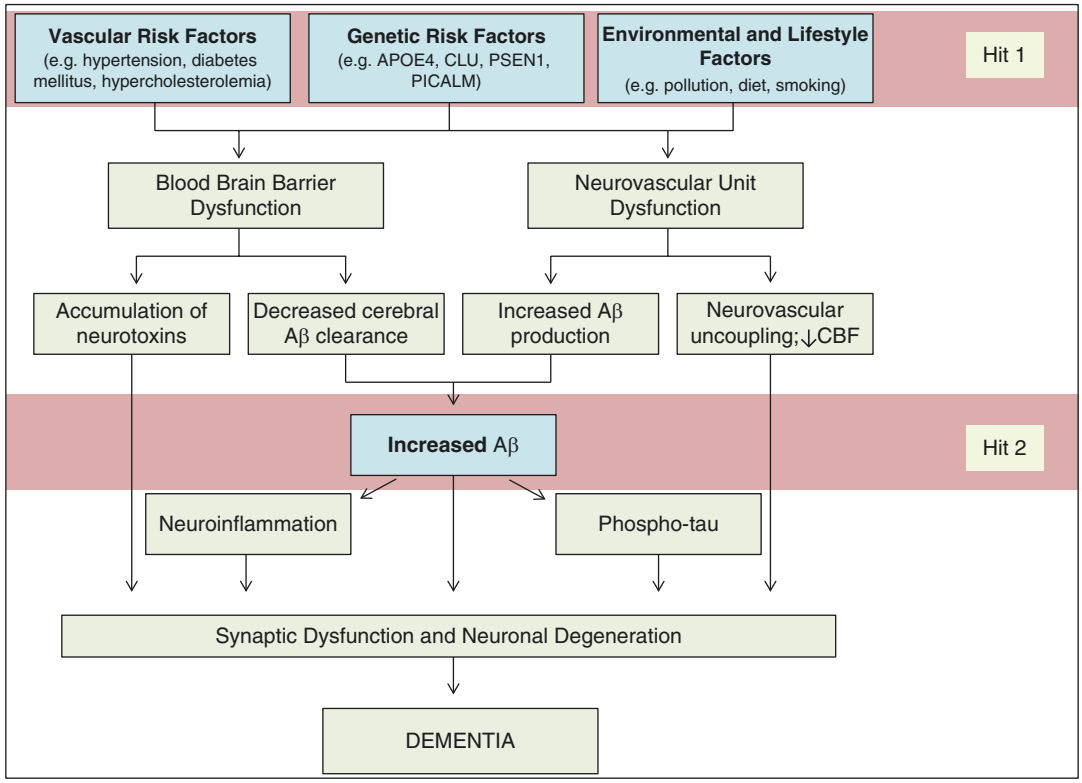

Fig. 1.2 The two-hit hypothesis. In this hypothesis, vascular, genetic, environmental, and lifestyle risk factors cause neurovascular unit (NVU) and blood-brain barrier (BBB) dysfunction in an amyloid beta (Aβ)-independent fashion (hit 1). Presenilin 1 (*PSEN1*) mutations lead to degeneration of cerebral microvessels and BBB breakdown and have been identified in autosomal dominant-AD patients. *CLU* encodes for clusterin (also known as APOJ), and *PICALM* encodes for phosphatidylinositol-binding clathrin assembly protein (PICALM). Both CLU and PICALM participate in Aβ clearance, and genetic variants of both proteins have been associated with sporadic AD. NVU dysfunction leads to neurovascular uncoupling, reduced cerebral blood flow (CBF), and oligemia which enhance the synthesis of Aβ. In addition, BBB dysfunction decreases the clearance of Aβ and facilitates the accumulation of toxins such as iron and reactive oxygen species, plasmin, and thrombin which are neurotoxic and proinflammatory. Aβ enhances neuroinflammation and has toxic effects on each of the cells that form the NVU. Aβ-dependent mechanisms of brain injury include endothelial dysfunction, pericyte and neuronal cell death, vascular smooth muscle cell hypercontractility, and astrocyte activation to a proinflammatory state (hit 2). Both Aβ-dependent and Aβ-independent mechanisms independently and/or synergistically lead to tau phosphorylation, enhance inflammation, and result in synaptic dysfunction and neuronal degeneration which manifest, clinically, with neurocognitive decline

1.5 Translational Aspects

The solid evidence linking traditional vascular risk factors to neurocognitive impairment suggests that a substantial number of the cases of dementia can be prevented. However, the randomized trials that evaluated the effect of vascular risk factor modification on cognitive decline have shown conflicting results. In the Systolic Hypertension in Europe (SYST-EUR) study, a reduction in systolic blood pressure (SBP) by at least 20 mmHg decreased the incidence of dementia at 2 years by almost 55% [29]. In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), the use of perindopril with or without indapamide reduced the rate of cognitive decline in the follow-up period of approximately 4 years by 19% [30]. However, several other studies, including the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRASCEND), Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS), Systolic Hypertension in the Elderly Program (SHEP), and others, showed no effect of lowering blood pressure on cognitive decline [20]. A recent scientific statement from the American Heart Association on the impact of hypertension on cognitive function concluded that "judicious treatment of hypertension, taking into account goals of care and individual characteristics (e.g., age and comorbidities), seems justified to safeguard vascular health and, as a consequence, brain health; however, evidence from randomized, clinical trials does not allow conclusive recommendations about treating hypertension throughout the life span to protect cognition" [31].

Similarly, the studies looking at diabetic control on cognitive decline have also shown disappointing results. In the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes Study (ACCORD-MIND), intensive glycemic control in patients with type 2 DM decreased brain atrophy but had no effect on cognitive outcomes [32]. Also, in the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial, insulin-mediated normoglycemia had a neutral effect on cognitive decline compared to standard of care [33]. A meta-analysis including more than 24,000 individuals with type 2 DM randomized to intensive or standard glycemic control showed no effect of treatment on cognitive decline [34]. Also, a recent Cochrane database systematic review concluded that there is limited evidence that any specific treatment, or treatment intensity, can prevent cognitive decline in type 2 DM [35].

Different factors may account for the lack of efficacy noted in these randomized studies, including differential attrition, short follow-up, inadequate statistical power, and heterogeneity in screening, treatment, and outcomes. In addition, there is a multiplicity of pathogenic mechanisms that contribute to cognitive decline. Thus, it has been suggested that single interventions may be insufficient to preserve brain vitality [20]. A recent study investigated the effect of early life cardiovascular health, defined by adherence to AHA's Life's Simple 7 on cognition (Table 1.2) [20]. In general, an increasing number of cardiovascular metrics at goal resulted in improved psychomotor speed, executive function, and verbal memory in midlife [36]. The results of three large randomized trials evaluating the effect of mutidomain interventions on cognitive decline have recently been reported (Table 1.3). Two randomized trials, the Prevention of Dementia by Intensive Vascular Care (preDIVA) study and the Multidomain Alzheimer Preventive (MAP) study, showed a neutral effect of multidomain intervention on cognitive decline [37, 38]. In contrast, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

Table 1.2 American Heart Association's Life's Simple 7

Health-related behaviors	1. Nonsmoking status 2. Physical activity at goal levels 3. BMI <25 kg/m^2 4. Healthy diet consistent with current guidelines
Health-related factors	5. Untreated BP <120/<80 mmHg 6. Untreated total cholesterol <200 mg/dL 7. Fasting blood glucose <100 mg/dL

Table 1.3 Multidomain-randomized clinical trials in neurocognitive decline

Study	Average age (*N*)	Planned follow-up (years)	Intervention	Cognitive outcome	Results
preDIVA Prevention of Dementia by Intensive Vascular Care	74.5 ± 2.5 (3,526)	6	Usual care versus multidomain intervention (smoking habits, diet, physical activity, weight, blood pressure, diabetes mellitus, and dyslipidemia)	Dementia (DSM-IV criteria)	No effect on dementia
MAPT Multidomain Alzheimer Preventive Trial	75.3 ± 4.4 (1,680)	3	Usual care versus multidomain intervention (cognitive training, diet, nutrition advice, and three preventive consultations ± omega 3 polyunsaturated fatty acids)	Free and Cued Selective Reminding test, ten Mini-Mental State Examination orientation items, Digit Symbol Substitution Test, and Category Naming Test	No effect of treatment on cognition
FINGER Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability	69.3 ± 4.7 (2,654)	2 (extended follow-up planned at 7 years)	Usual care versus multidomain intervention (diet, physical exercise, cognitive training, and intensive vascular risk factor monitoring)	Neuropsychological test battery	Improvement in cognition

(FINGER) study showed a statistically significant reduction in the rate of cognitive decline in favor of the multidomain intervention at 2 years with a between-group difference in the change of comprehensive neuropsychological total score per year of 0.022 (95% CI 0.002–0.042, $p = 0.030$) [39]. Albeit positive, the results of the FINGER study were rather modest raising the question of whether the beneficial effect of multidomain intervention would be perceived as significant at the individual level. preDIVA, MAP, and FINGER have similar limitations. In general, they had a short follow-up, included older patients, and there was a rather small difference in vascular risk factor control at baseline and in the follow-up period [20].

1.6 Conclusion

There is increasing evidence that confirms that subclinical functional, structural, and biochemical abnormalities occur very early in patients with traditional risk factors, and these herald the development of cognitive impairment [20, 22, 40]. Targeting vulnerable populations at midlife or earlier may be necessary to halt the initiation of neurodegenerative changes which, once triggered, can perpetuate in time. Cognitive decline, however, may become clinically evident after decades of neuropathologic progression. Thus, randomized trials targeting relatively younger individuals with extended follow-up are necessary. The development of these trials may be hindered by costs to carry out such studies, attrition associated with long-term follow-up, and other factors. Discovery of biomarkers of cognitive trajectory is needed in neurocognitive research to determine if changes in the levels of biochemical markers of disease, functional connectivity, and microstructural abnormalities assessed by using novel neuroimaging technology possess the sensitivity and specificity required to bridge existent study gaps.

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Post-stroke Cognitive Impairment

2

Jae-Sung Lim

2.1 Introduction

Post-stroke cognitive impairment (PSCI) is one of the most representative syndromes of vascular cognitive impairment (VCI). The current research on both the pathophysiology and the biomarkers of VCI is based on PSCI. However, cognitive decline is less interesting for those neurologists investigating stroke when compared to other stroke-related symptoms and signs, including hemiplegia and language disturbance. Conversely, memory clinic doctors exploring dementia are not greatly familiar with the differential diagnosis underlying cognitive impairment following stroke.

Post-stroke cognitive impairment is known to have a major impact on recovery after stroke. In contrast to Alzheimer's disease, a significant part of the disease is anticipated to be prevented by controlling vascular risk factors from the middle age. Indeed, a recent study that reported a reduction in the prevalence of dementia also suggested it to be a result of the decrease in vascular dementia [1].

Despite this implication for therapeutic and preventive effects, the mechanism behind the occurrence of PSCI, the sensitivity of its identification, and the ways it can be prevented and treated are still to be fully determined. Additional research is needed in many areas, such as in understanding its pathogenesis, developing appropriate biomarkers, and attempting the detection of successful treatments.

This chapter will summarize the knowledge about PSCI gathered to date and discuss the direction that researchers should strive to.

2.2 Epidemiology

2.2.1 Ischemic Stroke and PSCI

With regard to the epidemiology of PSCI, Pendlebury et al. summarized its prevalence and incidence rates at each hospital and community-based clinical setting, distinguishing between patients with a first-ever stroke and recurrent strokes [2]. In brief, about 10% of patients with a first-ever stroke and 30% of those with recurrent strokes also presented PSCI, which differed depending on whether they were included in hospital or community-based studies.

Furthermore, the time at which the cognitive function was assessed is crucial, considering that the post-stroke cognitive function changes dynamically and greatly varies depending on the time intervals between cognitive assessment and stroke onset. Most of the previous studies evaluated the baseline cognitive function at

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S.-H. Lee, J.-S. Lim (eds.), *Stroke Revisited: Vascular Cognitive Impairment*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1433-8_2

3–6 months following stroke onset, given the delirium and acute confusional state which immediately follow acute stroke [3–5]. However, such studies were conducted at very different time intervals; therefore, care must be taken when interpreting their results.

Additionally, PSCI prevalence may differ depending on the area of the cognitive domain assessed. Previous studies reported the impairment of memory and frontal function to be characteristic of PSCI [6]. In contrast, although the visuospatial function and language are believed to be relatively preserved, this is again dependent on the location of the stroke lesions and the eligibility criteria of the corresponding studies.

2.2.2 Hemorrhagic Stroke and PSCI

Important data related to intracerebral hemorrhage were recently obtained with the effort of the PITCH (Prognosis of Intracerebral Hemorrhage) cohort [7]. This study included a total of 218 non-demented patients with spontaneous intracerebral hemorrhage and reached a median follow-up duration of 6 years. The cumulative incidence rates of new-onset dementia in patients without any history of either stroke or transient ischemic attack were 14.6% and 21.8% at 1-year and 4 years post-intracerebral hemorrhage, respectively. In contrast, they were higher in patients with both previous strokes and lobar intracerebral hemorrhage. Multiple microbleeds (>5 in number), disseminated superficial siderosis, and higher cortical atrophy scores were identified as risk factors for PSCI following intracerebral hemorrhage. This provides information on the high-risk groups which require surveillance.

2.3 Classification

The existing classification of PSCI, for example, multi-infarct dementia and strategic infarct dementia, is based on both the location and the number of ischemic lesions observed in the brain imaging. In addition, its classification is linked to the time of cognitive impairment occurrence in relation to the time of stroke onset. Recent research revealed the causes of cognitive impairment to differ according to early- and late-onset PSCI [8]. For example, early-onset PSCI, which is usually defined when occurring within 6 months from the stroke, is mainly affected by stroke itself, including its lesion location and burden. However, delayed-onset PSCI, which arises past the 6 months following stroke, is associated with severe small vessel diseases [5]. Furthermore, although the amyloid pathology also affects delayed cognitive impairment, it has a greater impact on pre-stroke cognitive impairment. From a therapeutic point of view, a classification method reflecting the pathophysiology, rather than simply classifying by imaging findings, is needed.

For example, in the Alzheimer's disease field, the A/T/N classification system, which reflects the pathophysiology of the disease, is sought to identify patients at an early stage [9]. I propose to classify PSCI into mild vs. major (based on the neuropsychological finding) and early onset vs. delayed onset (based on the intervals between the onsets of cognitive impairment and stroke) and to describe the accompanying main pathology. For example, it can be classified as "delayed-onset major post-stroke neurocognitive disorder with superimposed amyloid pathology," "delayed-onset major post-stroke neurocognitive disorder with superimposed severe small vessel disease," or "early-onset major post-stroke neurocognitive disorders with strategic lesion." This method will help to recruit a relatively homogeneous group of patients in future clinical trials, enabling the identification of both the causes and the mechanisms underlying PSCI.

2.4 Clinical Characteristics

The clinical features of patients with PSCI are variable depending on both the location and the size of their lesion. Generally, decreased processing speed, dysexecutive symptoms, and memory impairment are well-known characteristics of PSCI [6]. However, when the lesion is too large,

the cognitive impairment may be overlooked due to other neurological deficits.

PSCI patients often also present gait disturbances, voiding difficulties, and behavioral symptoms, such as aggression, agitation, anxiety, and depression, during the early stage of the disease. However, further research concerning the reason behind the presence of these problems from the beginning of the disease are still required. Please note that gait disturbances, including frontal gait disorders, will be discussed in more detail in other chapters.

Furthermore, these symptoms are not fixed and greatly vary over time given the brain neuroplasticity after injury. In previous cohort studies, approximately 7.8% of the patients reported better cognitive function than the baseline, 14% had worse, whereas the rest remained at the same level [10]. In addition, Levine et al. suggested the changes in cognitive function prior to and following stroke to be also domain specific, enabling a better understanding of the dynamic changes in cognitive function due to stroke [11]. Specifically, a sudden drop and subsequent accelerated rate of decline in global cognition, but only a sudden drop in new learning and an acceleration in fluency rate of decline, were observed.

Considering that the PSCI encompasses a wide range of patients, determining both the selection criteria and the evaluation methods of the patients included in each study is fundamental for a better understanding of its clinical features.

2.5 Neuropsychological Evaluations

2.5.1 Brief Screening Tests

As mentioned earlier, considering the distinct clinical characteristics of PSCI from Alzheimer's disease, specific neurophysiological assessment tools are needed. Memory decline is one of its most prominent features, similar to other neurodegenerative dementia, while frontal-executive/attention deficit and decline of speed processing are also among the earliest features in PSCI patients [6]. Therefore, a tool able to sensitively detect cognitive decline in these domains is needed [12].

The most appropriate screening tool for evaluating PSCI is yet to be determined. To date, the consensus is known to be relatively favorable to Montreal Cognitive Assessment (MoCA), given that Mini-Mental State Examination (MMSE) is insufficient to evaluate the frontal function. In fact, previous studies showed that 32% of patients who did not report any abnormality in their MMSE scores had abnormal MoCA scores [6]. In addition, contrary to MMSE, the MoCA domain subtest score helped the differentiation between PSCI groups based on the abnormalities observed in both the executive function and attention domain [6]. Furthermore, another study indicated the cognitive decline with a baseline MOCA score lower than 26 to be associated with subsequent cognitive impairment (defined as clinical dementia rating ≥ 0.5), functional impairment (defined as modified Rankin scale >2), and death after 3 years of follow-up [13]. Additionally, the Addenbrooke's Cognitive Examination-Revised (ACE-R) was found to be more useful than the MMSE, considering its ceiling effect in discriminating between the mild cognitive impairment and normal groups [12].

The 5-min MoCA and the 5-min National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) vascular cognitive impairment harmonization standards neuropsychological protocol (VCIHS-NP), consisting of subtests of the MoCA, are designed to be tested verbally without the use of hands and may be useful in acute stroke patients with dominant hand paralysis or as a screening test through the telephone [14, 15].

Considering not only the type of the screening test but also the timing of the assessment is necessary. To confirm the diagnosis, the neuropsychological assessments should be performed at least 3 months following the stroke onset to rule out the effects of delirium or confusion in its acute phase. However, to identify the high-risk group for PSCI requiring early treatment, conducting an appropriate screening test within 1–2 weeks from the onset [6, 14] may be beneficial. Furthermore, follow-up

of the cognitive function through yearly screening or detailed examinations is also essential to confirm the occurrence of delayed cognitive impairment. Finally, the main risk factors known to date include older age, female sex, lower education levels, previous stroke history, severe white matter hyperintensities (WMHs), and multiple microbleeds [2, 7]. Patients at risk of developing future cognitive impairment should be informed and followed up regularly.

2.5.2 Detailed Neuropsychological Tests

A statement from the American Heart Association/American Stroke Association proposed that the vascular dementia diagnosis should be based on those neuropsychological test which assesses a minimum of four cognitive domains, including executive/attention, memory, language, and visuospatial function [16]. Furthermore, the diagnostic and statistical manual of mental disorders (DSM-5) recommends evaluating the following domains: complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition [17]. Additionally, an International Society for Vascular Behavioral and Cognitive Disorders (VASCOG) statement suggests the following cognitive domains need to be assessed in vascular cognitive disorders: attention and speed processing, frontal-executive function, learning and memory, language, visuoconstructional-perceptual ability, praxis-gnosis-body schema, and social cognition [18].

The NINDS-CSN proposed the VCIHS-NP as the standardized tests to evaluate cognitive function [19] in PSCI patients. It consists of a 5-, 30-, and 60-min protocol, with the 5-min protocol representing a constellation of MoCA subtests, as mentioned earlier. Given that the VCIHS-NP was indicated as a reliable evaluation tool for multinational and multicenter trials and to comprise sensitive and specific tests for patients with VCI, many countries published local norms and validation data. In addition, the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), which are usually used in patients with degenerative dementia, were used for the cognitive evaluation of VCI. Furthermore, the VDAS-Cog, a modified version of the ADAS-Cog, Cambridge cognition examination (CAMCOG), and several computerized cognitive evaluation tools are also employed.

2.5.3 Interpretation of Neuropsychological Tests

While determining the identification of cognitive impairment, most of the diagnostic criteria are presented in comparison with norms for age, gender, and education levels. In the case of mild neurocognitive disorders, a decrease between −1 and −2 standard deviations from the age-, sex-, education-adjusted mean of the normal distribution is observed, whereas major neurocognitive disorders are defined as a decrease of −2 standard deviations or more [17].

Attention should be paid not only to the type of tests but also to both the appropriate performance of such tests and the correct interpretation of the results. In addition to cognitive function, the presence of any physical barrier that may affect the test results should also be carefully examined. For instance, hearing loss and visual acuity abnormalities can have a significant impact on the test results. Either hemiplegia or visual field defect caused by stroke can influence the trail making test results, for example. Therefore, inspecting these conditions thoroughly before the neuropsychological evaluations and recording the situation in detail in each case is of fundamental importance for examiners.

Furthermore, the use of appropriate statistical methods when analyzing the change in cognitive function over time and when handling longitudinal data is necessary [20]. Each cognitive domain is not independent and affects each

other. In addition, the test results at a given point are affected by previous test results. Therefore, suitable analytical methods which consider such effects are needed [20]. Moreover, patients with severe neurological deficits or cognitive decline are more likely to be excluded from analysis during the follow-up, which may lead to attrition bias in clinical trials. Therefore, efforts should be made to prevent these patients from being overlooked, for example, by conducting either telephone-based cognitive testing or home visits [21].

2.6 Pathophysiology and Imaging Studies

Recent developments in the imaging technology enabled a better understanding of the complex pathophysiology of PSCI (Fig. 2.1).

2.6.1 Large International Multicenter Cohort for Lesion-Symptom Mapping: Identifying the High-Risk Location

In addition to the already well-known strategic locations, we recently opened a new chapter in lesion-symptom mapping through large collaborative studies, such as the meta-analyses on strategic lesion locations for vascular cognitive impairment using lesion-symptom mapping (META VCI MAP) (https://metavcimap.org). Collaborators are collecting large lesion-function datasets from all around world and creating a functional map of the brain, without neglecting any part of the brain. Future researchers will not only understand the cognitive map of the brain through this work but also help the selection of high-risk groups, vulnerable to cognitive decline.

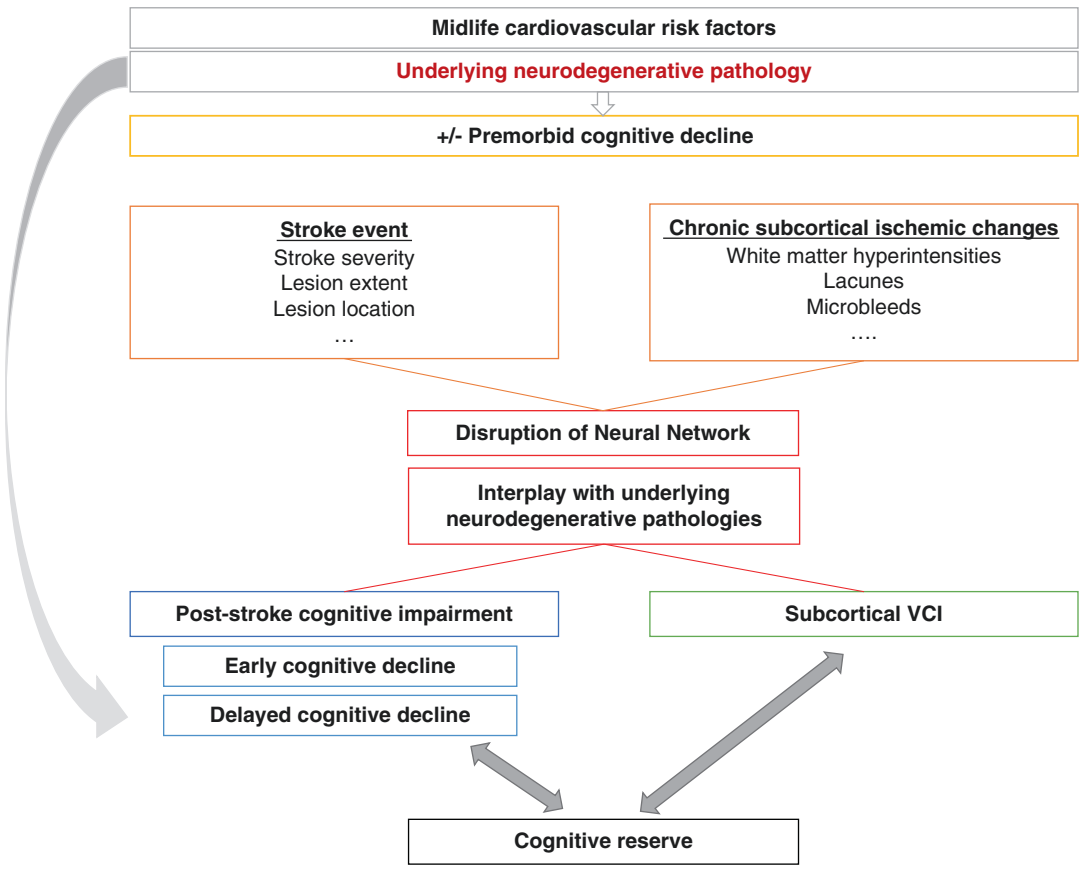

Fig. 2.1 A schematic diagram of post-stroke cognitive impairment pathophysiology

However, various obstacles exist, including the fact that lesion-symptom mapping studies are based on the accurate registration of patients' stroke lesions from a common template [22]. In fact, it was statistically tested that certain areas are related to cognitive disability. However, some points to consider are the following: (1) errors in the registration of lesions from the common template, (2) mapping errors due to the reconstruction of the functional circuit following stroke, and (3) the presence of few stroke lesions in certain areas, which may lead to their exclusion from the analysis.

2.6.2 Connectivity Analysis: Identifying a More Distributed Effect by Focal Lesions

In addition to the lesion-symptom mapping mentioned above, Duering et al. provided excellent insights into the mechanism by which stroke lesions lead to remote brain structural changes and cognitive impairment [23]. In fact, they revealed through diffusion tensor imaging techniques that a lacunar infarction located in the anterior thalamic radiation caused corresponding frontal cortical thinning and decreased frontal domain function.

The concept that a lesion of the same size has a significant effect on its cognitive ability when located in an important region, such as a hub [24, 25], is traditionally known as strategic infarction. Some lesions, including the anterior thalamus, caudate head, and medial temporal lobe, are recognized to cause a cognitive impairment after stroke. In addition to these observations, recent advances in the imaging techniques helped in understanding the reason behind such detrimental consequences of lesions in the whole brain (Fig. 2.2). After various connectivity analysis, it was shown that the brain network attributes, including network efficiency and characteristic path lengths, are worsened by focal lesions. These metrics provide us with an intuitive understanding of information processing efficiency in the brain.

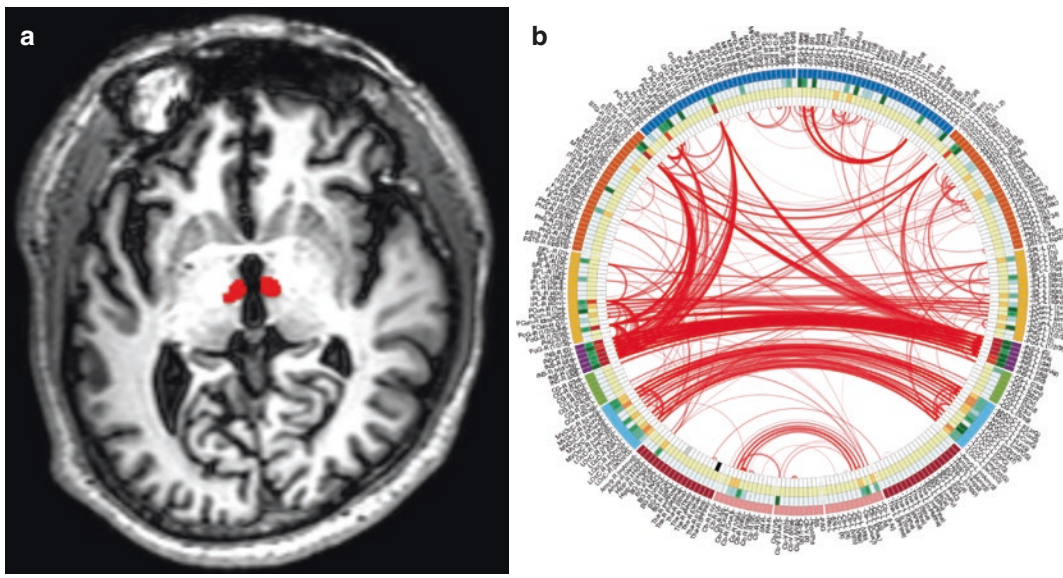

Fig. 2.2 Representative neuroimaging findings on post-stroke cognitive impairment. In the past, post-stroke cognitive impairment was classified and defined through both the location and the size of the lesion (**a**, red-colored lesion masks). Following the advancements in the neuroimaging techniques, the visualization of the effects of such strategic lesions on the whole brain connectivity is today possible (**b**). Magnetic resonance imaging (T1) of the bilateral paramedian thalamic infarction (artery of the Percheron territory). Whole brain connectome of the same patient identified using the resting-state functional MRI

Furthermore, the Corbetta group is actively studying the changes in functional neural network composition using the resting-state functional magnetic resonance imaging (MRI) [26]. The conceptual changes in the neural network structure, such as the reduction of network efficiency and modularity, are currently researched via well-designed studies, which showed that interhemispheric integration and intrahemispheric segregation are important for several behavioral impairments following stroke [26]. In addition, modularity was another useful indicator of post-stroke cognitive recovery [27].

The remaining challenges are to both facilitate the understanding of such discoveries by clinicians and to improve the effectiveness of diffusion tensor imaging and resting-state functional MRI for their application in the clinical field. Finally, the development of new imaging techniques, which can be intuitively understood, is also of crucial importance.

2.6.3 Superimposed Amyloid Pathology: Finding an Accomplice

Mok et al. conducted a study on stroke patients with amyloid positron emission tomography (PET) positivity and found them to have a steeper decline in cognitive function, as assessed by both MMSE and MoCA, compared with patients with amyloid PET negativity [3]. The amyloid pathology not only damages neurons but also affects cerebral blood vessels, given that amyloid deposits in blood vessels interfere with amyloid clearance through the disruption of the glymphatic system and consequently contribute to brain degeneration [28]. However, recent studies delivered conflicting results, as amyloid PET did not indicate any increase either inside or surrounding infarcted lesions [29], while tau depositions were observed nearby the ischemic lesions following stroke [30]. This superimposed amyloid pathology is thought to influence pre- and post-stroke cognitive function through several mechanisms.

2.7 Treatment

While research on biomarkers is actively being conducted, clinical trials on potential treatments are yet to show successful results, as determined by a valuable review published in *Nature Reviews Disease Primers* [31].

Briefly, the prevention of recurrent strokes and chronic ischemic changes is theoretically a reasonable therapeutic goal to consider. However, in the case of antiplatelet drugs, major clinical trials, including the PRoFESS (aspirin plus extended-release dipyridamole vs. clopidogrel) and the SPS3 (aspirin plus clopidogrel vs. aspirin plus placebo), failed to provide significant results [32, 33]. In fact, a critical appraisal of the study results indicated the absence of evident cognitive decline in the control group. In addition, the PRoFESS used the MMSE as its primary outcome variable, through which the sensitive detection of cognitive impairment is difficult [32]. Similarly, although patients with subcortical infarction were included in the SPS3, more than half of them had none or only mild WMHs, while little cognitive decline was observed in the control group, as described above [33].

Therefore, conducting further research by appropriately selecting a high-risk group able to show the therapeutic effect is fundamental. A recent PICASSO trial is awaiting for its results [34, 35], which are expected to be of great interest and value. This study was conducted on patients with multiple cerebral microbleeds and prior intracerebral hemorrhage, with a large number of the participants presenting moderate to severe WMHs. While this is known to distinguish the population at risk of cognitive decline following stroke, the effect of the trial drug cilostazol is expected to be clearly identified. Cilostazol has preclinical and clinical evidence for its protective effects on WMH progression [36], by decreasing amyloid beta accumulation and increasing regional cerebral blood flow, as well as the effect of preventing recurrent strokes [34, 37, 38].

Furthermore, although the results are not consistent for anticoagulants, recent studies in patients with atrial fibrillation indicated that

the use of anticoagulants may prevent dementia, suggesting that prevention of ischemic lesions may be effective to prevent cognitive decline [39].

In addition, the protective effects of other drugs, including statins, peroxisome proliferator-activated receptor (PPAR)-gamma agonists, and angiotensin-receptor blockers, on PSCI are currently under investigation.

Similarly, a non-pharmacological approach using multifaceted interventions, such as dietary modification, physical activities, and cognitive interventions, is actively researched. Although each individual intervention does not bring the desired effects, several interventions applied at the same time may prove effective, such as the FINGER trial [40].

Accordingly, the American Heart Association offers the "life's simple 7," promoting a healthy lifestyle for the middle age population [http://www.heart.org/en/professional/workplace-health/lifes-simple-7]. Specifically, it consists of the following suggestions, stop smoking, eat better, get active, lose weight, manage blood pressure, control cholesterol, and reduce blood sugar, and provides detailed advice on how to achieve each goal. Furthermore, the concept of optimal brain health, recently published in the *Stroke* journal as a presidential advisory from the American Heart Association/American Stroke Association, also addresses the direction in which such preventive strategies should be pursued [41] and offers advice on how to define, monitor, and protect optimal brain health.

2.8 Future Directions and Collaborations

As mentioned earlier, several research topics are yet to be solved. Large multicenter cohort studies, including the STROKOG and METACOHORTS, are being conducted to answer burning questions, such as the determination of the cognitive burden in stroke patients and the mechanisms by which cognitive functions change over time [42, 43]. In addition, studies like the META VCI MAP will reveal important cognitive maps, which were not previously known. By identifying the genetic predisposition to PSCI, important data on precision medicine are needed to develop some treatments tailored to the individual patient [44]. Furthermore, the DEMDAS cohort will provide longitudinal data covering various serum and neuroimaging biomarkers, including diffusion tensor imaging, resting-state functional MRI, and amyloid PET [4]. Finally, besides such well-known large cohorts, basic experiments using animal models and computational modeling will ensure the discovery of the pathophysiological mechanisms underlying PSCI. We hope that both the efforts of various research groups investigating the cognitive dysfunction following stroke and the knowledge gained will extend to the therapeutic trials.

Acknowledgment This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (Ministry of Science and ICT) (No.2017R1C1B5018132) and the Hallym University Research Fund (HURF-2017-03).

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3 Subcortical Vascular Cognitive Impairment

Yeo Jin Kim

3.1 Introduction

Subcortical vascular dementia (SVaD), also called subcortical ischemic vascular dementia (SIVD), is a type of vascular dementia caused by white matter ischemia and multiple lacunar infarctions in subcortical structures due to ischemia or occlusion of small vessels [1]. Unlike other vascular dementias, the disease progresses slowly [2], making it difficult to distinguish it from Alzheimer's disease (AD) at diagnosis. In AD, cognitive impairment is divided into dementia and mild cognitive impairment. Similarly, in SVaD, gradual progression occurs, people with cognitive impairment but with maintenance of activities of daily living are diagnosed with subcortical vascular mild cognitive impairment. Unlike degenerative diseases, an adjustable set of vascular risk factors contribute to the development of SVaD; modification of vascular risk factors should be used to treat this disorder. Thus, even if cognitive impairment has already occurred, the diagnosis of svMCI has been established in order to delay or prevent dementia deterioration by managing modifiable vascular risk factors. This disease is referred to as subcortical vascular cognitive impairment (SVCI) and includes both SVaD and svMCI.

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3.2 Epidemiology

The proportion of vascular dementia caused by small vessel disease ranges from 36% to 67% [3]. The prevalence of extensive WMH is 36.6%, lacunes 24.6%, and cerebral microbleeds 26.9% in the Asian population [4]. Studies performed in the USA and Europe report wide ranges for WMH from 22% to 96%, silent brain infarcts 3–28%, and microbleeds 3–24% [5–7]. These lesions are associated with advanced age and hypertension [4]. Clinical symptoms such as cognitive dysfunction and motor impairments are affected by WMH severity [8, 9]. After using $^{(11)}$C-Pittsburgh compound B (PiB) PET to detect amyloid deposition in vivo, it became possible to distinguish between pure SVaD and vascular dementia of mixed pathology. Of clinically diagnosed SVaD patients, 68.9% were negative for cortical PiB binding [10].

3.3 Pathophysiology

The development of SVaD can be largely explained by two pathophysiologies: Binswanger's disease and lacunar state (etat lacunaire) [1]. First, Binswanger's disease is caused by severe stenosis and hypoperfusion of multiple medullary arterioles, resulting in extensive incomplete infarction of deep white matter. The second, lacunar state, is

S.-H. Lee, J.-S. Lim (eds.), *Stroke Revisited: Vascular Cognitive Impairment*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1433-8_3

caused by the formation of lacunes, which is characterized by the occlusion of the arteriolar lumen due to arteriolosclerosis. These two pathophysiologies often coexist in the same person. In addition, it is not uncommon for small vessel and large vessel disease of the cerebrovascular system to coexist in the same person.

3.3.1 The Mechanisms by which White Matter Change and Lacunar Infarction Develop (Fig. 3.1)

The most important etiology for SVaD is small vessel disease caused by arteriolosclerosis. Arteriolosclerosis is initiated by wall thickening due to hyalinosis, narrowing of the lumen, and loss of smooth muscle cells in the tunica media, which then develop fibrinoid necrosis and disruption of the arteriole. It is also accompanied by enlargement of the perivascular space, pallor or swelling of adjacent perivascular myelin, loss of oligodendrocytes, damage to axons, and reactive astrogliosis [11].

Pathophysiological mechanisms involved in microcirculation dysfunction include hemorheological factors, increased resistance to flow, decreased autoregulation, dysfunction of the blood-brain barrier (BBB), endothelial changes, and dilatation of perivascular spaces. A combination of these effects induces hypoperfusion and incomplete infarction in deep white matter. One of the two important factors causing white matter hypoperfusion is hemorheological factors, especially a high concentration of RBCs and increased plasma viscosity, which increases blood viscosity and delays or stays blood flow in arterioles [12]. Hyperglycemia, hyperfibrinogenemia, hyperlipidemia, and red cell deformability have influences on white matter hypoperfusion. Another factor is autoregulatory change. A variation in mean arterial pressure between 60 and 150 mmHg in normal subjects can be compensated for by autoregulation [13, 14]. However, a person with chronic hypertension cannot cope with sudden changes in blood pressure due to impaired vascular reserve. Therefore, if blood pressure suddenly drops due to intensive hypertensive treatment, orthostatic hypotension, heart failure, cardiac arrhythmia, blood vessels cannot compensate for these changes, and ischemia occurs. Ischemia occurs when there is a lack of tissue perfusion and insufficient supply of components essential for cell metabolism including oxygen and glucose. This is influenced by differences in essential nutrient requirements according to brain cell type, regional differences in cerebral blood flow, and

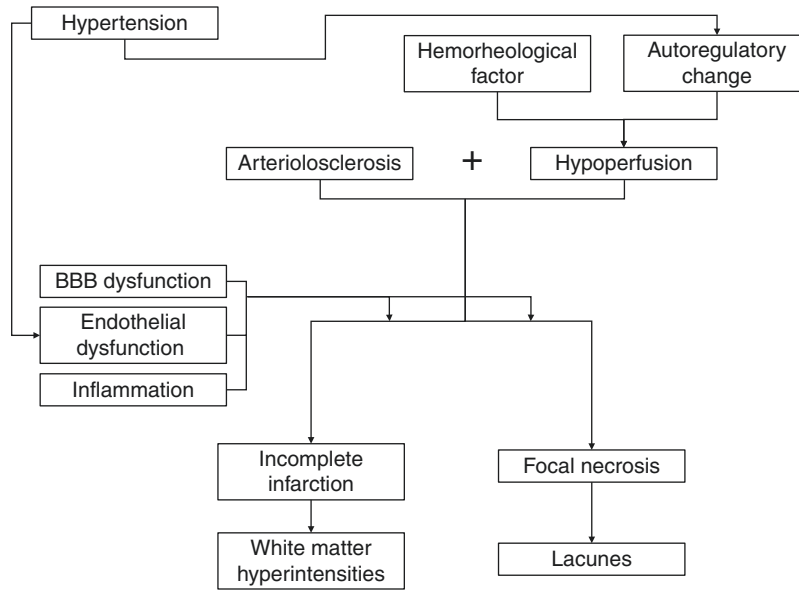

Fig. 3.1 Pathogenesis of white matter hyperintensities and lacunes

hypoperfusion duration [15, 16]. When hypoperfusion occurs below the critical perfusion threshold, only some types of cell are selectively lost. In acute infarction, selective neuronal cell loss occurs in the penumbra. However, in the deep white matter of patients with severe small vessel stenosis, selective loss of oligodendrocytes, myelin, and axons occurs. The selective loss of tissue components caused by ischemia is called incomplete infarction [16]. After small vessels undergo age-related changes, perfusion is altered, and lacunar infarction and microinfarcts develop. Lacunes are caused by occlusion of lenticulostriate, thalamo-perforating, and medullary arterioles. When ischemic injury is focal and sufficient to cause necrosis in a small area, this provokes lacunar infarction [11]. Lacunar infarcts usually result from progressive small vessel disease that might involve stenosis caused by hyalinosis [11].

Arteriolosclerosis promotes loss of vessel elasticity, which dilates and constricts with changes in systemic blood pressure or autoregulation leading to fluctuation of blood flow response and changes in tissue perfusion [11]. Due to small vessel pathology, chronic leakage of fluid and macromolecules in the white matter is likely caused by edema and damage to the BBB [17]. Deep cerebral structures and white matter are the most vulnerable areas because the blood vessels in these areas are end arteries with little anastomoses. Small vessel disease linked to hypertension has caused endothelial dysfunction by promoting decreased production and increased degradation of nitric oxide. Degrees of associated inflammation including the presence of vascular-specific lymphocytes or macrophages lead to further microvascular disease [18].

3.3.2 The Mechanism by which White Matter Change and Lacunar Infarction Affect Cognitive Function

Damage due to an accumulation of white matter ischemic lesions and lacunar infarctions in the caudate nucleus, globus pallidus, thalamus, and their connections, which constitute critical prefrontal-subcortical circuits and thalamocortical circuits (Fig. 3.2), leads to cognitive impairment. With respect to lacunar infarction, the presence of multiple lacunes [19] and lacune location are associated with decreased cognitive function. For example, the presence of lacunes in the thalamus is associated with low scores on the mini-mental state examination and poor motor control and executive function performance. Lacunes located in the putamen or pallidum

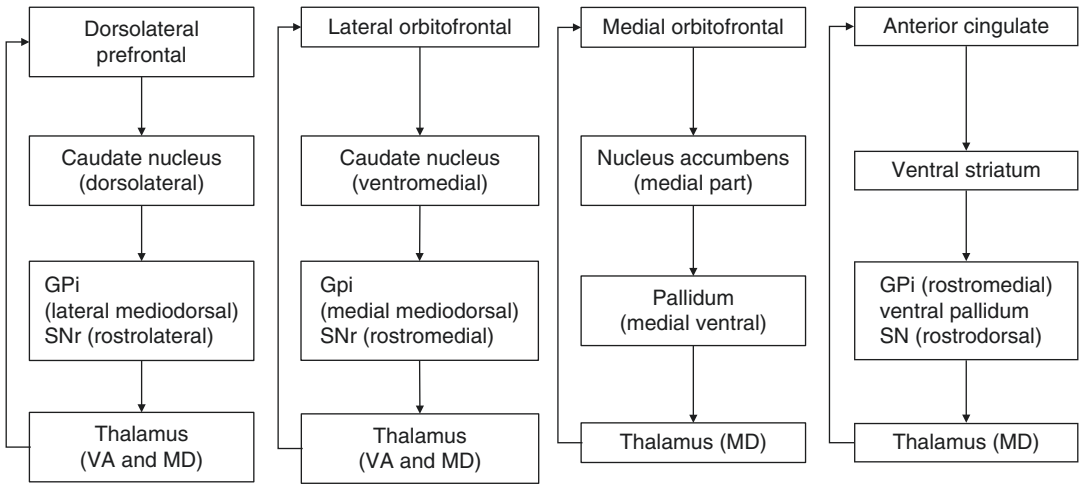

Fig. 3.2 Frontal-subcortical circuits. Based on the hypothesis by Bonelli and Cummings (*Dialogues Clin Neurosci*. 2007;9:141–151). *Gpi* globus pallidus interna, *SNr* substantia nigra, pars reticulata, *SN* substantia nigra, *VA* ventral anterior, *MD* mediodorsal

induce memory disturbances [20]. Even one lacunar infarction in the thalamus can lead to widespread hypometabolism or decreased cerebral blood flow to the frontal lobe or cerebellum. With respect to WMH, the mechanism is unclear but related to cognitive function as well as noncognitive symptoms [21–23]. WMH is not associated with global cognitive decline [24] but rather with specific cognitive deficits such as psychomotor retardation, deficits of attention, planning, and set-shifting, and dysexecutive syndrome [25]. Furthermore, there is a correlation between progression of WMH load and cognitive decline [8]. In addition, microinfarcts could occur in both cortical and subcortical areas, and multiple cortical microinfarction is known to be associated with cognitive dysfunction [26]. In the presence of cerebral amyloid angiopathy, cortical microinfarction area increases, suggesting that changes in hemodynamics such as hypotension and atherosclerosis might be related to the genesis of cortical microinfarction.

3.4 Clinical Features

3.4.1 Cognitive Symptoms

Frontal functions such as attention, performance, planning, and inhibition control are more impaired than memory and language dysfunction, due to frontal and subcortical lesions. Verbal fluency rather than naming ability is also decreased.

1. Memory function: Because hippocampal atrophy is a major pathogenesis of AD, patients with AD show abnormality in the process of memory registration and storage, but in SVaD, memory deficits are caused by damage to the prefrontal-subcortical circuit, so recognition memory tests are well performed. This indicates that retrieval failure is the most injured part of the memory process in SVaD. In addition, while AD is characterized by early episodic memory loss, SVaD is characterized by impaired working memory at the disease early stage, which is related to prefrontal function [27].
2. Language function: While AD patients show naming difficulty in the early disease stage, and lexicon impairment is prominent, SVaD patients show a pronounced impairment in verbal fluency and syntax impairment [28].
3. Visuospatial function: There is no difference between AD and SVaD in visuospatial construction ability, but as dementia progresses beyond moderate severity, more extensive visuospatial dysfunction might occur in patients with SVaD [27].
4. Frontal/executive function: While patients with AD initially show significantly lower memory function than frontal lobe function, the frontal lobe function of patients with SVaD is markedly impaired from the early stage to a level similar to memory impairment [1].
   (a) Dorsolateral prefrontal-subcortical circuits mediate executive dysfunction.

   Lesions to this circuit result in impairment to goal formation, initiation, planning, organizing, sequencing, executing, set-shifting and set-maintenance, and abstraction.
   (b) Orbitofrontal-subcortical circuits mediate frontal inhibition of the limbic system.

   Lesions to this circuit result in uninhibited behaviors, impulsivity, and personality changes.
   (c) The anterior cingulate (medial frontal)-subcortical circuit cortex mediates motivation.

   Lesions to this circuit result in apathy, abulia, and akinetic mutism.

3.4.2 Noncognitive Symptoms

1. Gait

   In the initial disease stage, patients show only mild slowing and subjective postural instability. After the disease progresses, a slowed, short-stepped, wide-based, or shuffling gait (marche a petits pas) develops. At the terminal stage, patients become bedridden [29].
2. Mood and behavior disorders

   Patients might present with depressive mood in the early stages of the disease but generally exhibit prefrontal lobe dysfunction

such as disinhibition, aggression, agitation or loss of volition (apathy), and akinetic mutism. Emotional bluntness, psychomotor retardation, and inertia are also present [29].

3. Loss of sphincter control

   Many patients show urinary incontinence, and some patients show fecal incontinence at the terminal stage of this disease [29].

4. Pseudobulbar palsy

   Patients present with dysarthria, dysphasia, and pathologic laughing and crying. Dysphasia in some patients becomes severe in the late stage, and percutaneous endoscopic gastrostomy might be needed. It is possible that dysarthria may become severe as the disease progresses, and this might result in unintelligible speech [29].

3.4.3 Neurological Examination

Mild upper motor neuron signs: drift, reflex asymmetry, incoordination.

Gait disturbances: apractic-atactic or small-stepped.

Dysarthria, dysphagia

Extrapyramidal signs: hypomimia, hypokinesia, axial and limb rigidity, loss of postural reflexes, frequent falls.

3.5 Diagnosis

3.5.1 Research Criteria for SVaD

The diagnosis of vascular dementia (VaD) is mainly based on the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'enseignement en Neurosciences (NINDA-AIREN) diagnostic criteria presented at an international workshop convened by NINDS. However, for SVaD research criteria, Erkinjuntti et al. modified the NINDS-AIREN criteria for probable VaD [30] (Tables 3.1 and 3.2).

Table 3.1 Clinical criteria of subcortical vascular dementia [30]

I. The criteria for the clinical diagnosis of subcortical vascular dementia include all of the following:
A. Cognitive syndrome
Dysexecutive syndrome: impairment in goal formation, initiation, planning, organizing, sequencing, executing, set-shifting and -maintenance, abstracting,
Memory deficit (may be mild): Impaired recall, relative intact recognition, less severe forgetting, benefit from cues Which indicate deterioration from a previous higher level of functioning and are interfering with complex (executive) occupational and social activities not due to physical effects of cerebrovascular disease alone
B. Cerebrovascular disease including both Evidence of relevant cerebrovascular disease by brain imaging (Table 3.2) Presence or a history of neurologic signs as evidence for cerebrovascular disease such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, dysarthria, gait disorder, extrapyramidal signs consistent with subcortical brain lesion(s)
II. Clinical features supporting the diagnosis of subcortical vascular dementia include the following:
(a) Episodes of mild upper motor neuron involvement such as drift, reflex asymmetry, incoordination
(b) Early presence of a gait disturbance (small-step gait or marche a petits pas, magnetic, apraxic-ataxic or Parkinsonian gait)
(c) History of unsteadiness and frequent unprovoked falls
(d) Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease
(e) Dysarthria, dysphagia, extrapyramidal signs (hypokinesia, rigidity)
(f) Behavioral and psychological symptoms such as depression, personality change, emotional incontinence, and psychomotor retardation
III. Features that make the diagnosis of subcortical vascular dementia uncertain or unlikely include:
(a) Early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging
(b) Absence of relevant cerebrovascular disease lesions on brain CT or MRI

Table 3.2 Brain imaging criteria for subcortical vascular dementia [30]

A. Computed tomography
Extending periventricular and deep white matter lesions: patch or diffuse symmetrical areas of low attenuation (intermediate density between that of normal white matter and that of intraventricular cerebrospinal fluid) with ill-defined margins extending to the centrum semiovale and at least one lacunar infarct
Absence of cortical and/or cortico-subcortical non-lacunar territorial infarcts and watershed infarcts, hemorrhages indicating large vessel disease, signs of normal pressure hydrocephalus, and specific causes of white matter lesions (e.g. multiple sclerosis, sarcoidosis, brain irradiation)
B. Magnetic resonance imaging
1. To include predominantly "white matter cases": extending periventricular and deep white matter lesions: extending caps (>10 mm as measured parallel to ventricle) or irregular halo (>10 mm broad, irregular margins and extending into deep white matter) and diffusely confluent hyperintensities (>25 mm, irregular shape) or extensive white matter change (diffuse hyperintensity without focal lesions), and lacune(s) in the deep grey matter
2. To include predominantly "lacunar cases": multiple lacunes (e.g. >5) in the deep gray matter and at least moderate white matter lesions: extending caps or irregular halo or diffusely confluent hyperintensities or extensive white matter changes
Absence of cortical and/or cortico-subcortical non-lacunar territorial infarcts and watershed infarcts, hemorrhages, signs of normal pressure hydrocephalus, and specific causes of white matter lesions (e.g., multiple sclerosis, sarcoidosis, brain irradiation)

3.6 Treatment

3.6.1 Management of Vascular Risk Factors

1. Hypertension

   Antihypertensive treatment shows conflicting results. Some observational studies report that antihypertensive treatment reduces WMH progression [31], but in randomized controlled trials, this treatment shows little or no effects [32, 33]. Similarly, in a small subcortical strokes (SPS3) trial, although lowering blood pressure had a beneficial effect, there was no significant reduction in recurrent lacunar stroke [34]. Rather, even a subclinical decrease in cardiac output was related to lower cognitive function. Reduced cardiac output is related to chronic reduced systemic perfusion, which induces the development and progression of WMH [35]. Thus, tight regulation of hypertension could be harmful.

1.1. Nimodipine

   Nimodipine is a calcium-channel antagonist, which has a vasodilation effect. A trial of nimodipine was the first to specifically address SIVD [36], which led to a larger multicenter European trial. This study failed to support its primary outcome measures but showed some benefits in secondary outcomes such as the mini-mental state examination and global deterioration scale [37].

2. Diabetes Mellitus

   Prolonged hyperglycemia contributes to more brain atrophy, larger WMH volumes, and more lacunar infarcts [38]. However, it is unclear whether thorough diabetes management can prevent the progression of small vessel disease. Because recurrent hypoglycemia can cause permanent cognitive impairment, it is also important to prevent hypoglycemia in the elderly [39].

3. Hyperlipidemia

   The relationship between hyperlipidemia and dementia is still unclear. Most lipid-lowering treatments including pravastatin show neutral results for WMH prevention [40].

4. Coronary artery disease, stroke, chronic kidney disease, atrial fibrillation, peripheral arterial disease, and heart failure increase the risk of vascular cognitive impairment [41].

5. Lifestyle factors

   Education level, diet, physical activity, alcohol consumption, smoking, obesity, and social networks are also important factors in cognitive function [41].

3.6.2 Medications Used in Alzheimer's Disease

3.6.2.1 Anticholinesterase Inhibitors

Cholinergic deficiency also affects symptoms in vascular dementia [42]. Because penetrating arterioles supply blood to the cholinergic nucleus of the basal forebrain, arteriole ischemia due to small vessel disease can cause cholinergic deficits. The CA1 region of the hippocampus is also one of the areas most vulnerable to ischemic injury [43]. Therefore, acetylcholinesterase inhibitors also show benefits for vascular dementia. Donepezil showed a significant reduction of cognitive decline in two clinical trials over 24 weeks [44, 45]. Galantamine showed some improved cognitive function compared to placebo in another study over 12 months [46]. Rivastigmine also showed benefits but only in a small open-label trial [47]. However, these effects on cholinergic neurons in clinical trials are not clear because of the lesser degree of loss of cholinergic neurons in vascular dementia compared to AD [48].

3.6.2.2 *N*-Methyl-D-aspartate Receptors

Memantine is a moderate-affinity noncompetitive antagonist of the *N*-methyl-D-aspartate receptor, which could block glutamate-induced excitotoxicity after ischemia. A placebo-controlled trial of memantine showed that in patients with mild to moderate vascular dementia, memantine improved cognition with no deterioration in global functioning and behavior [49].

3.6.3 Antiplatelet Agents

Because microinfarction is one of the important factors affecting brain atrophy and cognitive impairment, antiplatelet agents could be used to modulate small vessel disease to prevent secondary microinfarction [50, 51]. However, the effect of antiplatelet therapy on the primary prevention of VCI is not clear [41]. Any single antiplatelet agent is beneficial for preventing lacunar stroke [52]; however, long-term dual antiplatelet treatment in patients with lacunar stroke increases bleeding risk without reducing the risk of stroke recurrence [53].

3.6.4 Other Agents

Serotonin-specific reuptake inhibitors, including sertraline and citalopram, are used to treat depression and anxiety in patients with SVaD. However, tricyclic antidepressants are not recommended owing to their anticholinergic effects, including orthostatic hypotension.

Atypical antipsychotic drugs, such as risperidone and olanzapine, could be used in patients with agitation and disruptive behaviors.

3.7 Prognosis

Previous studies have reported that WMH progressed in 17.9–74% of study subjects over 3 years. The risk factors associated with WMH progression were aging and hypertension. Baseline WMH load also influenced disease progression. In other words, patients with a high WMH burden were more likely to develop further lesions. On the other hand, for clinical considerations, it was unclear if WMH progression was associated with cognitive decline. Rather, the severity of WMH increased stroke risk and gait disturbances. As the WMH volume increased, patients were more likely to experience gait deterioration and to develop falls than those with less severe disease [54]. Also, acute lacunar ischemic stroke could disappear or change to look like WMH. Cavitation occurred only in 20% of patients [55]. Clinically, most lacunes (89%) were clinically silent or manifested as subtle gait and cognitive impairments that were not recognized as stroke [1]. Recent PET developments to detect the accumulation of amyloid have led to the detection of amyloid deposition in vivo. SVaD patients with amyloid deposition show faster cognitive decline longitudinally. Thus, amyloid deposition is the strongest prognostic factor for cognitive deterioration in patients with SVaD [56].

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4 Gait in Vascular Cognitive Impairment

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4.1 Introduction

Gait function is an important factor in maintaining activities of daily living (ADL) in patients with older age or cognitive impairment. Abnormalities in gait and balance are found in about 35% of elderly over the age 70. Falls due to gait disturbances induce severe injury including fractures and traumatic brain injuries to the elderly, thereby increasing health costs and further promoting cognitive decline [1]. People with gait disturbances also show a faster rate of cognitive decline. However, there is not much research on gait compared to cognitive function. Their clinical features differ according to the degree and characteristics of the vascular insult. For example, when a brain lesion occurs in a nigral or brain stem region, parkinsonism can appear but unilateral, and gait disturbances are not prominent. White matter hyperintensities (WMH), on the other hand, is known to cause slow progression of gait disturbance [2]. Therefore, in this chapter, we describe the characteristics of gait [3] in vascular cognitive impairment and consider its pathophysiological mechanisms.

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4.1.1 Gait Cycle (Fig. 4.1)

- Right heel strike: gait cycle begins when one heel strikes the ground.
- Left toe off: supported by the stance of the right leg, body weight shifts forward as the left leg flexes at the hip and knees.
- Left leg swing: left leg swings forward.
- Left heel strike: left heel strikes the ground.
- Right toe off: weight then shifts forward onto the left leg, right leg flexes at the hip and knees.
- Right leg swing: right leg swings forward.
- Right heel strike: again, the right heel strikes the ground.

4.1.2 Examination of Gait

Observe individuals as they walk in a straight line and note if there is any difficulty in rising from a chair, initiating gait, or turning.

- Record the components below:
  - Velocity: distance covered in a given time
  - Cadence: steps per minute
  - Stride length: distance covered by the gait cycle
  - Step length: distance covered during the swing phase of a single leg
  - Step width or base: distance between the left and right feet while walking

S.-H. Lee, J.-S. Lim (eds.), *Stroke Revisited: Vascular Cognitive Impairment*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1433-8_4

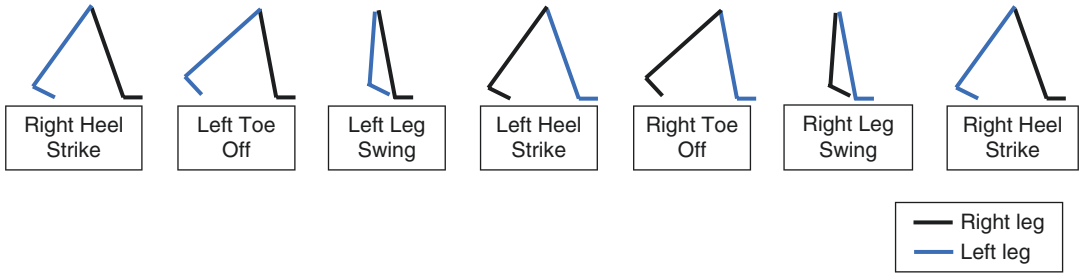

Fig. 4.1 Gait cycle

- Observe posture, arm swing, the height of each step, leg stiffness, or side-to-side lurching.
- Check muscle strength and tone in the legs, sensation, and reflexes.
- Test for the Romberg sign, tandem gait, and heel or toe walking.

4.2 Relationship Between Gait and Cognition

Decreases in gait are associated with declines in cognitive function [4] and might be an early sign of dementia [5]. Similarly, a decrease in gait velocity could predict persistent cognitive impairment [6]. Unsteady gait, frontal gait, and hemiparetic gait are related to the risk of vascular dementia in particular [7].

4.2.1 Cognitively Normal Elderly

Executive function is associated with decreased gait velocity, slower pace, reduced cadence, and gait variability. Especially, the degree of stride time variability, which is a sensitive marker of gait stability, is related to executive dysfunction. Immediate memory is linked to gait dysfunction and falls. Worse memory function is associated with reduced cadence and impaired gait velocity in single and dual task conditions. A meta-analysis showed there is also a correlation between faster gait speed and better performance on memory tests. However, the relationship between memory function and gait ability is not consistent. Visuospatial function is correlated with gait velocity and double support phase variability, which is associated with fall risk. Slower processing speed is associated with poor performance on many gait measures, including gait velocity, rhythm, step time, step length, and double support phase variability [8].

4.2.2 Cognitively Impaired Elderly

Executive dysfunction is associated with reduced gait speed and increased variability in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Only the executive function component of cognitive function is associated with a longitudinal decrease in gait speed. Lower episodic memory is associated with increased dual task cost in both patients with amnestic and non-amnestic MCI, which represents deterioration in motor performance [8].

4.2.3 Stroke Patients

Patients with TIA or minor stroke show worse performance on turn time (increases), step length, gait speed (slower), and double support (prolonged). That means people with TIA or minor stroke have gait and balance dysfunction despite having no obvious physiological impairments [9]. The problem is poststroke patients with gait and balance problems show an increased risk of developing cognitive dysfunction. This relationship can be explained by the hypothesis that deficits in attention, executive function, and motor processing functions induce gait dysfunction in stroke patients [10–12].

Therefore, gait speed and other motor signs can be used as predictors of future cognitive impairment development [10, 13].

On the other hand, stroke patients present with hemiparesis including foot drop, which induces poor ambulation [14]. Poor ambulation is also associated with greater cognitive impairment.

4.3 Neural Basis of Gait Disturbance in Cognitive Impairment

4.3.1 Hippocampus

Hippocampal atrophy is mainly associated with memory dysfunction, but the hippocampus is also strongly associated with gait. The hippocampus contributes to sensorimotor integration that combines internally and externally generated sensory information into voluntary motor activity [15]. Internally and externally motor-related sensory information are related to the head direction essential for spatial orientation and navigation [16]. The hippocampus also forms the orientation of the body in space and incorporates visual, vestibular and proprioceptive sensory signals, and contextual information into the spatial map [17, 18]. The hippocampus is functionally correlated with the prefrontal cortex, mediated through the entorhinal cortex and the nigrostriatal system.

4.3.2 Prefrontal Cortex

The prefrontal cortex is known as an important area for executive function including attention and working memory. The prefrontal cortex receives information from virtually all sensory systems and has preferential connections with motor processing structures. It has an important role in the cognitive control of motor performance [19]. Its function is enhanced during arousal, and it is vulnerable to normal aging. The prefrontal cortex is additionally involved in motor performance in the elderly. The elderly are more likely to depend on bilateral activation of the frontal cortices during motor performance [20]. The prefrontal cortex has a role in gait through its connections to the striatum and hippocampus.

4.3.3 Periventricular White Matter

In the periventricular white matter, there are circuits that connect to distant parts of the brain. They include cortico-cortical circuits, such as the fronto-hippocampal circuit, and cortico-subcortical circuits, such as the fronto-striatal system. Cognitive impairment due to disconnection of periventricular white matter could be a risk factor for gait disturbances. For example, patients with impaired executive function including divided attention cannot safely cross a busy street by foot [21].

4.3.4 Corpus Callosum

The genus of the corpus callosum connects to the prefrontal cortex and has a role in the cognitive function required to prepare motor responses [22, 23]. The splenium of the corpus callosum is connected to the superior parietal and occipital cortices that are important for the integration and interhemispheric transfer of visual and somatosensory inputs [23].

4.3.5 Cerebellar Peduncle

The superior cerebellar peduncle is associated with gait. The superior cerebellar peduncle has predominantly efferent projections to the premotor and primary motor cortices. In addition, it has a role in mental rehearsal of movement and motor learning. Whereas, the inferior cerebellar peduncle includes both cerebellar efferent and afferent fibers to and from the vestibular nuclei that carry information about eye movements and the orientation of the head and body as well as afferent spinal fibers carrying ipsilateral proprioceptive information important for posture, locomotion, and muscle tone control. It is associated with mobility impairment but not with gait. The middle cerebellar peduncle contains connections

from the pontine nuclei to the cerebellum carrying information from the cerebral cortex, mostly from the motor and somatosensory areas. However, the middle cerebellar peduncle is not associated with mobility impairment [24].

4.3.6 Cingulum

The cingulum is frequently associated with slowing of gait. The cingulum is interconnected with the cingulate gyrus and the dorsal and medial prefrontal cortices, which have a role in converting short-term memory to long-term memory and cognitive function [25]. The cingulum affects gait through reduced cognitive function rather than as a direct effect [26].

4.4 Gait Disturbances Associated with Small Vessel Disease

4.4.1 White Matter Hyperintensities (WMH)

WMH burden is associated with gait disorders. WMH has an effect on gait, according to location and severity. Especially, white matter lesions in the frontal lobe, the centrum semiovale, the posterior limb of the internal capsule, and the genu and splenium of the corpus callosum are related to gait dysfunction [27]. WMH is also associated with low cerebellar volume [28]. There is also a dose-effect relation between WMH severity and gait velocity [28]. A longitudinal study showed both baseline WMH and WMH progression predict increased fall risk [29, 30]. A population-based study showed that the relationship between WMH burden and gait function is constant in both middle and late ages [28].

WMH is linked to gait velocity, stride length, and step width [27]. Another study reported that WMH was associated with most spatiotemporal gait parameters and was borderline significant for variability in stride length. Especially, WMH in the sub-lobar (basal ganglia, thalamus, internal and external capsule, insula), limbic areas, and frontal lobe were related to a lower gait velocity, due to a shorter stride length [28]. However, the association between WMH and cadence was not significant [26]. This suggested that cadence was less influenced by WMH than stride length, and it was a similar feature seen in Parkinson's disease and normal pressure hydrocephalus.

Periventricular WMH predominantly located in the frontal lobe was associated with lower gait velocity, shorter stride length, and broader stride width. Frontal WMH contained fibers connected to bilateral prefrontal cortex [26]. Periventricular WMH was more associated with a clinical rating gait scale than deep WMH [31].

Deep WMH were associated with dual task gait speed, and this relationship was mediated by global cognition and executive function [32]. Increased WMH volumes might result in a disruption to the deep frontal-subcortical neuronal networks that interconnect various cortical areas, which is likely to have a direct impact on gait [33].

4.4.2 Lacunar Infarction

Lacunar infarction is also associated with slower gait and a lower volume of supratentorial white matter [28]. Similar to WMH, lacunar infarction location and severity influence gait. Lacunar infarcts in the thalamus and frontal lobe are associated with lower gait velocity due to, respectively, a shorter stride length and lower step frequency. Lacunar infarction in the brain stem is also related to lower cadence [34]. There is a dose-effect relation between the severity of lacunar infarcts and gait velocity. Like WMH, lacunar infarction is also independently associated with most spatiotemporal gait parameters and is borderline significantly associated with stride length variability [28].

4.4.3 Cerebral Microbleeds (CMB)

A higher number of CMB are associated with lower gait performance. CMB are independently related to shorter stride length and borderline

significantly associated with a longer double-support percentage. CMB in the frontal and temporal lobe and basal ganglia are significantly related to shorter stride length. And CMB in the temporal lobe shows an association with lower gait velocity. CMB in the thalamus are also related to gait [35].

4.5 Gait Disturbance Associated with Vascular Cognitive Impairment and Vascular Dementia

4.5.1 Vascular Cognitive Impairment

Subcortical VCI is associated with reduced cadence, increased variability of single and double support times, and a reduced single support phase [36]. Patients with vascular cognitive impairment no dementia (VCIND), a preclinical stage of SVaD, walk more slowly and have lower static balance [37]. They show impaired dynamic balance performance, rigidity, and bradykinesia [38]. Combined with this feature, VCIND patients show gait disturbances and gait-related motor impairments.

4.5.2 Vascular Dementia

Compared to AD, vascular dementia (VD) patients show slower gait velocity and reduced step length. In a study, 79% of patients with VD showed gait and balance disorders, while 25% of patients with AD showed gait and balance disorders [39]. In a longitudinal study, all types of dementia patients showed a decline in mobility, but the progression rate was faster in VD than in AD. A faster physical decline was also observed in patients with the fastest dementia progression [40].

In SVaD, both lacunar and Binswanger types showed a gait disturbance classified as frontal gait [39]. Its manifestation was walking with a wide base, decreased velocity and step length, static and dynamic instability, truncal ataxia, disturbance in gait initiation, shuffling, and apractic-atactic gait. More severe disease was associated with more prominent gait changes [41].

4.6 Association Between Gait Disturbance and Falls in Cognitively Impaired Patients

Both cognitive dysfunction and gait disturbance are independent risk factors for falls. AD and VD patients fall more frequently than cognitively normal elderlys [42]. Interference under dual task conditions is a predictive marker for falls [43]. In cognitively normal elderlys, executive dysfunction is associated with a high risk of falling [44]. Attention, processing speed, and visuospatial performance are also related. In MCI patients, executive function and visuospatial function are linked to higher fall risk [45]. Among gait parameters, slower gait velocity and reduced stride length are the predictors of falls [46].

4.7 Treatment

4.7.1 Physical Activity

Physical activity is associated with reduced dementia risk. Physical activity improves cognitive function and gait in cognitively normal elders [47]. It also has a beneficial effect on cognition in MCI patients, while the results in dementia patients are less consistent. Moreover, there is insufficient evidence that exercise is effective in patients with VCI. Research on the effect of physical activity on gait is less frequent than on cognitive function. Larger and good quality studies are needed to identify the beneficial effects of physical activity on gait [8].

4.7.2 Cognitive Training

Several studies have shown that cognitive interventions, mainly based on dual task training, improve gait function. However, as previous

studies had small sample sizes and tasks were heterogenous, it is difficult to confirm this effect. The mechanisms and effects of cognitive training are still unclear. More systematic research is required [8].

4.7.3 Medications Used in Alzheimer's Disease

Both cholinesterase inhibitors and memantine have a lack of evidence. In AD, several studies of cholinesterase inhibitors showed gait improvement. However, its effect on VD patient gait is unclear [8].

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5 Behavioral and Psychological Symptoms in Vascular Cognitive Impairment

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5.1 Introduction

Through the very vigorous activity of International Psychogeriatric Association (IPA) behavioral and psychological symptoms of dementia (BPSD) taskforce led by Sandy Finkel, the concept and description of BPSD have advanced the understanding of behavioral phenomenology and neuropsychiatric symptoms in dementia [1]. This activity has encouraged more appropriate attitudes in caring for people with dementia and provided the opportunity to examine more rational approaches not only to therapy and management but also research. BPSD has some adverse effects on the lives of patients and their families [2]. BPSD is responsible for increased numbers of the early placement in facilities for person with dementia. It diminishes the quality of life, both for patients and caregivers, and causes excess disability in patient with dementia, more than it would be expected due to cognitive deficits alone. Besides, this increases the direct and indirect financial costs as well as caregivers' stress and burden significantly.

Cerebrovascular diseases include heterogeneous disorders that occur in various brain vessels [3]. Cerebrovascular disease is known to be the second most common cause of acquired cognitive impairment including dementia. It is also presumed that cerebrovascular disease participates in cognitive decline of neurodegenerative dementia. It has been known that prevalence of Alzheimer's disease is approximately 50% and that of vascular dementia is 25–30% using traditional diagnostic classification criteria [4]. Several hospital-based studies demonstrated that up to a third of stroke patients had dementia within 3 months of stroke [5]. Concepts of vascular dementia have historically been based on stroke and the multi-infarct model [3].

However, it has been continuously recognized that various vascular pathologies can also cause cognitive impairment or dementia [6–8]. Therefore, the current definition of vascular dementia should be expanded because of the important role of cerebrovascular disease in several cognitive disorders, including hereditary vascular dementia, multi-infarct dementia, post-stroke dementia, subcortical ischemic vascular disease, mild cognitive impairment, and neurodegenerative dementia [4].

The awareness of the close relationship between vascular dementia and Alzheimer's disease has also increased. Recently, hypertension [9, 10], diabetes [11, 12], smoking [13], and hypercholesterolemia [14, 15] have been considered risk factors in AD as well as in vascular dementia. Also, vascular dementia and Alzheimer's disease pathologies work together [16], and mixed dementia of these disorders is observed in most populations [17].

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S.-H. Lee, J.-S. Lim (eds.), *Stroke Revisited: Vascular Cognitive Impairment*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1433-8_5

In order to develop solutions to traditional knowledge, concept, and additional questions about vascular dementia, IPA has engaged in special meetings on vascular cognitive impairment with worldwide experts of this field [4]. Also present were representatives from Alzheimer's Disease International, the World Federation of Neurology Dementia Study Group, the US Food and Drug Administration, and the European Commission for Medicinal and Pharmaceutical Compounds [4]. During the series of meetings, the current state of scientific knowledge on vascular brain burden was checked, and the core topics necessary for research and treatment for this area were discussed [4]. Traditional dementia standards are based on the concept of Alzheimer's disease and require a significant memory impairment that is not necessarily the primary symptom of vascular dementia. Therefore, clinically significant cognitive impairment associated with vascular disease does not meet these criteria [4]. The term "vascular cognitive impairment" for the prevention of scientifically strict definitions of vascular dementia can cover all types of cognitive disorders, regardless of severity, which are associated with or attributed to cerebrovascular disease. Consequently, this term includes vascular cognitive impairment without dementia and vascular mild cognitive impairment primarily suspected of vascular basis. Vascular cognitive impairment is caused by a variety of cerebrovascular diseases including multiple cortical infarcts, multiple subcortical infarcts, or both, silent infarcts, strategic infarcts, small-vessel disease with white-matter lesions, and lacunes [4].

Here we review the differences in clinical manifestation, prevalence, and mechanism of neuropsychiatric symptoms between vascular cognitive impairment and other dementias and differences in characteristics of these among subtypes of vascular cognitive impairment.

5.2 Behavioral and Psychological Symptoms After Stroke

Characteristics and pathogenesis of the neuropsychiatric symptoms after stroke are thought to be significantly different from those of BPSD in vascular cognitive impairment. Therefore, based on the papers reported so far, we will review the differences between BPSD in vascular cognitive impairment and neuropsychiatric symptoms after stroke.

Traditional classification of neuropsychiatric symptoms after stroke includes catastrophic reaction or voluntary dysregulation of emotion, depression, apathy, anxiety, psychosis, and aggressiveness [18, 19].

5.2.1 Voluntary Emotional Dysregulation After Stroke

Outburst after stroke can be triggered by usually nonspecific stimuli without any subsequent change in mood. Emotional dysregulation can be expressed as forced laughing or crying that is beyond social control [18]. Not only does it distress and embarrass the patient but also upset relatives and carers. Furthermore, it may interfere with rehabilitation [18].

A variety of terms have been used such as pathological laughing and crying, pseudobulbar affect, emotionalism, emotional lability, involuntary emotional expression disorder, and post-stroke emotional incontinence [19]. Pseudobulbar affect, one of most commonly used terms, includes pseudobulbar crying, laughing, weeping, and pseudobulbar palsy. However, this term is considered inappropriate because episodes may occur without pseudobulbar palsy [20] and symptoms are not always associated with the corticobulbar tract [21]. Pathological crying or laughing used by Wilson [22] has been described as exaggerated, forced, involuntary, uncontrollable laughing or weeping [19], but this is also inappropriate because it can also occur in other brain pathologies including gelastic epilepsy [23] and some psychiatric disorders not related to brain pathologies such as hysteria or depression [24]. Emotional lability or affective lability is used to indicate symptoms similar to pathological laughing and crying [25]. Emotional incontinence is another term frequently used [19]. It includes a broad range of symptoms, from simple excessive emotional display to severe pathological laughing or crying, and

clearly indicates that they are related to neurologic disorders.

The prevalence of post-stroke emotional incontinence ranges 6–34% of stroke patients [19]. Frequency of emotional incontinence after stroke is 11–35% [25]. This seems to more often develop in the subacute stage than in the acute or chronic stage [19].

Recent advances in brain imaging technologies have shown that lesions affecting frontal-internal capsular-pontine base circuitry most often produce post-stoke emotional incontinence [19]. Cerebellar, basal ganglionic, and thalamic lesions are also occasionally associated with post-stroke emotional incontinence. These symptoms have been known to be associated with lesions in the frontal lobe, the pons, and the medulla [25]. Stroke-induced disruption of the serotonergic raphe nuclei in the brain stem or their projections may cause emotional incontinence. The development of emotional lability has also been associated with cognitive impairment and large lesions on imaging.

5.2.2 Depression After Stroke

Depression is the most common psychiatric disorder that occurs after stroke. Many studies have demonstrated high rates of depression in the year following stroke, with rates of 30–40% in the first year and most (perhaps 80%) cases developing in the first few months following stroke [26, 27].

Stroke patients frequently complain of insomnia, loss of appetite, poor concentration, loss of libido, and poor energy. However, one of the most challenging problems in neuropsychiatry is how to diagnose depression when the symptoms of neurological illness overlap with those of the affective disorder [28]. A 2-year follow-up study found that suicide ideation, idea of reference, and pathological guilt were more prominent in acute stroke patients compared to those with DSM-IV major depression [29]. This study also found 100% sensitivity of DSM-IV criteria for major depression during acute stroke period and 96% sensitivity at the 2-year follow-up. Another study performing a factor analysis of ten depressive symptoms in depressed and nondepressed stroke patients found no significant difference between post-stroke depression and primary major depressive disorder for either psychological or somatic symptoms of depression [30]. The effect of depression on rehabilitation after stroke was proven by the longer length of hospital stay in stroke patients with depression compared to those without depression [31].

There are several studies investigating causative factors for post-stroke depression. Some studies investigated lesion location associated with depression after stroke. Through a follow-up study of 103 patients for 2 years, Robinson and Price reported that frontal lobe infarctions in the left hemisphere were associated with depression but that demographic variables and cognitive impairment were not associated with depression [32]. A comparison study of cortical and subcortical lesions in the production of post-stroke depression reported that stroke patients with left anterior lesions, either cortical or subcortical, had significantly greater frequency and severity of depression than those with any other lesion location [33]. And this study found that a strong correlation between the severity of depression and proximity of the lesion to the frontal pole was observed for both left cortical and subcortical groups. In a large-scale systematic review of 48 studies, there was no evidence of a positive relationship between lesion location and post-stroke depression [34]. The pooled (random effects) relative risk of depression after a left hemisphere stroke, compared with a right hemisphere stroke, was 0.95 (95% CI 0.83–1.10). For depression after a left anterior lesion compared with all other brain areas, the pooled (random effects) relative risk was 1–17 (0.87–1.62). A meta-analysis of studies regarding lesion location for post-stroke depression found that there was a significant inverse correlation between severity of depression and distance of the lesion from the frontal pole among 163 patients with left hemisphere stroke but not among 106 patients with right hemisphere stroke [35]. Later studies regarding lesion location related to post-stroke depression have been conducted, but the results were inconsistent.

There are several studies about time since stroke as main confounding factor for development of post-stroke depression. Shimoda and

Robinson reported that the frequency of depression 2 weeks after stroke was significantly higher for patients with left hemisphere strokes compared with those with right hemisphere strokes, but there was no significance of between-group differences in the frequency of depression at 3–6 months and 1–2 years after stroke [36]. A significant association between post-stoke depression and both physical and functional deficits has been consistently demonstrated, but this association is a complex one [28]. A significant association between post-stroke depression and more severe cognitive impairment has been consistently demonstrated in both hospital and community setting [28, 33, 37–39]. Although hypercortisolemia has been known to be associated with post-stroke depression, the underlying mechanism except for disruption of the fronto-subcortical structures remains unclear [40]. A past history of depression, a positive family history, social isolation, and larger volume of infarction have all been associated with the development or depression [26, 41–43]. However, there is a little more consistency regarding these risk factors.

Conclusively, depression after stroke appears to be a complex mixture of non-stroke factors (past and family psychiatric history, social functioning, possibly sex) and stroke-related factors which may include early emotional disturbance, intellectual handicap, and, possibly, lesion location [18].

5.2.3 Anxiety

Anxiety after stroke occurs commonly but has received only relatively little attention in clinical and research field. Impact, clinical correlations, and management are less understood than those of post-stroke depression [44].

Anxiety is present in at least 20% of stroke patients already in the acute phase and once present tends to run a chronic course [44]. Examining a series of 309 admission to a stroke unit for anxiety symptoms, Castillo et al. reported that patients were divided into groups of no anxiety (59.2%), worried but not fulfilling generalized anxiety disorder (GAD) criteria (13.9%), and GAD (26.9%) [45]. They also suggested that anxiety disorder (independent of depression) is not related to background characteristics or to severity of impairment but is, in part, influenced by the brain structures that are injured. Follow-up studies of psychiatric patients with panic disorder have shown an abnormally high mortality rate in men due to cardiovascular and cerebrovascular events [46]. These studies reported that in the New Haven portion of the Epidemiologic Catchment Area program, the risk for stroke in persons with lifetime diagnoses of panic disorder was over twice that in those with other psychiatric disorders or no psychiatric disorder. Fiedorowicz et al. found in a representative cohort of 5692 patients that vascular disease and risk factors (diabetes, hypertension, and obesity) were associated with anxiety (generalized anxiety disorder, post-traumatic stress disorder, or obsessive-compulsive disorder) and that anxiety disorders were more strongly associated with vascular disease in men [47]. Angstrom performed a 3-year follow-up study of generalized anxiety disorder in stroke patients and found that the initial high prevalence of 28% did not significantly decrease throughout the 3-year follow-up period. Less than a quarter had recovered at 1 year, suggesting it to be a chronic disorder [48].

Clinical manifestations related to anxiety after stroke are ruminating worries about recurrence of stroke or limitation of activities of daily living [44]. Sudden panic-like outbursts of anxiety may be triggered by fear of falling. Agitated anxiety may occur in sudden complex situations that a patient with cognitive difficulties finds overwhelming, typically in situations where the disabled individual is assisted in daily life. Numerous physiological arousal symptoms associated with anxiety may accompany, such as heart pounding, shortness of breath and choking sensation, numbness and tingling, nausea, and increased muscle tone. A study for ethical analyses of cognitive, emotional, and social sequelae of stroke showed that psychological aspects of stroke adaptation include the risk for depression and anxiety, changes in identity and personality processes, and potential for social isolation [49]. Depression and anxiety are heterogeneous constructs and can

affect individuals' emotional functioning and cognitive abilities. Fearful emotions and worry are normal emotions in patients with acute stroke, but they often continued despite physical recovery and sometimes develop into anxiety syndrome that seriously interfere with the patients' emotional and cognitive functioning and adaptation to the illness.

Anxiety and depression often occur simultaneously. The suggestion that an anxiety-related location is the right cerebral hemisphere [45] or basal ganglia [50] is interesting, but not widely acknowledged unlike in depression. The common pathophysiological mechanism behind different anxiety syndrome may be dysregulation of the neurocircuitry that controls the primary emotion (fear), thus leading to a more pervasive state (anxiety) [51]. The classical limbic structures and regions associated with anxiety disorders are the amygdala, the hippocampus, and the insula. Neuroanatomical and neuroimaging research in anxiety disorders has centered on the role of the amygdala, reciprocal connections between the amygdala and the prefrontal cortex, and, most recently, alterations in integration of internal bodily information by the anterior insula [52]. Amygdala activation in post-traumatic stress disorder, social phobia, and specific phobia is relatively heightened. Activation in the insular cortex appears to be heightened in many of the anxiety disorders. Unlikely other anxiety disorders, post-traumatic stress disorder is associated with diminished responsiveness in the rostral anterior cingulate cortex and adjacent ventral medial prefrontal cortex.

5.2.4 Apathy

Apathy is a disorder of motivation [53]. Patients with apathy show difficulties in initiating, sustaining, or finishing any goal-directed activity. They lose self-activation or self-initiated behavior and may present emotional indifference. Traditionally, apathy has been viewed as a symptom indicating loss of interest or emotions. An apathy syndrome is defined as a syndrome of primary motivational loss, that is, loss of motivation not attributable to emotional distress, intellectual impairment, or diminished level of consciousness. Loss of motivation due to disturbance of intellect, emotion, or level of consciousness defines the symptom of apathy [54]. The major syndromes of diminished motivation are apathy, abulia, athymhormia, anhedonia, and/or emotional indifference [55]. Abulia is a severe form of apathy. This is a lack of will, expressed by absence or reduction of spontaneous acting and thinking [56, 57]. Athymhormia defines the loss of psychic, motor, or affective autoactivation [56, 57]. Anhedonia means the lack of pleasure or interest in activities that the patient once enjoyed. In other words, this is the inability to experience pleasure from activities usually found enjoyable, such as exercise, hobbies, singing, sexual activities, or social interactions. Emotional indifference represents a lack of emotions that usually arouse an individual [56, 57].

Apathy is frequent in stroke patients affecting one in every three patients [53]. A study investigating the frequency of apathy in 80 patients with cerebrovascular lesions found that 18 patients (22.5%) showed apathy, 9 patients of who were also depressed, and 18 patients (22.5%) showed depression in the absence of apathy [58]. Although depression and apathy may exist independent of one another, major depression (but not minor depression) was associated with an increased frequency of apathy. The neural mechanisms of apathy are postulated to involve the brain stem and forebrain circuits that mediate goal-directed behavior. The functions of these circuits provide a model for understanding a provisional classification of apathy syndromes into cognitive, sensory, motor, and affective subtypes [55, 59–61]. Cognitive apathy is a motivational disturbance with impairment of executive functions, related to dysfunction of the fronto-dorsolateral cortex. Motor apathy is a motivational disturbance with extrapyramidal motor dysfunction, due to an impairment of the motor-striate regions. Sensory apathy is a motivational disturbance, which is manifested also by anosognosia, due to a dysfunction of the right parietal or prefrontal cortex. Emotional apathy is without any of the previous associated disturbances, related to

dysfunction of neuronal circuits involving the amygdala and the cingulum.

Stroke lesions encompassing the frontal lobe, the cingulum, or subcortical structures such as the pallidus, internal capsule, caudate, putamen, and anterior or medial thalamic nuclei are associated with apathy [53]. Cognitive impairment is three times more frequent in apathetic than in non-apathetic patients [53]. There is no consistent evidence to support the association between apathy and right-sided stroke lesions [53].

5.2.5 Aggressiveness

Aggressive behavior might affect adversely interpersonal relationships and occupational functioning and cause legal problems [62]. Aggressiveness increases the length of hospital stay in rehabilitative settings, reduces the quality of life, and causes distress for the patients and their families [63]. It is one of the common causes for admission in psychogeriatric services and might substantially limit the patient's competency in self-determination. Aggressiveness can occur often in the acute, subacute, and chronic phases of stroke. This neuropsychiatric symptom is not only related to the emotion of anger directly but also associated with the anger trait, hostility, impulsivity, disruptiveness, confusion, agitation, anxiety, depression, and some cognitive changes which could be specific or not to the localization of the vascular lesion.

A variety of terms related to aggressiveness have been used, but these terms may have slightly different meaning [63]. Anger is a basic emotion characterized by indignation, dislike, belligerence, rage, or wrath as a dimension of feeling and attitude. In other words, this represents the emotional or affective component of the aggressive behavior. Trait anger is a personality trait, a general temperament of low threshold reactivity for angry feeling. Irritability is defined as the condition of being easily angry and correlates with a mood state that predisposes toward certain emotion (anger), cognitive state (e.g., hostile appraisals), and certain actions (aggression). Hostility is a cognitive dimension of anger and corresponds to a negative evaluation of persons and things accompanied with a desire to harm or attack them. Aggression means the translation of aggressiveness into its behavioral forms. Aggressiveness and related states and behaviors are often associated with psychomotor agitation and appear disproportionate to the context. For aggressive patients, the perception of the environment and interpersonal interactions are often distorted by states of threat, victimization, or disrespect, and in this context, provocation and retaliation are critical factors. Aggressiveness and aggression can manifest with verbal or motor behaviors against objects, people, and toward self. Impulsivity is a multidimensional concept that involves the tendency to act quickly without reflection, overthrowing normal control mechanisms on emotions, behaviors, and cognition. The psychological construct of impulsivity includes deficits in planning (inability to plan ahead), cognition (making up one's mind quickly), and regulation of motor acts (acting without thinking). Disruptiveness corresponds to a subjective evaluation of the examiner on the intensity of the aggressiveness of the examined. For example, physical aggression is the most disruptive from of aggressiveness.

Post-stroke aggression has not been systematically studied. Paradiso et al. reported that subjective anger and aggression were common after stroke and that outbursts were associated with left anterior hemisphere and cognitive impairment [64]. This study examined a population of patients hospitalized with acute stroke. The percentage of patients with cognitive impairment in the angry outburst group (66%) was greater than the control group (22%). Chan et al. found that 25% of patients showed irritability or aggression [65].

Post-stroke disorders that might manifest with aggressiveness include dysexecutive syndrome, emotional dyscontrol and disinhibition, loss of empathy, catastrophic reactions and Wernicke aphasia, personality changes, mania, delusion and misidentification, delirium, misoplegia and somatoparaphrenia, depression, anxiety, pain and fatigue syndrome, and vascular dementia [63].

The link between aggressiveness and regional brain dysfunction remains still poorly understood

[63]. Angered patients had a higher frequency of anterior left hemisphere lesions (46.7%) compared with controls (29.4%) [64]. Irritability or aggression was related to lesions proximal to the frontal pole [65]. Kim et al. reported that inability to control anger or aggression after stroke was present in 47 of 145 patients (32%) and was closely related to motor dysfunction, dysarthria, emotional incontinence, and lesions affecting frontal-lenticulocapsular-pontine base areas [66].

5.3 Behavioral and Psychiatric Symptoms in Vascular Cognitive Impairment

Numerous behavioral mental symptoms have been mentioned within the context of dementia, but classification of these symptoms has been subject to confusion due to the various terms and meanings applied [18]. The International Psychogeriatric Association has developed the concept of behavioral and psychological symptoms in dementia (BPSD) to unify terminology for research in this field [67]. BPSD is defined as signs and symptoms of disturbed perception, thought content, mood, or behavior that frequently occur in patients with dementia.

Several classification methods have been proposed. One way is to classify these symptoms into psychological symptoms such as delusion or hallucination that can be identified through interviews and behavioral symptoms that can be found through observation, for example, aggression or agitation [67]. Frisoni et al. described a three-factor model of BPSD in AD: mood syndrome (anxiety, apathy, and depression), psychotic syndrome (irritability, lability, delusions, hallucinations, and agitation), and frontal syndrome (euphoria and disinhibition) [68]. Aalten et al. identified four neuropsychiatric subsyndromes: hyperactivity, psychosis, affective syndrome, and apathy [69]. Bettney et al. have divided BPSD into three distinct subsyndromes: mood/apathy (e.g., depression, apathy, sleep disturbance), hyperactivity (e.g., agitation, euphoria, irritability, disinhibition, aberrant motor behavior), and psychosis (e.g., hallucination, delusion) [70]. A previous study suggested three main BPSD syndromes: agitation (including aggression and restlessness), psychosis, and mood disorders [71].

5.3.1 Psychosis

Within the context of dementia, Burns et al. classified psychosis into three main categories: delusion, hallucination, and delusional misidentification [72].

Delusion has been classically defined as false, unshakable ideas or beliefs that are held with extraordinary conviction and subjective certainty [72]. The types of delusions that occur in dementia include delusion of theft (the belief that one's possession is being hidden or stolen), delusion of abandonment (the belief that someone is going to be abandoned, deserted, or thrown out of their home), delusional jealousy (the belief that one's partner is having an affair), delusion of reference (the belief that somebody is being talked about), and delusion of persecution (the belief that somebody else is to bring harm to somebody) [73]. To be defined as a delusion, it must be reiterated on at least two occasions more than 1 week apart for differentiation of this symptom from confabulation and delirium [72]. Hallucinations were described as percepts in the absence of a stimulus and have to be reported directly by either the patient or indirectly via an informant to be classified as a psychotic presentation (i.e., they could not be inferred from observed behaviors) [72]. Delusional misidentification is a kind of peculiar delusions, strictly speaking, a false belief or thought due to recognition failure on external stimuli [72]. Delusional misidentification include the Capgras syndrome (the belief that a person, object, or environment has been replaced by a double or replica), delusional misidentification of visual images (the belief whereby figures on television or in photographs are thought to exist in the real environment), delusional misidentification of mirror images (the perception of one's reflection as the image of a separate person), and the phantom boarder delusion (the belief that strangers are living in or visiting the house).

Psychosis in vascular cognitive impairment was of less interest in most studies regarding the frequency compared to that in Alzheimer's disease. The most commonly studied psychotic features are delusions, which have a mean prevalence of 33% [18]. A comparative study regarding to neuropsychiatric aspects between multi-infarct dementia and Alzheimer's disease reported that the nature and prevalence of delusion were not significantly different between two types of dementia (30% of patients with Alzheimer's disease and 40% of those with multi-infarct dementia) and that delusion was primarily paranoid in type and involved elementary misbeliefs concerning theft or infidelity [74]. A previous study indicated that delusion had occurred in 45% of patients with Alzheimer's disease and in 38% of those with multi-infarct dementia, occurring most frequently during the first year of illness [75]. Patients who experienced psychiatric symptoms showed higher MMSE scores and were less impaired in functional disability measures. There were no significant differences between AD and MID patients: 53% of psychotic symptoms were found to be paranoid delusions while 47% were delusional misidentification. One study examining a hospital case register sample of 92 patients with vascular dementia found an overall prevalence of psychosis of 46% (22% visual hallucination, 36% delusions, 23% delusional misidentification) [76]. An investigation regarding neuropsychiatric symptoms of dementia patients in a clinical setting showed that patients with vascular dementia exhibited a high incidence of paranoid and delusional ideation (71.9%) [77]. The Lund Longitudinal Dementia Study identified that hallucination and delusions were more prevalent in the large-vessel vascular dementia compared to the small-vessel one [78]. Another study found that patients with small-vessel vascular dementia had more hallucination, apathy, and aberrant motor behavior than those patients with large-vessel vascular dementia [79]. Lyketsos et al. reported a lower prevalence of key psychotic symptoms in patients with vascular dementia compared to those with Alzheimer's disease [80]. Flynn et al. suggested that delusional patients had more behavioral disturbance such as aggression than non-delusional patients. Furthermore, they exhibited more severe cognitive impairment [81].

5.3.2 Depression

Since depression in dementia may considerably cause distress to the patients, this can put stress on the carers and carry an adverse prognosis with regard to morbidity and mortality.

It is important to realize that the relationship between depression and dementia is complex and that differential diagnosis is not always straightforward [82]. Depression in the absence of dementia can still be associated with cognitive impairments which are sometimes misdiagnosed as dementia [83]. However, it is one of the symptoms that occur commonly in various dementia patients. Therefore, particularly in the early stage of dementia, clinical distinction between pure depression and depression in dementia is often difficult. In the absence of a coexistent depression, particular signs and symptoms of dementia (such as apathy, agitation, or sleep disturbance) can be wrongly diagnosed as signifying the presence of a depressive illness [82].

Depression is one of the common neuropsychiatric symptoms in patients with dementia, but there are several problems in the diagnostic criteria. Terminology can be confusing, because the word "depression" can be used in a lay sense to mean normal transient sadness, as a means of describing the symptom of depression mood, and as a term defining a psychiatric illness with a characteristic clinical profile and course [82]. It is usually quite easy to separate the transient sadness which is a part of normal experience from pathological changes in mood. Transient feeling of sadness are common, usually occur in reaction to external events, are experienced by the individuals and those around them as part of "normal" experience, and are not associated with other features such as sleep and appetite disturbance, feelings of self-harm, or loss of interest in other activities. In contrast, clinically significant depressed mood is characterized by a feeling of low mood which differs both in quality and dura-

tion from that of normal sadness. The quality is more intense, less inclined, to vary over the day. The diagnosis of depression would need to be accompanied by other signs and symptoms of depression such as anhedonia, irritability, appetite loss (gain), weight loss (gain), sleep disturbance, decreased energy, feeling of worthlessness or guilt, difficulty thinking, suicidal ideation, agitation, etc. [82].

However, the differential diagnosis of dementia is often difficult to differentiate due to various causes [82]. Patients with aphasia are unable to express depressed mood, even if they have typical depression [82]. Some symptoms, particularly nighttime disturbance, appetite changes, apathy, loss of motivation, and agitation, are all very common as part of a dementing illness and do not necessarily indicate the presence of coexisting depression [82]. The problem then is difficult to decide whether such symptoms are part of a depression or dementia [82]. One useful guide is whether there has been a change from previous functioning. A demented person who suddenly becomes agitated, or whose agitation increases significantly, is far more likely suffering from a depressive episode. The occurrence of other features of depression is also important. An increase in agitation on its own would be unlikely to be caused by depression. However, if agitation is accompanied by depressed mood, tearfulness, early morning awakening, and loss of appetite, diagnosis of depression would be clearer. A past or family history of depression may be helpful in the differential diagnosis of depression. In general, major life events have been known to be independent of depression in demented patients. On the contrary, clinical experience indicates that at least those with milder degrees of cognitive impairment are likely to develop depressive episodes after major life events such as a bereavement or change in accommodation. It is also important to rule out other general medical conditions which may cause depressive symptoms [82]. These include a number of widely prescribed drugs, including steroids, beta-blockers, digoxin, and NSAIDs, and conditions such as hypothyroidism, electrolyte disturbances, infection, myocardial infarction, hip fracture, and neoplasia. Another reason for the difficulty in distinguishing depression is that the clinical manifestations of depression in later life are significantly different from those in young people [84]. Older depressed patients may often deny feeling sad, report a lack of feeling or emotions, or acknowledge a loss of interest and pleasure in activities. Furthermore, depressive symptoms in dementia, particularly in Alzheimer's disease, are different from those in the non-demented elderly and considered to be an atypical syndrome of depression such as irritability or social isolation [85]. Dementia patients with depression significantly have more "motivational symptoms" and had a lower prevalence of "mood symptoms" [86]. Patients with Alzheimer's disease are more likely to report concentration difficulty or indecisiveness [87]. And they were less likely to experience sleep disturbances and feelings of worthlessness or excessive guilt during major depressive episodes. It is also necessary to differentiate between depression in dementia and "vascular depression" which was proposed in the late 1990s [88]. This "vascular depression" hypothesis postulates that cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes. Disruptions of prefrontal systems or their modulating pathways by single lesions or by accumulation of lesions exceeding a threshold are hypothesized to be central mechanisms in vascular depression [88].

In dementia, various behavioral psychological symptoms including depression are known to occur. Fewer studies have reported the very diverse frequency rates of depression in vascular dementia. The reasons why the results were not consistent for each study may be differences in sample size, method of selection, study design, and diagnostic criteria which strongly affect symptom frequency [18]. Some study examining anxiety, depression, and psychosis found that depression was significantly more common in patients with vascular dementia (19%) [76]. Another study of behavioral symptoms of 484 patients with vascular dementia reported that the prevalence rate of depression was 45% [79]. A recent study examining the relation between depression and dementia in older people found that depression and dementia frequently occurred

together. Depression occurred in up to 20% of patients with Alzheimer's disease and up to 45% of patients with vascular dementia [89]. Another recent study regarding neuropsychiatric symptoms in Alzheimer disease, vascular dementia, and mixed dementia identified that vascular dementia patients (48%) had significantly more depression than Alzheimer's disease (20%) [90]. However, what is much more consistent across studies is the difference between vascular dementia and Alzheimer's disease patients [18]. Certain studies of depression frequency have reported a higher prevalence of depression in vascular dementia, and some studies of severity also have suggested that depression was significantly more severe in patients with vascular dementia compared to those with Alzheimer's disease [91, 92]. An investigation of neuropsychiatric symptoms in different types of dementia showed high incidence of affective disturbances (46.9%) in vascular dementia [77]. In general, the prevalence of neuropsychiatric inventory (NPI) items is similar between Alzheimer's disease and vascular dementia. However, results using the logical regression model revealed that patients with vascular dementia were more likely to have delusion, while those with vascular dementia were more likely to have depression [80]. Comparison studies between the clinical profile in Alzheimer's disease and vascular dementia reported that depression and anxiety were more often in patients with vascular dementia than in those with Alzheimer's disease [93, 94]. A comparison study of behavioral differences between white matter lacunar dementia and Alzheimer's disease found that depression and apathy were the most frequent behavioral changes, occurring in 59 and 55% of patients with Alzheimer's disease and in 85% and 78% of patients with white matter lacunar dementia [95]. A systematic review of neuropsychiatric symptoms in vascular cognitive impairment revealed that depression and apathy were the most frequent BPSD, followed by irritability, anxiety, and agitation [96]. In white matter lacunar dementia, depression was not related to the severity of cognitive impairment [95].

There are three main themes underlining biological investigations in depression, and all of these have been examined in relation to depression in the context of dementia: dysregulation of the hypothalamic-pituitary-adrenal axis or hypercortisolemia, dysregulation of the monoamine systems (particularly serotonergic or noradrenergic system), and structural and functional changes in areas for the mood regulation (e.g., cingulate cortex, dorsolateral prefrontal cortex, and basal ganglia) [82].

5.3.3 Aggression and Agitation

Aggression is common among people with dementia [97]. Aggressive behavioral problems are one of the most common causes for neuropsychiatric help or institutionalization. Aggression threatens the safety of the patient with dementia and causes distress to the caregivers. Aggression can adversely affect the prognosis because of the side effects of psychotropic agents or secondary complications of accidents.

There is no generally agreed definition of aggressive behavior, particularly in patients with dementia. Most definitions of aggression include the notion of intention within them [97]. Possibly the most useful definition of aggression in the elderly with dementia is that "aggressive behavior is an overt act, involving the delivery of noxious stimuli to (but not necessarily aimed at) another organism, object or self, which is clearly not accidental" [98]. The determination of aggression should be based on the observed manifestations and should be avoided as far as possible in general assumptions that they are expected in patient with dementia [97]. In other words, whether an act is classified as aggressive or not should not be dependent on the consequence of the behavior, e.g., "someone being hurt." An operational definition of agitation has been developed by Cohen-Mansfield and Billing. They defined agitation as "inappropriate verbal, vocal or motor activity that is not explained by needs of confusion per se" [99]. They described that it always was inappropriate and manifested in three categories of inappropriateness: First, the person may be abusive toward self and other. Second, appropriate behavior may be performed with

inappropriate frequency, such as constantly asking questions. Third, behavior may be inappropriate according to social standards for a specific situation.

Physical aggression occurs in 18–65% of patients with dementia [97]. Up to 20% of the families of people with dementia report physical violence [100, 101]. Strong relationship was demonstrated between staff psychological disturbance and aggression from residents [100]. A study of behavioral and psychological symptoms in vascular dementia reveals that prevalence rate of agitation/aggression was 40% [79]. Furthermore, patients with large-vessel vascular dementia had a higher severity of agitation/aggression than those with small-vessel vascular dementia. A recent population study identified irritability in 18% of patients with vascular dementia and 20% of those with Alzheimer's disease [80]. Another study of neuropsychiatric symptoms in vascular cognitive impairment found that agitation/aggression appeared to be equally prevalent in cortical-subcortical vascular dementia (62.9%) and in subcortical vascular dementia (47.62%) and that agitation was significantly more prevalent in cortical-subcortical vascular dementia than in vascular cognitive impairment, no dementia (VCI-ND) [96].

In vascular dementia associated with ischemic white matter subcortical changes and lacunar infarction, the severity of aggression and irritability was correlated with cognitive decline [95]. Agitation and aggression were more common in participants with advanced dementia [80]. Aggressive behavior is a rare presentation of acute posterior cerebral artery stroke, which may be difficult to diagnose in patients presenting with hemianopsia as the only concomitant neurological sign. The postulated mechanisms include dysfunction of the limbic or serotoninergic system [102].

5.3.4 Apathy

A large multicenter clinical study investigating behavioral and psychological symptoms in vascular dementia revealed that apathy (65%) was the most prevalent symptom and that patients with small-vessel vascular dementia had a higher severity of apathy than those with large-vessel vascular dementia [79]. Another community-based study reported that apathy (27%), depression (24%), and agitation/aggression (24%) were the most common in participants with dementia [80]. Some studies regarding neuropsychiatric symptoms in vascular dementia showed the highest prevalence of apathy [103, 104]. Apathy domains in patients with cortical vascular dementia were significantly higher than those in the patients with AD [104]. However, other studies have demonstrated different results, for example, with the highest frequency of depressed symptoms, followed by agitation/aggression and apathy [80, 105].

Brain lesion related to apathy may involve the caudate, internal globus pallidus, putamen, or a part of wide circuit that includes the medial nucleus of the thalamus and certain frontal regions connected with the limbic system such as the anterior part of cingulate gyrus [53]. In subcortical vascular dementia, apathy was unrelated to the severity of dementia [95].

5.3.5 Anxiety

Depression has been the focus of research in patients with dementia, while anxiety has been of less interest relatively. Diagnosis has been a problem as none of the anxiety scales have been specifically validated in people with dementia [106].

A study of 158 dementia patients identified that 22% had subjective anxiety, 11% experienced autonomic anxiety, 38% experienced tension, 13% experienced situational anxiety, and 1.8% had panic attack. Tension and subjective anxiety of the specific symptoms appear to be common, but panic attacks are unusual [107]. Anxiety appears to be equally frequent in people with Alzheimer's disease and dementia with Lewy bodies [108]. A hospital-based study of 92 patients with vascular dementia identified a frequency of 72%, a significantly higher prevalence among those with Alzheimer's disease (38%) [76]. More than 50% of these patients had a generalized anxiety disorder, but only 4% experienced panic attacks. A quarter

of people experienced their anxiety in the context of a major depression. Lyketsos et al. reported significant anxiety symptoms in 19% of vascular dementia patients from a population sample [80].

In subcortical vascular dementia, anxiety was not related to the severity of dementia [95]. Cognitive impairment was significantly associated with the presence of anxiety symptoms [107]. Three main categories of anxiety symptoms were evident: anxiety related to depression, anxiety related to psychosis, and anxiety related to interpersonal situations. Severe vascular dementia patients (94%) were the most likely to be anxious [76].

There is little research on the causes of anxiety in dementia. Patients with milder cognitive impairment and insight of deficit may experience social anxiety [107]. Loss of cognitive and problem-solving skills in people with dementia makes many situations anxiety provoking [109]. No studies examined the biological correlates of anxiety, but Chen et al. reported a relationship between loss of 5-hydroxytryptamine receptors in the frontal cortex and anxious depression [110]. Given the link between white matter hyperintensities and late-life depression, anxiety in vascular dementia may be explained in this context. Furthermore, approximately half of people with anxiety disorders and dementia will have concurrent depression [111].

5.3.6 Hypomania

On the basis of DSM-5, symptoms of hypomania include abnormally and persistently elevated, expansive, or irritable mood and increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day [112]. Other features are inflated self-esteem or grandiosity, decreased need for sleep, talkativeness rather than pressure to keep talking, flight of idea, distractibility, and increase in goal-directive activity [112].

It can be developed de novo in the context of a dementia illness, particularly after a vascular insult, or may present in those with long-standing bipolar illness which has become more unstable with the onset of organic brain disease [18]. Hypomania is much less common in demented patients than depression [82].

There are very little data regarding specifically to vascular dementia [18]. A large multicenter study examining 484 patients with vascular dementia reported that the prevalence of euphoria was 6% [79]. In another study, a higher prevalence of euphoria was identified in VCI-ND than vascular dementia (7.14% vs. 3.13%) [113].

5.3.7 Abnormal Vocalization

Vocalizations are part of the spectrum of "negative" behavioral and psychological symptoms of dementia including passive restlessness, wandering, purposeless hyperactivity, apathy, social isolation, and withdrawal [114–116].

In clinical practice, abnormal vocalizations are usually seen in people with dementia who are residing in care facilities. The problem is usually referred to by care staff as "shouting," "screaming," or constant demands for "attention." The term "abnormal vocalization" sounds a little overelaborate; it does have the advantage of encompassing the broad range of manifestations, which include, for example, yelling/shouting, loud talking, mumbling, singing, chattering, sighing, howling, groaning, and shrieking. The different characteristics of the sound production may be important in identifying the cause of the problem and hence have implications for treatment [106].

Patients describe an inner urge or a local premonitory sensation, which increases anxiety or agitation. Anxiety and agitation are often relieved by performing the vocalization suggesting that these behaviors may provide a form of "self-soothing." Nearly all disruptive vocalization is related to a form of brain injury; most have dementia due to Alzheimer's disease or cerebrovascular disease [115, 116]. Disruptive vocalizers were more functionally impaired and were more likely to receive a diagnosis of dementia. They were also more likely to display a higher activity level and to experience sleep disturbance and to be prescribed neuroleptic medications [115]. In susceptible persons, vocalization can be triggered by a variety of stimuli, including the

physical environment, stress, anxiety, or caregiver behaviors [117].

In general, vocalizations are particularly common in residential care, nursing homes, and hospital environment [106]. However, there is considerable gap in frequency of these behaviors among people with dementia living in the community. A prevalence of 11–30% has been reported within care facilities [115, 116, 118]. A study found that 87% of people reported as having abnormal vocalizations by care staff experienced the problem at a clinically significant level that was disruptive to staff and other residents, of whom 75% experienced the behavior constantly [119].

5.3.8 Eating Disorders

Several eating disorders are recognized in the context of dementia, including a change in preference for sweet things (10–33%), increased (20–35%) or decreased (22–41%) food consumption, and inedible substances (3%) [120–122]. Other problems include difficulties with feeding (such as coordinating cutlery, messy eating, or drooling), forgetting that meals have been consumed, and forgetting to eat [106].

Inappropriate menu planning, depression, clinical and subclinical swallowing problems, and poor dental health and oropharyngoesophageal function can all be important associations of poor food intake or reduced appetite [106, 121, 123, 124]. Abnormal eating attitude, akin to those seen in anorexia nervosa, may be linked to low weight and reduced food intake in some people with mild cognitive impairment but are often not recognized [125]. Decreased food consumption was significantly associated with less severe cognitive impairment [12]. Eating of inedible substances and hyperorality appear to be associated with widening of the third ventricle, bilateral temporal lobe atrophy, and other clinical features of Klüver-Bucy syndrome in a study of patients with Alzheimer's disease [120]. Hyperphagia may be linked to increased caloric need in patients with hyperactivity such as wandering or frontal lobe pathology. However, it does not appear to cognitive impairment [126].

5.3.9 Inappropriate Sexual Behavior

In nursing homes, extreme sexual behavior is one of the most challenging behaviors in dementia. According to recent theoretical perspectives, extreme sexual behavior may be regarded as a part of disinhibited behavior or could be considered as an independent neuropsychiatric symptom [127].

In a multicenter study examining dementia people (n = 179) residing in nursing homes, multivariate analysis of covariance with gender showed that residents with observed extreme sexual behavior (n = 43) only showed a higher score on neuropsychiatric symptom "disinhibition," as compared to residents with non-observed sexual behavior (n = 136). These findings indicate that among residents with dementia, extreme sexual behaviors should not be considered as an independent neuropsychiatric symptom [127]. In a community-dwelling cohort of 97 people with dementia, a study reported a prevalence of 5% for inappropriate sexual comments, but none of the people assessed were displaying any inappropriate sexual behavior or had exposed themselves [122]. A systematic review regarding inappropriate sexual behaviors in dementia described that the most likely change is indifference [128]. This suggested that two types of inappropriate sexual behavior, intimacy-seeking and disinhibited behaviors, can occur in relation to dementia type and severity. They may usually be seen in moderate to severe stages of Alzheimer's disease and early stages of frontotemporal dementia.

However, in vascular dementia, little is known about the incidence of inappropriate sexual behavior.

5.4 Conclusion

Neuropsychiatric symptoms are also common in vascular cognitive impairment. However, because of the diverse location, size, and number of brain lesions causing neuropsychiatric symptoms as well as frequent atypical manifestations, there are many difficulties to define symptoms and localize brain areas. In addition, pathologic findings such as subcortical ischemic changes, which occur in

vascular cognition disorder, may also be found in neurodegenerative diseases including Alzheimer's disease, so it is difficult to specify neuropsychiatric symptoms in vascular cognitive impairment. Impairment of executive function, either indirectly caused by subcortical ischemic changes or directly influenced by vascular lesions on the frontal lobe, makes it difficult to distinguish from pure neuropsychiatric symptoms in dementia. Therefore, more active research in this field should be conducted to investigate the causes of these neuropsychiatric symptoms based on consistent and accurate epidemiologic findings.

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6 Cognitive Evaluation in Patients with Vascular Cognitive Impairment

Jae-Sung Lim

6.1 Introduction

Cognitive function testing is divided into screening tests and comprehensive tests, depending on the objective. The former is intended for screening patients with a cognitive problem, usually consists of tests that can be performed within 5–15 min, and is used mainly in large-scale epidemiological research. The latter is a collection of individual tests used to examine for more subtle cognitive dysfunction or to evaluate for abnormalities within specific cognitive domains. Generally, two or more tests are performed for each cognitive domain.

6.1.1 Conduction of Neuropsychological Evaluation

Before looking at each test individually, let us first look at the common principles that need to be applied when conducting any test. Cognitive testing should be performed in an environment where the patient and the examiner can focus on the examination. In order to prevent interference by the caregiver, only the patient and the examiner should participate. Any necessary clinical information can be obtained from the caregiver before or after the evaluation. The examiner should create a comfortable atmosphere that allows the patient to follow the instructions and to fully focus on the neuropsychological tests. If proper evaluation of the patient is not possible due to physical problems such as a hearing difficulty or decreased visual acuity, then these physical barriers should be overcome with hearing aids or glasses. In addition, if you suspect that the test has been affected for any other reason than cognitive impairment during the test, it is necessary to specify this information so that there is no error when interpreting the results later.

In patients with post-stroke cognitive impairment, the timing of when tests are usually performed is between 1 month and 6 months after the index stroke in order to avoid the interfering effects of the acute stroke. Several cohorts, including CASPER, CogFAST, DEDEMAS, GRECOG-VASC, STRIDE, and STROKDEM, perform testing at the aforementioned times [1]. The Canadian Stroke Best Practices recommendations state that all stroke patients should be regularly screened for cognitive impairment, although when this should occur is not specified [2]. Screening tests for cognitive impairment in acute stroke in high risk groups have also been proposed. Taking the symptoms of patients with

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S.-H. Lee, J.-S. Lim (eds.), *Stroke Revisited: Vascular Cognitive Impairment*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1433-8_6

neurological sequela, such as hemiparesis, into consideration, tests that can be conducted entirely verbally were designed, and their usefulness was reported on in several studies [3, 4].

6.1.2 Interpretation of Neuropsychological Evaluations

Interpretation of cognitive function tests involves the following four steps: (1) adjustment of cognitive score for demographic factors, (2) the type of score combination, (3) the statistical index used to determine a cutoff, and (4) the selection of the cutoff [5].

The abnormalities identified in a cognitive function test are interpreted by referring to the control study conducted in that language and region. As reported in a recent study, a single cutoff score is not universally applicable to all patients [6]. Depending on the age, sex, and level of education, patient abnormalities will vary, even if the patients receive the same score. With former diagnostic criteria, including the NINDS-AIREN criteria, the definition of cognitive impairment was not specified, and different cutoff values were applied at each institution, for example, a decrease by more than −1.5 or −2 standard deviation (SD) from the age- and educational level-adjusted mean. However, the recently published Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and VasCog statements overcame the ambiguity of the diagnosis by specifying criteria for cognitive impairment. The NINDS-AIREN criteria and the AHA-ASA criteria, which were widely used in the past, defined cognitive impairment as a level of impairment that would interfere with daily life [7]. As reported in the DSM-5 recently, a major neurocognitive disorder is described as a decrease of below −2 SD in more than one cognitive domain, while mild neurocognitive disorder is defined as a decrease between −1 SD and −2 SD. The criteria for determining cognitive impairment was extended from −1.5 SD to −1 SD, enabling cognitive impairment to be detected early [7]. The VasCog statement specified the criteria for vascular dementia as a decrease of below −2 SD compared to the average in one or more cognitive domains [8]. However, the above criteria have been presented as a result of consensus by experts for application in general cases; it is necessary to carefully refer to the symptoms and signs of patients and information from caregivers to establish a proper diagnosis in the clinical field. Instead of applying the test scores unconditionally, the diagnosis should be made while considering the effects of the aforementioned environment, the patient's condition on the day of the examination, and any accompanying physical disability.

It is also necessary to use the appropriate testing tools according to the objective of the test, for example, whether it is for the purposes of a community epidemiological survey or for early detection purposes in a tertiary care center. For the purposes of community epidemiological surveys, screening tests that are relatively simple and sensitive in detecting abnormalities may be useful. These tests allow the examiner to determine whether further evaluation is required or whether the cognitive function over time is deteriorating or improving. In order to identify the exact differential diagnosis and specific cognitive decline in tertiary institutions, a more comprehensive cognitive function test should be performed, and, depending on the patient's symptomatology, more detailed and sensitive tests should be added to examine specific cognitive domains.

6.2 Neuropsychological Evaluation Tools

6.2.1 Mini-Mental State Examination (MMSE)

The most widely used screening test is the MMSE [9]. This is a test commonly used in patients with various neurodegenerative dementia diseases, including Alzheimer's disease, and has the advantage of being easy to use, easy to learn for examiners, and ample previous research to refer to. However, it is an examination which was originally designed to assess the cognitive function of

psychiatric patients and, as is well known, is somewhat inadequate in evaluating frontal lobe disorders or executive functions, as the main constituent questions of the MMSE are focused on orientation, memory, and language [10]. As a result, although a high sensitivity and specificity have been reported for diagnosing moderate dementia, a bias against identifying mild cognitive impairment (MCI) is detrimental in situations where an early diagnosis is important [11]. There are also an increasing number of centers that no longer use the MMSE due to copyright issues.

6.2.2 Montreal Cognitive Assessment (MoCA)

The MoCA was originally developed to screen for mild cognitive impairment [12]. It has advantages to supplementing the shortcomings of the MMSE when assessing frontal executive function by including the clock drawing test, modified trail making test, and verbal fluency test. Following the accumulation of many previous studies in patients with vascular cognitive impairment, the National Institute for Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) vascular cognitive impairment harmonization standard (VCIHS) committee recognized the MoCA as part of the standard neuropsychological assessment when evaluating for VCI.[14] Previous studies have reported that the MoCA is useful for differentiating between normal and vascular cognitive impairment with no dementia (VCIND), as well as normal and vascular dementia [13]. Another advantage is that it can be used without needing permission, free of charge, and can be used for noncommercial purposes by any research or medical institutions (copyright Ziad Nasreddine, MD). On the other hand, the time required for the examination is longer than the MMSE at about 15 min, and the result is significantly influenced by the education level [13].

Several comparative studies that have been conducted up until recently report the MoCA to be superior to the MMSE and Addenbrooke's cognitive examination (to be described later) for identifying cognitive impairment [14]. In addition, the 5-min MoCA, which was proposed as a more abbreviated form of the test, was designed so it can be performed by only answering questions, with no need of drawing or moving a hand. Recent studies have shown that conducting a cognitive assessment telephonically using the 5-min MoCA is useful [15]. Given that many longitudinal clinical studies with cognitive function as a variable suffer from high dropout rates, specific tools that enable telephonic assessments will play an important role in overcoming attrition bias [16]. The MoCA also has the advantage of being widely used because it has been translated into different languages in various countries and has been studied to determine normal standards [17]. In addition, despite only being a screening test, the index score for each cognitive domain can be calculated so that the overall pattern of cognitive impairment can be understood in more detail [18].

6.2.3 Addenbrooke's Cognitive Examination-Revised (ACE-R)

Addenbrooke's Cognitive Examination-Revised (ACE-R) is a 100-point scale that includes the MMSE test and additional items that test for executive function and attention [19]. For this reason, ACE-R may also be a good alternative to evaluate the cognitive prognosis in stroke patients. In a recent study, the sensitivities and specificities of the MMSE, MoCA, and ACE-R for identifying MCI after 1 year of stroke were compared using the NINDS-CSN VCIHS protocol. In this study, the MoCA and ACE-R showed good results, but the MMSE failed to show useful results due to the ceiling effect [14].

6.2.4 Hasegawa's Dementia Screening-Revised

Hasegawa's Dementia Screening-Revised (HDS-R) was originally developed to screen for dementia [20]. It consists of a total of 30 points spread over the following items: orientation to age, time and place, repeating three words, serial subtraction

of 7s, repeating digits backward, delayed recall of three words, and recalling five objects and vegetables. It assigns more points to the memory tests than the MMSE and includes an item to evaluate frontal lobe function. An advantage of the HDS-R is that it can be used in the elderly who have limited physical ability, as it does not include tasks that require physical activity that are typically used for evaluating visuospatial constructional ability and execution function. However, it is currently mainly used in Asian countries.

6.2.5 Telephone Interview for Cognitive Status (TICS)

This is a phone-based cognitive assessment tool similar to the 5-min MoCA mentioned above. It consists of 11 test items, evaluates global cognitive function, and typically takes less than 10 min. TICS has been reported to have a good correlation with the MMSE score, [21] and recent studies also have shown good sensitivity and specificity in distinguishing multiple-domain and single-domain MCI from both the general population and stroke patients [22]. Although it has the advantage of tracking changes in cognitive function over time, it is required to check with the caregiver whether the environment is appropriate before the test is executed for accurate assessment. It is also important to note that when interpreting the test results, there are disadvantages to not being able to perform a test that requires physical activity, including visuo-executive items.

6.2.6 Comprehensive Neuropsychological Protocols

Patients with abnormal results obtained from using the screening tools described above will subsequently receive a more detailed assessment. In general, it is common to use two or more kinds of test tools to evaluate each cognitive domain, such as attention, memory, language, visuospatial function, praxis, executive function, and social cognition. The American Heart Association/American Stroke Association Vascular Cognitive Impairment criteria states a minimum of four cognitive domains should be evaluated, namely, executive/attention, memory, language, and visuospatial function, before diagnosis [23]. Various cognitive test tools have been developed in different countries and translated into numerous languages. These cognitive testing tools, used primarily in VCI patients, can be compared using the recent data from the international consortium STROKOG [24]. This is a consortium studying cognitive dysfunction after strokes, and the authors summarized which cognitive assessment tools were used in each of the participating cohorts. Owing to the participation of large VCI cohorts in this consortium, it reveals which tests are mainly being utilized in current clinical practice and research. The tests conducted in common for each cognitive domain are as follows: trail making test A, digit symbol coding, and digit span forward for attention/processing speed; verbal learning test, Rey complex figure test: recall, story recall for memory; Boston Naming Test, categorical verbal fluency, Token test for language; Rey complex figure test: copy, clock drawing for construction (visuospatial); and trail making test B, phonemic verbal fluency, digit span backward, Stroop test for executive function/abstract reasoning [1]. However, in some cases, the same test is categorized into different cognitive domains according to research groups, requiring caution in interpreting it.

The representative neuropsychology test battery used in clinical practice is the Vascular cognitive impairment harmonization standard-neuropsychological protocol (VCIHS-NP) proposed by the National Institute of Neurological disorders and Stroke-Canadian Stroke Network (NINDS-CSN). The VCIHS-NP was published in 2006 by Hachinski et al. after expert consensus, allowing the use of standard protocol as a way to accelerate the development of this field by making the studies comparable and integrating knowledge [3]. To date, many countries, including France, the UK, South Korea, and Hong Kong, have used this protocol to evaluate patients, and this has been reflected in their studies [14, 24–26]. A list of specific tests can

be found by referring to Table 6.1. The VCIHS-NP was composed with the intention to obtain as much information as possible using well-validated tests, while improving clinical efficiency by using as few tests as possible. For example, asking the patient to generate a list of words from a category provides information on language, activation, processing speed, set shifting, working memory, and executive control. This single short test could evaluate function encompassing multiple cognitive domains and was included in the protocol [3, 27]. In contrast, more detailed tests assessing for semantics and syntax such as Pyramids, the Palm Trees Test, the Token Test, and various tests for evaluating apraxia were not included in the standard protocol but are recommended to be performed if necessary [3].

Table 6.1 Vascular cognitive impairment harmonization standards-neuropsychological protocol

5-min protocol
MoCA subtests
5-word memory task (registration, recall, recognition)
6-item orientation
1-letter phonemic fluency
30-min test protocol
Semantic fluency (animal naming)
Phonemic fluency (Controlled oral Word Association Test)
Digit symbol coding from the Wechsler Adult Intelligence Scale, Third edition
Hopkins Verbal Learning Test
Center for Epidemiologic Studies-Depression Scale
Neuropsychiatric Inventory-Questionnaire Version (NPI-Q)
Supplemental: MMSE, trail making test
60-min test protocol
Executive/activation
Animal naming (semantic fluency)
Controlled Oral Word Association Test
WAIS-III digit symbol coding
Trail making test
List learning test strategies
Future use: simple and choice reaction time
Language/lexical retrieval
Boston Naming Test 2nd Edition, Short Form
Visuospatial
Rey-Osterrieth complex figure copy
Supplemental: complex figure memory
Memory
Hopkins Verbal Learning Test-Revised
Alternate: California Verbal Learning Test-2
Supplemental: Boston Naming Test Recognition
Supplemental: digit symbol coding incidental learning
Neuropsychiatric/depressive symptoms
Neuropsychiatric Inventory-Questionnaire Version
Center for Epidemiological Studies-Depression Scale
Other
Informant Questionnaire for Cognitive Decline in the Elderly, Short Form
MMSE

Revised under the permission of Stroke [3]

In the VCIHS-NP, a 60-min, 30-min, and 5-min protocol were put forward, with the length of the protocol used depending on the purpose. The 60-min protocol is the standard protocol described above. The 30-min protocol consists of some tests of the 60-min protocol, which includes the following tests: semantic and phonemic fluency, digit symbol coding and the revised Hopkins Verbal Learning Test, the Center for Epidemiologic Studies Depression (CES-D) scale, and the Neuropsychiatric Inventory-Questionnaire Version (NPI-Q). The 5-min protocol is designed to be used by primary care physicians, nurses, and other allied health professionals in the office or at the bedside. It is also designed for use in large-scale epidemiological studies or clinical trials and should be easy to apply while also remaining sensitive to identifying cognitive abnormalities. In addition, the 5-min protocol allows all elements of the test to be conducted verbally, which makes it suitable for use over the phone. Among the subtests of the MoCA, the five-word immediate and delayed memory test, six-item orientation task, and one-letter phonemic fluency (the letter F) test are included. In order to supplement the shortcomings of the 5-min protocol, additional items such as the cube and clock drawing task, three-time picture naming task, and short "Trail B" test can be performed, and the original trail making test can be done if necessary. If the MMSE is also required, it is recommended to be performed on another day or at least 1 h after the VCINP 5-min protocol [3].

Furthermore, the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) to identify the premorbid cognitive decline [28],

the Geriatric Depression Scale to screen for depression, and the Neuropsychiatric Inventory-Questionnaire Version (NPI-Q) to evaluate behavioral symptoms [29] are also performed together with the standard protocol. Please refer to Hachinski's original *Stroke* paper as to why each test was included and what additional suggestions are there [3].

6.3 Neuropsychological Construct in Patients with Vascular Cognitive Impairment

VCI patients are characterized by a decrease in frontal function, including processing speed, early in the disease process. In a recent study, 404 stroke patients were tested with the VCIHS-NP 6 months after the index stroke, with processing speed and executive function showing the most pronounced decline −1.32 ± 1.36 and −1.29 ± 1.34 z-scores, respectively, followed by a decline in the language domain of −0.87 ± 1.38, and lastly a deterioration in long-term memory and visuo-constructional abilities of −0.50 ± 1.38 and −0.47 ± 1.51 [30]. However, the patterns of these cognitive disorders may vary depending on the location of the lesion. Several cognitive and behavioral syndromes, including various forms of apraxia and disconnection syndrome, have been revealed through studying stroke patients. While the evaluation methods for each cognitive and behavioral syndrome are beyond the scope of this chapter, these symptoms are often difficult to identify properly unless the examiner understands the lesion's characteristics and does a thorough and extensive evaluation.

On the other hand, "behavioral and psychological symptoms of dementia (BPSD)" are also easy to overlook. It has been reported that patients with VCI are more likely to have behavioral symptoms such as depression, anxiety, and aggression, beginning at the early stages of the disease. Therefore, tools are needed to properly assess these symptoms. The most commonly performed NPI-Q is scoring the severity of the symptoms and distress felt by the caregiver, centering around 12 neurobehavioral symptoms frequently observed in patients. The 12 neurobehavioral symptoms are as follows: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors, and change in appetite/eating.

The characteristics of these neuropsychological symptoms may vary according to ethnicity or the nature of the underlying vascular disease. Recently, related research has been carried out by the STROKOG consortium, and it is expected to be able to identify the differences in the patterns of cognitive impairment according to ethnicity. Furthermore, we will be able to confirm the differences in cognitive impairment according to the features of the vascular disease (e.g., the cerebral microbleed burden or the presence of cerebral amyloid angiopathy) from various cohorts such as CASPER, CogFAST, DEDEMAS, GRECOG-VASC, STRIDE, and STROKDEM mentioned above.

6.4 Longitudinal Neuropsychological Evaluations

Identification of longitudinal changes in cognitive function is important for the differentiation of the underlying disease processes and prediction of prognosis. Important factors in the assessment are how actively we track and monitor the cognitive function of the patient in question and how appropriately we interpret these results from a time perspective. Levine's results show that the cognitive function changes before and after the index stroke [31]. In terms of global cognition and verbal memory, there is an acute decline compared to the pre-stroke slope followed by an accelerated rate of decline, whereas processing speed also worsens at an accelerated rate but without an acute decline. The global cognitive function after stroke, expressed using the Clinical Dementia Rating-Sum of Boxes (CDR-SB), also varies with time after 3 months, 1 year, and 2 years [32]. Therefore, it is necessary to approach post-stroke cognitive assessments with this point in mind, since it may show different results

depending on when and what evaluation tool is used.

Patients with VCI are often lost to follow-up due to concomitant physical disability and recurrence of vascular events. Recently, Pendlebury et al. shared these difficulties of cognitive study through a series of papers [16]. These papers suggest that it is important to proactively evaluate the prognosis of cognitive function through various methods, i.e., by conducting cognitive evaluation tests via the telephone and confirming progression to dementia using medical records.

Another element is to properly analyze the time-varying data obtained. As the subject grows older (e.g., ages 79–80), the criteria for different age groups are applied to deriving the standard scores (from the norm category of 75–79 to the category of 80–84), which may significantly change the standard scores. In addition, in some cases, each cognitive domain may show different longitudinal progressions. The pattern that begins with frontal dysfunction and subsequently decreases the memory or visuospatial function may be the effect of a neurodegenerative process, such as superimposed Alzheimer's disease or dementia with Lewy bodies. Furthermore, a test that is designed to mainly evaluate one cognitive domain may not only evaluate the domain in question but also related domains, so it is necessary to pay attention when interpreting the results. In the case of memory testing, frontal function is involved in encoding the word list and in the retrieval process. Indeed, considering the interaction that occurs among these cognitive domains, we have found that the results of the analysis vary according to the statistical methods used [33].

Recently, in the area of Alzheimer's disease, the repeated failure of clinical drug trials has raised the question of the suitability of the cognitive assessment to determine treatment effect. A new index, Alzheimer's Diseases Composite Score (ADCOMS) incorporating the two MMSE items and all six CDR-SB items into the four Alzheimer's Disease Assessment Scale-cognitive subscale items, which was used as the outcome variable in previous studies, has been developed and applied to clinical drug trials [34]. Despite these efforts, however, critics point out that the basic assumptions underpinning the current view of dementia drug development are wrong. By analogy, it is said that improving symptoms of diabetic polyneuropathy cannot be the endpoint for deciding on the success of an antidiabetic drug, rather it should be to identify changes in the HbA1c. In other words, although cognitive function is the most important indicator of brain function, we cannot confidently say that it accurately reflects the effects of the therapeutic drug, namely, slowing or halting of the disease process. The US Food and Drug Administration (FDA) understands these concerns and has sought alternatives for evaluating therapeutic effects using surrogate markers such as imaging biomarkers. However, this issue needs further discussion by researchers, the pharmaceutical industry, and health authorities.

Vascular cognitive impairment also shares the same problem as Alzheimer's disease in the absence of an effective treatment. In many clinical trials up to now, various tests have been used as outcome variables and as a result have failed to show significant therapeutic effects. The MMSE and Cognitive Abilities Screening Instrument (CASI) were used in the PROFESS and SPS3 clinical trials to confirm the cognitive protective effect of antithrombotic agents [35, 36]. In clinical trials testing the effects of some antihypertensive agents, diabetic agents, and statins, specific frontal function subtests such as a digit symbol substitution test were used as outcome variables. However, cognitive decline in both the treatment and control groups was not observed as much as expected in the above clinical trials. While there may be an issue with the eligibility criteria, the tool itself used to assess cognitive function may not have been sufficiently sensitive. New indicators are needed to overcome these shortcomings and to more sensitively reflect the changes in cognitive function.

6.5 Future of Neuropsychological Evaluations

Recently, advancements in various technologies have led to the development of numerous forms of cognitive function evaluation. There is a

computerized test that has been designed to track a patient's eyes when performing the trail making test, for use in patients who cannot use their arms due to paralysis [37]. In addition, many tests have been computerized to exceed the limits of conventional paper assessments. Computerized cognitive assessment tools are being developed to evaluate cognitive function not only by implementing existing techniques with a keyboard, mouse, and tablet but also in completely different forms. Some research groups used the Internet of Things (IoT) and virtual reality (VR) to simulate specific situations that the subjects will experience in their daily life in a virtual reality and quantify them to derive cognitive domain scores [38, 39]. Some commercial programs, such as Lumosity and CogniFit, offer a variety of computerized interfaces to assess cognitive function and also strengthen cognitive function in symptom-free healthy subjects. Although not replacing conventional classical paper testing in the near future, human cognition surrogates using computerized cognitive testing, the IoT, and VR in a variety of areas will be applied at the frontline and in research environments.

Acknowledgment This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (Ministry of Science and ICT) (No.2017R1C1B5018132).

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7 Pathophysiology of Vascular Cognitive Impairment (I): Theoretical Background

Di Yu, Walter Swardfager, and Sandra E. Black

7.1 Introduction

Vascular cognitive impairment (VCI) is defined as a syndrome with evidence of clinical stroke or vascular brain injury associated with cognitive impairment affecting at least one cognitive domain [1]. It includes to a full range of cognitive deficits secondary to cerebrovascular cerebral vascular injury, with vascular dementia being the most severe manifestation. Cerebrovascular pathology has been recognized as the second most common cause of dementia, as well as the commonest pathological comorbidity in Alzheimer's dementia, highlighting the importance of cerebrovascular factors in cognitive decline from a global perspective. Risk factors for VCI include aging, vascular disorders such as hypertension, diabetes, smoking, and genetic mutations. Historically, VCI was attributed to occlusive large artery disease leading to multiple lacunes or focal territorial, cortical-subcortical infarcts, as suggested by Hachinski's term "multi-infarct dementia," introduced in the 1970s to distinguish vascular dementia from the neurodegenerative disorders (Fig. 7.1) [1]. Advances in neuroimaging, and autopsy studies, have revealed new substrates in the pathogenesis of VCI, including subcortical white matter hyperintensities, microinfarcts, microbleeds, and

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S.-H. Lee, J.-S. Lim (eds.), *Stroke Revisited: Vascular Cognitive Impairment*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1433-8_7

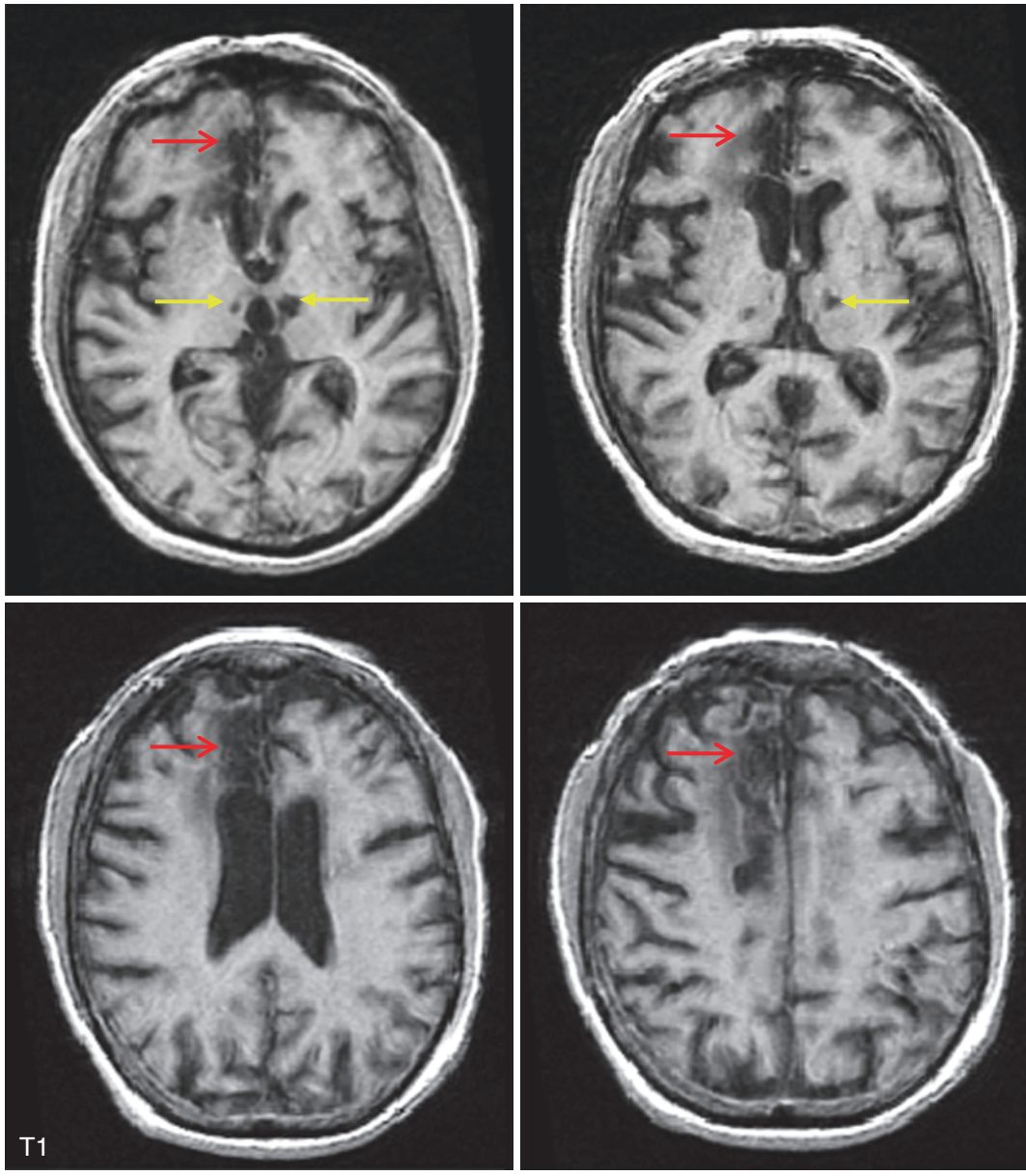

Fig. 7.1 A T1-weighted MRI of a 70-year-old woman with multi-infarct dementia who suffered bilateral dorsal medial thalamic infarcts (yellow solid arrows) causing marked short-term memory loss, followed by a right medial frontal infarct (red open arrows) a few years later causing profound apathy and loss of initiation of mental and physical activity

other subtler changes including a decline in the microstructural integrity of brain tissue appearing normal on anatomical brain scans, particularly mild VCI or in early stages. Because the pathogenic mechanisms of VCI are complex and heterogenous, the pathophysiology of VCI remains yet to be fully understood. In this chapter, the known pathophysiological mechanism of VCI will be reviewed. The roles that concepts such as the neurovascular unit, neurotransmitter system, and large-scale neural network may play will be discussed.

7.2 The Neurovascular Unit (NVU)

The cerebral vasculature provides numerous critical functions. It forms a selectively permeable barrier that orchestrates the crossing or exclusion of molecules to and from the brain parenchyma; it sends and senses signals to accommodate dynamic demands for cerebral oxygenation and glucose; and it fulfills immunological roles to support the defense of the brain against invading microorganisms or harmful materials. To fulfill these roles, the endothelial cells and the vascular smooth muscle cells (VSMC) of the cerebral vasculature work closely with multiple types of cellular components, including pericytes, astrocytes, microglia, and neurons, which collectively form the neurovascular unit (Fig. 7.2). Each of these NVU components plays critical roles in times of neural vascular injury, acting as important determinants of VCI outcomes and progression. The known specific contributions of the NVU components to VCI are reviewed in the following sections.

7.2.1 The Blood-Brain Barrier (BBB)

Cerebral blood vessels are free of fenestrae—small holes that permit the free diffusion of materials across the vessel walls. Instead, endothelial cells conjoined by occludins and claudins form a physical barrier that impedes the bidirectional diffusion of polar molecules between blood and the brain, which protects the brain from potentially harmful substances from the peripheral circulation. Instead, molecules cross the BBB via active transport due to the presence of multiple transporters, which are critical for the maintenance of cerebral homeostasis, carrying across important substances such as apolipoproteins and pumping out potentially harmful waste products.

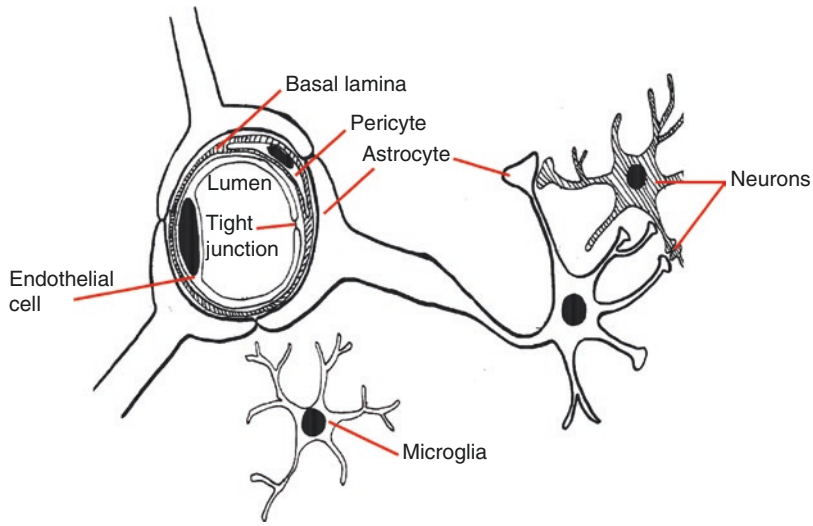

Fig. 7.2 A cross-sectional schematic representation of the neurovascular unit. The NVU is made of cerebral vasculature (endothelial cells and vascular smooth muscle), pericytes, astrocytes, microglia, and neurons, which work collectively to ensure cerebral homeostasis. The cerebral endothelial cells are conjoined by tight junctions that impede the bidirectional diffusion of polar molecules between blood and the brain. The endothelial cells are surrounded by pericytes embedded in the basal laminal matrix, which are important for maintaining both cerebral blood flow and BBB integrity. Neurons modulate cerebral hemodynamics via astrocytes, star-shaped cells that encase the cerebral blood vessels in their end feet. Microglia are the resident macrophages of the human brain; they work closely with astrocytes to fulfill the immunological roles of NVU. In contrast to the arterioles, pericytes are more plentiful in the capillaries and venules, fulfilling many structural, contractile, immunological, and phagocytic functions in the smaller vessels

BBB integrity is found frequently to be compromised in VCI, manifested as elevated albumin in CSF and detection of fibrinogen and immunoglobulins in injured white matter [1]. The two major causes of BBB leakage appear to be pericyte injury and endothelial dysfunction. Pericytes, the mural cells of cerebral capillaries, have been shown to be critical for the maintenance of BBB integrity [2]. BBB leakage has been reported in multiple rodent models that have pericyte deficiency [2]. Arterial atherosclerosis, stroke, and vascular risk factors like hypertension and diabetes have well-established associations with BBB leakage. In stroke-prone hypertensive rodent models, BBB leakage was found to be associated with ischemic injuries [1], even in the absence of arteriolar occlusion.

One harmful substance in the CNS affected by disruption of BBB integrity is cerebral amyloid, which can be elevated in the CNS due to disruption of active transporter expression. Cerebral amyloid beta (Aβ) is primarily cleared through the perivascular spaces surrounding the penetrating venules and the active transporters like low-density lipoprotein receptor-related protein-1s (LRP-1) across BBB [3]. Impaired Aβ clearance has been linked to LPR-1 deficiency and enlarged perivascular spaces [3]. Thus, BBB defects might result in an elevation in CSF Aβ concentration, which may contribute to the early formation of amyloid plaques on the cerebral vasculature. Amyloid deposition on blood vessel walls ("cerebral amyloid angiopathy") can further aggravate endothelial dysfunction, resulting in microbleeds, white matter hyperintensities (WMH) visible on T2-weighted MRI, and elevated risk of larger intracerebral hemorrhage (Fig. 7.3). The fibrillation of amyloid beta 42 leads to deposition as

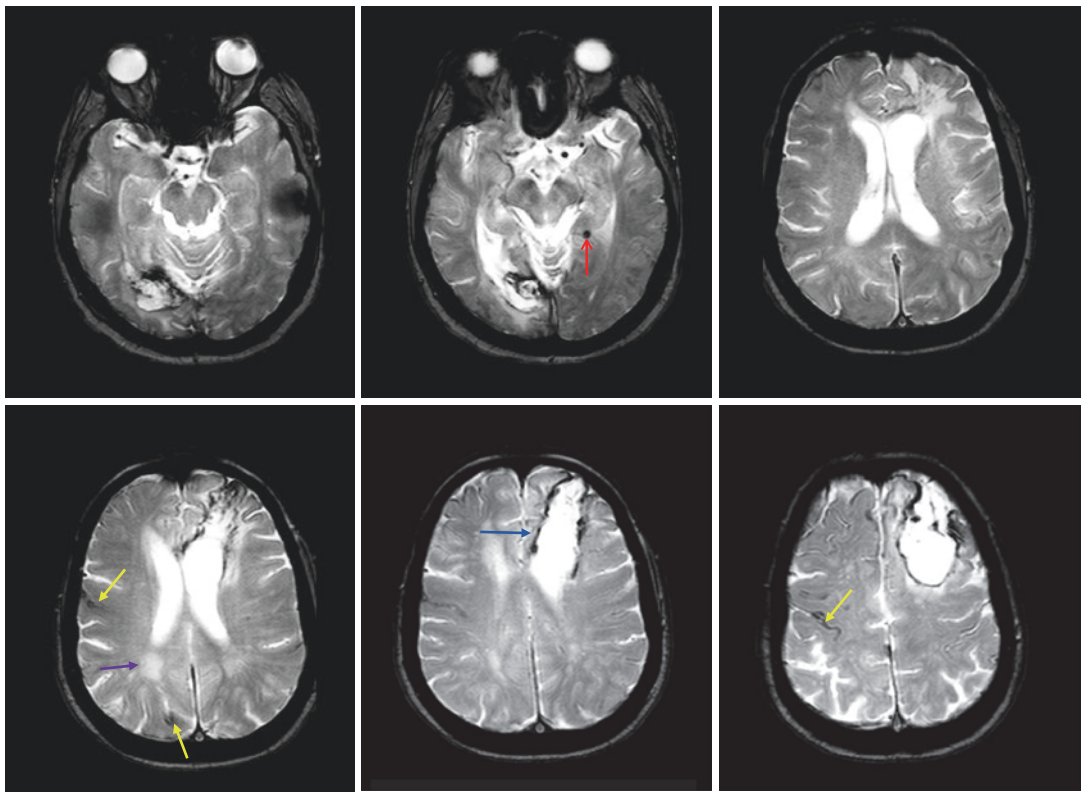

Fig. 7.3 A gradient echo MRI illustrating different manifestations of cerebral amyloid angiopathy in an 81-year-old woman, including large left frontal lobar hematoma cavity surrounded peripherally by hemosiderin (iron-containing macrophages and glial scar; blue arrow). Cerebral microbleed (red open arrow), superficial siderosis (yellow solid arrows), and white matter hyperintensities are also seen (purple)

amyloid plaques in the neuropil, a well-established feature of AD, are associated with further damage seen as cerebral atrophy and usually cognitive deficits, while the perivascular deposit of amyloid beta 40 is associated with microbleeds. Lobar microbleeds have also been linked to deficits in global cognition and in visuospatial and executive functions [4].

The presence of BBB defects in both VCI and AD brains suggests a potential interaction between cerebrovascular dysfunction and AD pathology; however, the causal relationships between BBB defects and AD pathology remain to be fully clarified. One hypothesis, proposed by Zlokovic, is that AD is a vascular disorder involving two distinct "hits" as opposed to a pure amyloid pathology (Fig. 7.4) [5]. Zlokovic proposed that the earlier phase of AD could be non-amyloidogenic and purely vascular. The pathogenesis might be initiated by neuronal injuries and white matter infarcts (first hit) secondary to BBB leakage and small vessel hypoperfusion, which might facilitate the development of amyloid accumulation (second hit). This would also be consistent with the observed changes in the transporters that clear Aβ from the brain found in vascular injury, with deficits in perivascular drainage suggested in more recent studies, and with reports that vascular brain changes on MRI can precede amyloid deposition [6]. Under this hypothesis, VCI could be an intermediate phase in the development of some cases of AD, and amyloidosis might contribute to some cases of VCI, placing pure AD and pure VCI on opposite ends of continuous spectrum. Ongoing studies seek to uncover the key determinants of the two-hit pathology model and to clarify the complex interrelationships between cerebral vasculopathy and AD.

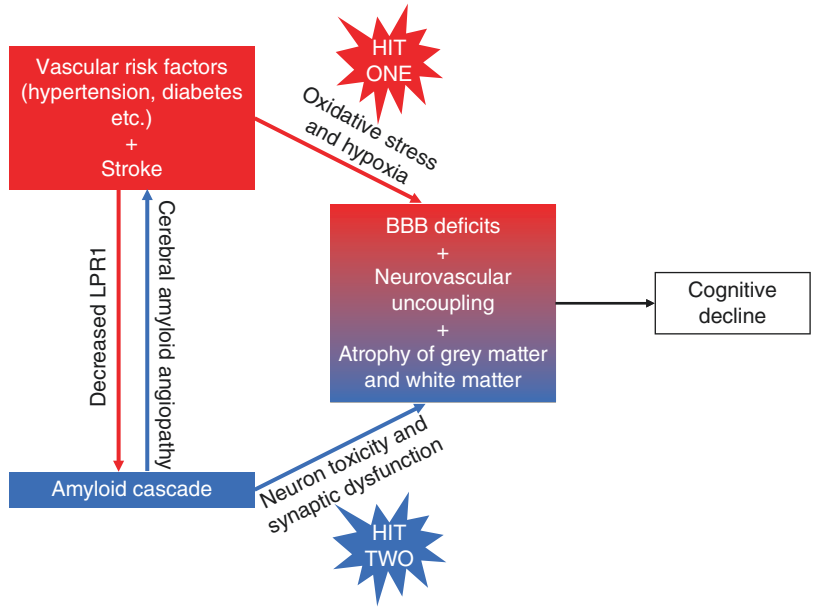

Fig. 7.4 The two-hit hypothesis of neurodegeneration due to Alzheimer's disease and VCI. The two-hit hypothesis [6] postulates cerebral vascular injury as the "first hit" in a two-fold causality of cognitive decline. Cerebral vascular injury caused by vascular risk factors and stroke is considered to damage the blood-brain barrier (BBB), the neurovascular unit, and the surrounding gray and white matter through hypoxia or oxidative stress. The second hit is considered to be amyloid cascade, which damages neurons directly through neuronal toxicity and synaptic dysfunction. These two concomitant insults interact. Amyloid deposited along the arteries gives rise to cerebral amyloid angiopathy (CAA), which compounds vascular injury and impedes amyloid clearance, while BBB deficits further impair the clearance of amyloid, for instance, due to a decrease in LPR1 expression. Under this hypothesis, cerebral vascular pathology and amyloid deposition can lead to cognitive decline due to their reciprocal interaction. Moreover, VCI could be an intermediate phase in the development of some cases of Alzheimer's disease

7.2.2 Cerebral Vasculature and Neurovascular Coupling

The cerebral vasculature adopts an "outside in" distribution pattern. Cerebral arteries arise from the circle of Willis (located at the base of the brain) and give rise to a rich network of pial vessels along the brain surface. These superficial arteries then divide into long and narrow penetrating smaller arteries and arterioles, without collaterals, to supply blood to the deep subcortical areas. Therefore, any reduction in the blood flow of larger vessels due to occlusion or carotid stenosis would be exaggerated in the smaller vessels, which cannot be compensated for by adjacent vessels. To accommodate this specialized vascular distribution, the high demand for energy consumption, and the lack of local metabolic reserves, the cerebral vasculature has developed a set of well-coordinated signaling mechanisms that facilitate "functional hyperemia," ensuring sufficient blood flow to distinct cerebral regions. As neural activity changes, vasoactive agents released by endothelial cells and astrocytes act to shape regional hemodynamics. Vascular smooth muscle cells (VSMC) and pericytes (particularly in the smaller vessels) also act to maintain homeostasis by sensing and regulating blood flow directly in the vessels via chemical or physical signals, in a process called autoregulation.

Attenuated cerebral blood flow (CBF) and impaired neurovascular coupling are typical features of VCI. Reduced global resting CBF has been detected in patients with vascular comorbidities or with a heavy burden of white matter injury. Areas surrounding WMH are typically found to have lower vascular reactivity [7]. Interestingly, there is evidence of venous disease in the vicinity of WMH, in addition to arteriolosclerosis. In men with coronary artery disease, CBF was related to poorer global cognitive function and to obesity measures; however, the mechanisms underlying these observations remain to be fully elucidated [8]. Since the deep white matter is particularly vulnerable to CBF deficits, and white matter injury has been linked to executive and psychomotor processing speed, chronic CBF reduction is a likely contributor to cognitive decline. Venous collagenosis further exacerbates alterations in CBF by increasing resistance [9]. Chronic insufficiency in blood supply might also be associated with neuronal loss and brain atrophy, owing to the high demand for energy consumption in neurons.

Different NVU compartments, including VSMCs, endothelial cells, pericytes, and astrocytes, all contribute differently to the impaired CBF and neurovascular coupling. VSMCs, as the sole controller of arterial blood flow, were found to contribute to impaired functional hyperemia [10]. During functional hyperemia, VSMCs hyperpolarize upon the release of nitric oxide released from neurons and endothelial cells, dilating the arteries to increase local blood flow. The VSMC layers also ensure a relatively uniform arterial pressure through autoregulation, preventing the pressure of downstream microvessels from swinging dramatically during cardiac systole and diastole. Therefore, direct injury to the VSMCs affects both resting CBF and functional neurovascular coupling. Stiffness and loss of arterial smooth muscle elasticity secondary to vascular risk factors have been associated with reduced resting white matter CBF and loss of the ability to adapt CBF to metabolic need [1]. Similarly, since the release of NO from endothelial cells directly induces VSMC relaxation, endothelial dysfunction secondary to ischemia or vascular risk factors (e.g., hypertension) can also impair functional hyperemia (Fig. 7.5).

Dysfunction of the pericytes and astrocytes can contribute to deficits in neurovascular uncoupling detected in VCI. Pericytes are mural cells embedded in the basement membrane of cerebral capillaries and pre- or postcapillary mirovessels. Pericytes have a direct modulatory effect on capillary blood flow. In rodent models that lack pericyte coverage on part of their capillaries, a delay in stimulus-driven vasodilatory response was observed. Comparing the covered and non-covered capillaries, there was a reduction of capillary blood flow in the non-covered ones [11]. In the same loss of function model, a reduction in global CBF was detected, indicating the critical role of pericytes and capillary vascular coupling in both functional and resting blood flow. Pericyte

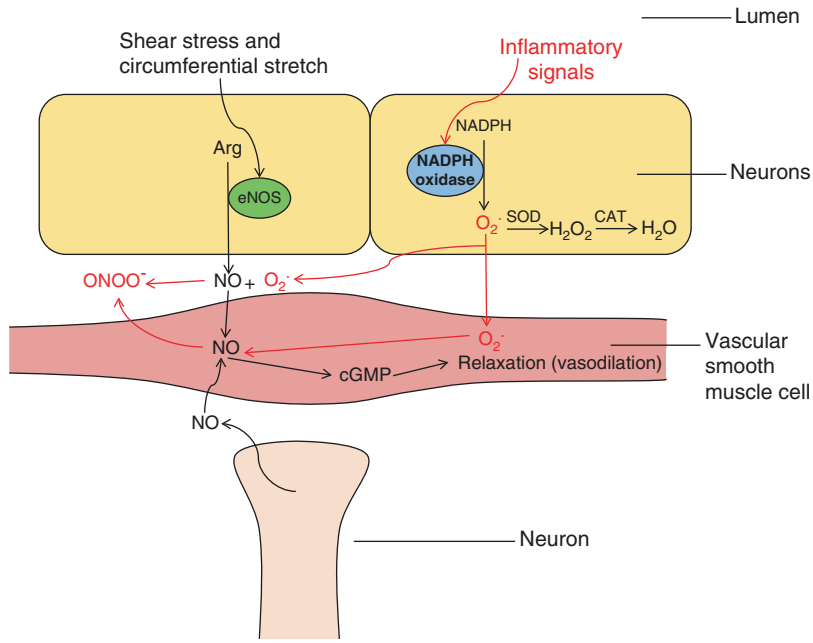

Fig. 7.5 Oxidative stress and neurovascular uncoupling. The synthesis of free radicals in the brain can be initiated by the production of superoxide ($O_2^{\cdot}$) as a product of NADPH oxidase activation. NADPH oxidase can be activated in the presence of inflammatory signals or under conditions of cellular stress. The $O_2^{\cdot}$ generated can be deactivated by superoxide dismutase and catalase into water or give rise to a hydroxyl radical ($OH^{\cdot}$). These reactive oxygen species can bind to adjacent lipids, proteins, or DNA, leading to cellular damage. Superoxide can also directly affect neurovascular coupling through the consumption of nitric oxide (NO), which is the major vasodilatory signal under functional hyperemia. NO is synthesized by eNOS, residing in the endothelial cells, upon activation by factors such as shear stress or muscarinic cholinergic receptor 1 activation during times of neuronal activity. The generated NO will then relax the vascular smooth muscle via cGMP activation, resulting in vasodilation. $O_2^{\cdot}$ can react with NO and give rise to another longer-lived free radical species, peroxynitrite ($ONOO^{-}$), which can also covalently bind to adjacent macromolecules and cause cellular injury. The consumption of NO also impairs the vasodilatory signal, causing defects in neurovascular coupling

degeneration is a frequent feature of VCI and brains with evidence of subcortical ischemic vascular disease (SIVD) [11]. Pericyte malfunctioning has also been proposed to contribute to postischemic white matter injury. By adopting a hypercontractile phenotype following ischemic attack, they stall capillary blood supply following stroke and contribute to the secondary microvessel hypoperfusion and white matter injury [12].

Astrocytes are glial cells that serve to intermediate between neurons and cerebral vasculature. They are found to have modulatory effects on both arteriolar and capillary tone, through their interactions with VSMCs and pericytes. The interactions are mediated by astrocytic Ca^{2+} oscillation and the release of arachidonic acid lipid metabolites, which can result in vasodilation or vasoconstriction through the phospholipase A2 or phospholipase D2 pathways [10]. Presumably, astrogliosis or direct injury to astrocytes would negatively affect neurovascular coupling and CBF. However, the specific mechanisms and the effect size of astrocytic modulation on VSMCs and pericytes remain controversial due to the variable results generated under different experimental settings, which still need to be resolved by future studies.

One of the mechanisms that could injure the NVU directly is oxidative stress. Animal studies have demonstrated a direct connection between cerebral hypoperfusion and oxidative stress [1]. Clinical studies have also reported elevation of isoprostanes, cytokines, and adhesion proteins in both the damaged white matter and the systemic

circulation of VCI patient, while peripheral lipid hydroperoxide concentrations were found to be reflective of deep WMH caused by hypertension [13]. At the molecular level, superoxides are generated by nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) in the cerebral endothelial cells in response to hypoxia, inflammation, or hypertensive stimuli, which could react directly with the surrounding macromolecules and lead to endothelial, neuronal, and pericyte dysfunction (Fig. 7.5). The superoxide anion generated can also react with nitric oxide (NO), consuming this critical vasodilator released by both neurons and endothelial cells. Oxidative stress mediators can thus directly reduce CBF and functional hyperemia by inactivating NO (Fig. 7.5). The association between SIVD and oxidative damage to lipid molecules also suggests the potential for oxidative stress to interfere with arachidonic acid lipid-mediated vasodilatory capacity [13]. Perhaps even more importantly, superoxide gives rise to other reactive oxygen species (ROS) or reactive nitrogen species (RNS) like hydrogen peroxide (H_2O_2), hydroxyl radicals (OH^-), and peroxynitrite ($ONOO^-$), which initiate a chain of additional redox reactions. It is thought that ROS and RNS generated through these chain reactions propagate injury to multiple components of the cerebral vasculature and NVU and to the adjacent white matter. Accordingly, interventions attempting to reduce free radicals have shown promise in rodent models of cerebral ischemia, and clinical trials are underway.

7.2.3 Glial Cells and Neuroinflammation

In people with vascular disease, inflammation has been associated with cognitive decline and dementia [14]. Upregulation of cerebral cytokines and chemokines was detected in hypertensive mice models and has been directly related to cognitive decline [15]. Even though the mechanism remains unclear, the presence of neuroinflammation has been reported in VCI patients [16], presumably due to both cerebral vascular injury and crosstalk between the periphery and the central nervous system. Neuroinflammation has been proposed to be one of the major mechanisms mediating postischemic secondary cell death and neurovascular dysfunction [17]. In mouse models of vascular dementia, elevated astroglial NF-kB expression has been shown to contribute to white matter damage [18]. Even though the direct link between inflammatory markers and cognitive function in VCI patients remains scarce, animal models have shown the association between elevation of central or peripheral cytokines and cognitive deficits [19], highlighting the potential role of inflammation in VCI.

The specialized foot soldiers of the innate cerebral immune responses are astrocytes, microglial cells, and perivascular macrophages. Astrocytes and microglial cells frequently communicate through the release of inflammatory signals. Just as astrocytes serve as an intermediary between neurons and the cerebral vasculature, they also act as an inflammatory intermediary between multiple cell types. Astrocytes express interleukin receptors, and they are capable of secreting cytokines. Astrocytes can be activated by IL-1β and TNF released from microglia and then release further cytokines that are sensed by the microglia to establish either a feed-forward cycle or a regulatory negative-feedback signal. Constantinescu et al. reported that astrocytes are sensors of hypoxia, becoming activated and releasing proinflammatory cytokines like interleukin (IL)-23 [20], which initiates and perpetuates an IL-17-mediated inflammatory response [20]. A similar inflammatory response mediated by interferon-γ (IFN-γ) has also been associated with postischemic injury in animals.

Microglial cells are the macrophages resident in the human brain. They are activated within 2 h post-stroke, releasing IL-1β and TNF and becoming voraciously phagocytotic, enabling them to remove cellular debris [21]. The release of inflammatory factors upon microglial activation, including IL-1β and TNF, IL-17, IL-6, and chemokine ligands (CXCL), can contribute to tissue damage resulting from

postischemic neuroinflammation in animal studies, in a cascade ultimately intended to resolve into active post-inflammatory tissue repair [20].

Microglial cells and astrocytes can polarize into different phenotypes depending on the activation signals presented. Secrotome studies have found a shift of astroglial cytokine profiles upon activation by IL-1β and TNF, indicating the potential for astrocytes to change their secretome under inflammatory conditions [22]. Microglia were found to adopt either pro-inflammatory or anti-inflammatory phenotypes following activation [21]. The specific mechanisms driving the polarization of glial cells remain to be fully understood; however, the polarization phenomenon is well preserved among many types of immune cells. One potential mechanism might involve the release of cytokines from populations of pro- and anti-inflammatory peripheral immune cells, which have been shown in animal studies to modulate postischemic brain injury [20]. The polarization phenomenon makes astrocytes and microglial cells potential targets for preventing ischemia-related brain injury and functional recovery.

The mechanisms contributing to the resolution of neuroinflammation following vascular injury also remain under investigation. The presence of both inflammatory and anti-inflammatory T cells has been reported in ischemic tissue. A set of anti-inflammatory regulatory T cells (Treg) can be developed from naïve T helper (Th) cells, in the presence of IL-10 or TGF-β. Experimental depletion of Treg expression in animal models exacerbates functional deficits following ischemia [20]. Further studies are necessary to elucidate the crosstalk between glial cells and Tregs and to harness their potential to reduce postischemic injury mediated by neuroinflammation. Moreover, inflammatory signals which are harmful at one stage may be beneficial at another. For instance, the release of IL-23 or IL-17 may exacerbate postischemic injury but also stimulate the release of growth factors (e.g., brain-derived neurotrophic factor) that participate in angiogenesis and neurogenesis and the repair of the NVU.

7.3 Strategic Pathways of Neurotransmitters

Synapses are considered to be the basic units of neural connectivity. The release of neurotransmitters in synaptic spaces enables the communication between individual neurons and neuronal groups within a certain region and between regions. For instance, glutamatergic and GABAergic neurons that reside universally in the brain will release glutamate/GABA locally, which allows for communication with proximal neurons, whereas cholinergic neurons innervate the entire cortex via long axonal projections emanating from the basal forebrain.

Neurochemical studies and imaging studies in VCI have found abnormities in neurotransmitter systems, even though the underlying mechanisms and the relationship of these defects to neurovascular pathologies remained uncovered. The cholinergic system appeared to be the most commonly impaired system in VCI, manifested as decreases in choline acetyltransferases and cholinergic receptor expression in animal and autopsy studies, respectively [23]. Glutamate, which serves an essential physiological role in long-term potentiation, has also been studied extensively in VCI due to its role in excitotoxicity. Even though memory loss is less pronounced in VCI compared to Alzheimer's disease, memory deficits are often key features of dementia with vascular contributions.

7.3.1 The Cholinergic System

The cerebral cortex is endowed with a rich system of cholinergic networks, originating from the basal forebrain and the brain stem (Fig. 7.6). Pedunculopontine tegmental (PPT) and laterodorsal tegmental (LDT) nuclei residing in the brain stem mainly project to subcortical regions, which provide cholinergic innervation to the thalamus and the striatum, while basal forebrain cholinergic nucleus, consisting of medial septal nucleus (MS ch1), the diagonal band of Broca nucleus (vDB ch2(v) + 3(h)), and nucleus basalis of Meynert (NBM, ch4) of the substantia

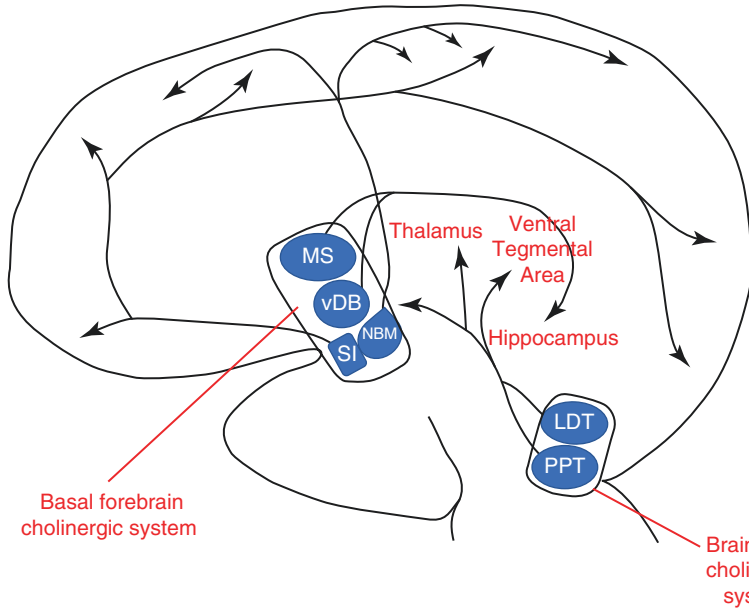

Fig. 7.6 A schematic illustration of cerebral cholinergic projections The cerebral cholinergic network originates from two different nuclei systems, the basal forebrain cholinergic nuclei and the brain stem cholinergic nuclei. Pedunculopontine tegmental (PPT) and laterodorsal tegmental (LDT) nuclei reside in the brain stem. They mainly project to subcortical regions, which provide cholinergic innervation to the thalamus and the striatum. The basal forebrain cholinergic nucleus consists of four different nuclei, the medial septal nucleus (MS ch1), the diagonal band of Broca nucleus (vDB ch2(v) + 3(h)), and the nucleus basalis of Meynert (NBM, ch4) of the substantia innominata (SI). The basal forebrain cholinergic nuclei are the major cholinergic inputs for the cerebral cortex, the hippocampus, and partially the thalamus

innominata (SI), is the major cholinergic input for the cerebral cortex, the hippocampus, and partially the thalamus.

Cholinergic neurons play critical roles in cognitive functions, ranging from executive function and memory to emotional processing. Impaired cholinergic cortical innervations have been associated with overall cognitive decline, particularly with reductions in executive function. Clinical trials have shown some potential cognitive benefits of cholinesterase inhibitors in VCI patients [24]. Cholinergic depletion secondary to cerebral vascular injuries is most commonly observed in the lateral projection of basal forebrain cholinergic nuclei, which passes through the external capsule (capsular division) and the claustrum (perisylvian division). The disruption of lateral cholinergic projections is likely to be linked to both white matter lesions (external capsule) and infarctions to the nuclei (claustrum), which in turn reduce cholinergic innervations to the cortex [25]. Direct insult to the NBM due to elongation of the internal carotid artery has also been associated with atrophy and cognitive deficits, indicating a role for large vessel disease [26].

Cholinergic neuronal loss due to cerebral infarction has been reported in several studies; however, the extent of cholinergic loss in VCI appeared to be contradictory [23]. Animal models of VCI utilizing choline acetyltransferase activity as the marker of cholinergic neurons have reported cholinergic depletion in the temporal cortex and the hippocampus; however, a MRI study in patients with multi-infarct vascular dementia found no neuronal changes in the NBM nuclei [27]. It has been hypothesized that this might be because neuronal arborization volume, but not neuronal cell numbers, was impaired in VCI [23]. Another potential mechanism behind the vascular injury-induced cholinergic reduction is proposed to be the decrease in receptor-ligand affinity, supported by the detection of modulated

muscarinic expression in VCI [23]. Further studies comparing the volume of cholinergic nuclei between controls and distinct types of VCI are necessary.

Cholinergic tracts disrupted by WMHs (identified through CHIP) have been linked to executive function decline in multiple studies [28]. However, most of the lesions are identified through visually rated white matter hyperintensities that appeared in the cholinergic pathways which does not specify the spatial injuries to the cholinergic microstructure. Cholinergic microstructural changes might also lead to "large-scale network disruption" [29, 30].

A reciprocal correlation between cholinergic system function and cerebral blood flow has been identified, suggesting that changes in either cholinergic signaling or cerebral blood flow could influence the other. Animal studies show that of NBM cholinergic nuclei increased cortical blood flow, either through direct actions of acetylcholine or by activating nitric oxide synthase [23]. Reduction in CBF was suggested to be one of the underlying mechanisms of greater executive function decline in elderly people taking anticholinergic agents [31]. Therefore, the cholinergic system might also represent and important intrinsic link between cerebral blood flow and cognitive function, contributing to cognitive decline induced by vascular injuries.

7.3.2 The Glutamatergic System

Glutamate is the sole excitatory neurotransmitter of the central nervous system. Unlike the cholinergic pathways, which originate from certain nuclei and then divide into multiple subprojections, glutamate neurons are dispersed throughout the brain, with multiple origins. Glutamate receptors can also be found universally in diverse types of neurons. The loss of glutaminergic synapses, indicated by the reduction of vesicular glutamate transporter 1, has been detected in the temporal cortex of VCI patients, though the glutamate synapse in the frontal cortex seems to be preserved [32]. Since glutamate is also the major player of cerebral excitotoxicity following ischemic or hemorrhagic attacks, research has focused on the utilization of antiglutamatergic agents in reducing ischemic stroke related neurodegeneration. For instance, memantine was suggested to be potentially beneficial for patients with mild to moderate vascular dementia [33]. The impact of memantine on post-stroke functional recovery is currently under clinical investigation. Moreover, the excitotoxic tryptophan metabolites along the kynurenine pathway amplify glutamatergic signaling and apoptosis, and this has been implicated in post-stroke cognitive impairment [34].

Glutamate is essential for long-term potentiation (LTP), which is the underlying mechanism of learning and memory formation. Both animal studies and clinical studies have confirmed the contribution of glutamate receptors to memory formation, especially the NMDA and AMPA receptors. Both pharmacological and genetic modification of NMDA signaling could affect learning and memory formation in rats [35]. In humans, administration of an AMPA agonist, Ampakine CX516, was shown to have some benefits on short-term memory retention [32].

Even through glutamate has been shown to play an essential role in cognition and ischemia-related neurodegeneration, studies focusing on aspects of glutamatergic pathways in VCI remain scarce. One of the major underlying mechanisms of glutamatergic contribution to VCI might be strategic infarcts disrupting either the frontal parietal, the ventral tegmental, or the temporal glutaminergic projections to other neurotransmitter networks. A study utilizing transcranial magnetic stimulation found that glutamatergic defects might be involved dementia secondary to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [36]. Another clinical study has found correlations between temporal and frontal vesicular glutamate transporter (VGLUT1) concentrations and Cambridge Cognition Examination (CAMCOG) scores. The concentration of VGLUT was also reported to be higher in the frontal cortex of post-stroke patients who didn't develop dementia [32], suggesting the potential correlation

between loss of glutaminergic synapses and cognitive impairment in VCI.

7.4 Large-Scale Neural Network Perspectives

Human brains have evolved a set of intricate, interconnected, and functionally crucial networks. Different brain regions may be functionally connected in co-activating networks. The white matter tracts that interconnect these regions are often interrupted in VCI. This is thought to lead to patterns of atrophy, which co-occurs in functionally connected gray matter regions. Each of these types of networks, and their contributions to VCI, will be discussed in the following subsections.

7.4.1 Functional Networks

Functional magnetic resonance imaging (fMRI) allows the partitioning of brain into large-scale functional networks, which is more of a statistical concept built upon the correlations between spatially distinct regions that have common temporal activation patterns. The functional synchronicity between distinct brain regions is most often captured through low-frequency fluctuation signals of cerebral blood oxygen level-dependent (BOLD) fMRI. These functional networks remain relatively stable within a certain state, but they are much more plastic than anatomical networks as we switch between a resting state and various tasks. A single cerebral region could participate in different functional networks and change its connectivity with other regions according to different tasks.

Altered functional connectivity has been detected in multiple neurodegenerative disorders, including AD, multiple sclerosis, and VCI [37]. Alternations usually manifest as decreased or increase in connectivity or simply as changes in regional BOLD signal strength. It is useful to overlap anatomical and fMRI images to study the mechanisms underlying cognitive decline in VCI patients. Cognitive deficits associated with VCI more frequently manifest as decline in executive functions, attention, and psychomotor processing speed, rather than amnesia, particularly in early stages of subcortical VCI. Multiple studies utilizing resting-state fMRI have proposed the possible association between default mode network (DMN) connectivity deterioration and executive defects [38, 39].

DMN is a functional network conjoining frontal cortex, parietal cortex, and subcortical regions. It involves three major hubs, including posterior cingulate cortical (PCC), medial prefrontal cortical, and angular gyrus, as well as several medial temporal subregions of the hippocampus, parietal lobe, and retrosplenial cortex. DMN plays a critical role in externally orientated tasks. In healthy people, DMN is activated when the subject is in a wakeful state but not when focusing on a specific task. It is normally suppressed at times of focused attention [40].

The disruption of DMN resting functional connectivity in SIVD, particularly the connection between PCC and the frontal-subcortical pathways, has been directly linked to slower psychomotor processing speed, poorer executive function on the Stroop test, and decreased memory scores, indicating the role of the DMN in SIVD-induced cognitive impairment. Sun et al. reported disruption of resting functional connectivity in frontoparietal DMN pathways in 16 patients with VCI [38]. The suppression of resting functional connectivity with the PCC was detected in the left middle temporal gyrus, the left anterior cingulate cortex, the left and right middle frontal gyrus, and the left medial frontal gyrus, which overlaps with the DMN. It is thought that the decline in anterior parts of DMN connectivity might be compensated for by enhanced connectivity between PCC and the right inferior temporal cortex, left middle temporal gyrus, and the superior parietal lobule, accounting for these observations of both enhanced and diminished connectivity [38]. These results were confirmed by Yi et al. in 2012 [39], who also reported increased resting-state connectivity between the posterior components of DMN and decreased connectivity between the anterior components of DMN.

The default mode is an example of a large-scale functional network, which has helped to understand how vascular brain changes can interrupt brain circuits, producing some of the most salient cognitive symptoms in VCI. Other circuits, for instance, the attention network that is activated during times of focused mental effort, are activated when the DMN is suppressed, which is also affected in VCI [41].

7.4.2 Network Anatomical Connectivity

The anatomical connections between different cerebral regions can be interrupted by pathology related to VCI. Subcortical WMH burden detected on MRI images has been closely linked to the cognitive decline in both healthy aging population and VCI patients. In cognitively intact elderlies, increasing WMH volumes has been linked to gait disturbance and memory decline [42]; however, depending on the location and the volume of WMHs, the cognitive consequences associated with the WHMs may differ. Strategic WMH disrupting anterior thalamic white matter tracts and forceps were found to inversely correlate to executive function psychomotor processing speed [43], while the WMH load on the cholinergic tracts has also been reported to impair attention in SVD regardless of the overall cognitive status [44].

More subtle changes compromising the microstructure of axon tracts connecting the subcortical structures and the frontal cortex, but not visible on a T2 MRI, might be another underlying cause of functional connectivity defects. Diffusion tensor imaging (DTI) can be used to examine specific bundles of parallel nerve fibers, delineating individual white matter tracts by tracking the diffusivity of water molecules. The two measures most commonly generated from DTI are fractional anisotropy (FA), a measure of water diffusivity in a common orientation, and MD, a measure of the magnitude of water diffusion in any direction. FA is an indicator of microstructural change, which is frequently used to track white matter bundles. A decrease in FA may be an indicator of demyelination or other white matter defects. MD is considered to be more of a measure of cellularity and membrane density, which is inversely related to cell number. Therefore, edema would cause an elevation in MD measurements, while neoplasia would be linked to a decrease in MD values.

In cognitively normal patients with coronary artery disease, Santiago et al. reported significant associations between executive function and normal-appearing white matter microstructural integrity, measured as FA and MD [45]. Psychomotor processing speed and executive function were positively correlated with mean FA in the left parahippocampal, cingulum, and inferior fronto-occipital white matter tracts. Mean MD in the right parahippocampal cingulum, left inferior fronto-occipital, and left superior longitudinal white matter bundles was negatively associated with processing speed and executive function [45]. These indicate a contribution of white matter microstructural changes in early VCI.

The contribution of white matter tract injury at the microstructural level to disrupted functional networks was shown in a study of 20 healthy individuals, combining DTI and fMRI. Microstructural compromise of the cingulate white matter bundle conjoining the PCC and the lateral or medial temporal lobes was reported to correlate with suppressed functional connectivity between those regions [46]. Further studies combining DTI and fMRI in VCI patients would help to elucidate specific roles of white matter microstructural l damage in disrupting the neural circuits involved in executive function.

7.4.3 Structural Covariance Networks

The combination of statistical approaches and structural imaging allows the investigation of structural covariance networks (SCN), which are built based on the correlations between the structural characteristics (cortical thickness, white matter hyperintensity, brain-parenchymal fraction, etc.) of spatially distinct regions of interest

(ROI). The SCN approach allows for the isolation of gray matter structural networks and the study of cross tract lesions. By examining covariance, much as in fMRI studies, SCNs overcome the limitation that important structural changes may be related even between regions that are not directly connected by white matter tracts. Yi et al. [39] proposed that gray matter atrophy might contribute partially to the decrease in DMN resting functional connectivity, since accounting for gray matter loss attenuated the differences in functional connectivity between VCI and controls. This finding suggests relationships between the anatomical and functional network changes.

Gray matter networks can be constructed through statistical approaches examining the covariance between the cortical thickness of ROIs. Tuladhar et al. reported an inverse relationship between interhemispheric frontoparietal ROIs' cortical thickness covariates and white matter burdens [47], describing the contribution of white matter injuries to brain atrophy. Similarly, Nestor et al. showed the connection between subcortical white matter injury and gray matter atrophy in AD patients with SVD. They found that subcortical white matter volume was inversely related to covariance in cortical thickness within the hubs of DMN in AD [48]. Another study by Swardfager et al. reported a significant impact of WMH on verbal recall due to a specific covariance pathway mediated in serial by left temporal lobe atrophy and poorer verbal learning [49]. Further longitudinal studies combining SCN measures and cognitive outcomes are now necessary to confirm relationships with cognitive deficits in VCI.

7.5 Conclusion

VCI, as the second most important cause of dementia, is defined as a full range of heterogenous cognitive disorders attributed to cerebrovascular injuries. Damage to the neurovascular unit, disruption of neurotransmitter systems, and disconnection within large-scale neural networks contribute distinctly to the pathogenesis of VCI. The primary pathogenic mechanisms are considered to be cerebrovascular injuries (endothelial dysfunction, neurovascular uncoupling, etc.) caused by oxidative stress and neuroinflammation secondary to vascular risk factors and stroke, which not only affect BBB integrity and the clearance of Aβ but also impair the resting CBF and functional hyperemia. The interaction between cerebrovascular injuries and Aβ homeostasis reveals a potential link between VCI and AD, suggesting that VCI can contribute to cases of AD dementia. The cerebral hypoperfusion resulting from NVU disruption affects the firing of neurons and interrupts neurotransmitter systems, notably the cholinergic system, and the glutamatergic overstimulation, which has been linked to functional decline and post-stroke cognitive impairment, respectively. The resulting hypoperfusion can also injure the subcortical white matter tracts interconnecting functionally related regions, leading to distinct patterns of atrophy and changes in functional connectivity within neural networks, collectively contributing to psychomotor slowing, executive dysfunction, behavioral inactivation, and also to memory deficits.

Acknowledgments We would like to gratefully acknowledge the support from our colleagues, Sabrina Adamo and Fuqiang Gao from Sunnybrook Research Institute, for their contribution to the processing and labeling of the MR images. W.S. gratefully acknowledges support from the Alzheimer's Association (US), Brain Canada, The Canadian Partnership for Stroke Recovery, Sunnybrook Health Sciences Centre Department of Psychiatry, Sunnybrook Research Institute Hurvitz Brain Sciences Program, and the University of Toronto Department of Pharmacology and Toxicology. S.E.B. gratefully acknowledges financial and salary support from the Fondation Leducq, Canadian Institutes of Health Research (#125740 & #13129), Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Hurvitz Brain Sciences Research Program at Sunnybrook Research Institute, and the Linda C. Campbell Foundation. S.E.B. would also like to thank the Sunnybrook Research Institute, Sunnybrook Health Sciences Centre Department of Medicine, and the Brill Chair Neurology, University of Toronto, for financial and salary support.

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8 Pathophysiology of Vascular Cognitive Impairment (II): Amyloid Contribution in Vascular Cognitive Impairment

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8.1 Introduction

Amyloid plaques formed from β-amyloid accumulation is one of the two pathological hallmarks of Alzheimer's disease (AD). The other hallmark is neurofibrillary tangles formed by pathological tau [1]. A few decades ago in the dementia field, researchers or clinicians tended to categorize patients into distinct etiology groups. AD was considered the commonest type of dementing disease, while vascular dementia was considered the second most common. AD was seen as a "neurodegenerative" disease, which differs from vascular dementia in terms of etiology, clinical, and risk factor profile. Various diagnostic criteria were devised to differentiate vascular from AD or vice versa [2–4]. Although mixed dementia (i.e., AD with cerebrovascular diseases) has long been recognized [5], relatively much less attention has been paid to this phenomenon. Is there an association between β-amyloid, vascular risk factors, and cerebrovascular disease? What is the influence of β-amyloid upon cognition in subjects with stroke? These questions have not been explored until the recent two decades.

In this chapter, we will first review the clinical and preclinical evidence that has emerged over the last two decades supporting a vascular contribution to AD. This will set the stage for the second section, which will focus on the role of AD pathology in the context of stroke and poststroke dementia. If AD pathology is associated with vascular factors, then it should also be frequently found in subjects with stroke [6], given the strong relationship between vascular risk factors and stroke. Elucidating potential vascular contribution to AD, as well as AD contribution to

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S.-H. Lee, J.-S. Lim (eds.), *Stroke Revisited: Vascular Cognitive Impairment*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1433-8_8

poststroke dementia, is crucial in designing effective preventive or treatment strategies for these common dementing disorders.

8.2 Vascular Contributions in AD

In the late 1990s and early 2000s, several large longitudinal studies have consistently demonstrated that midlife hypertension, or hypertension occurring at least a decade before the onset of dementia, is associated with late-life dementia, including AD dementia [7–9]. Apart from blood pressure, other classical vascular risk factors (e.g., diabetes, hypercholesterolemia, smoking, obesity), if occurred at midlife or years before the onset of dementia, were also found to be associated with Alzheimer's dementia [7, 10–13].

There are few plausible reasons explaining this association between vascular risk factors and AD. One mechanism is that vascular risk factors induce "silent" cerebrovascular lesions (e.g., white matter hyperintensities [WMH], lacunes, microbleeds, cerebral microinfarcts), producing an additive or synergistic effect on the underlying AD pathology upon cognition, thereby reducing the threshold for dementia. Indeed, recent autopsy studies suggested mixed dementia, which is defined as AD with cerebrovascular disease, is the most common etiological subtype of dementia in the elderly [14, 15]. The landmark Nun study showed that lacunes have a synergistic effect with AD pathology by significantly enhancing the clinical manifestation of dementia in subjects with AD pathology. The Nun study further showed that less amount of AD pathology was required to produce dementia in the presence of lacunes [16]. Similar findings were noted in the Honolulu-Asia Aging Study, which showed that the presence of cerebrovascular lesions was associated with a marked excess of dementia particularly in cases with low amyloid plaque frequency, while the Religious Order Study showed that cerebral infarctions independently contribute to the likelihood of dementia but do not interact with AD pathology to increase the likelihood of dementia beyond their additive effect [17]. In a large autopsy study, almost 80% of subjects with the pathological diagnosis of AD harbored some forms of vascular pathology (e.g., large infarcts, multiple microinfarcts, lacunes, subcortical arteriosclerotic leukoencephalopathy, and hemorrhages), and vascular pathology was more common in AD than in other neurodegenerative disorders.

Another reason for explaining the association between vascular risk factors and AD is that vascular risk factors may enhance directly the accumulation of β-amyloid. An early study (Honolulu-Asia Aging Study) showed that elevated systolic blood pressure in midlife was associated with a greater number of amyloid plaques in both the neocortex and hippocampus, while diastolic blood pressure was associated with a greater number of tangles in the hippocampus [18]. These findings are supported by the recent Atherosclerosis Risk in Communities-PET Amyloid Imaging Study, showing that an increasing number of midlife vascular risk factors were significantly associated with elevated amyloid deposition as quantified by Pittsburgh Compound B (PiB) PET [19]. Such an association was not significant for late-life risk factors. In another recent study analyzing the ADNI (Alzheimer's Disease Neuroimaging Initiative) data via a multifactorial data-driven method, biomarkers reflecting vascular dysfunction were found to precede β-amyloid deposition in the AD cascade [20]. Overall, the above findings are consistent with a direct role of vascular factors in the etiological development of AD. A meta-analysis suggested that worldwide population-attributable risks (PAR) for AD of the following vascular risk factors are as follows: midlife hypertension (5.1%), midlife obesity (2%), diabetes (2.9%), smoking (13.9%), and physical inactivity (12.7%) [21]. Considering all potentially modifiable risk factors together, a third of AD may be preventable. Further analysis suggested that assuming only a 10% reduction in the prevalence of risk factors per decade, the future prevalence of AD in the United States, Europe, and the United Kingdom would be reduced by 0.8 million, 1.5 million, and 0.2 million, respectively, by 2050 [21]. So how may vascular risk factors directly lead to AD?

8.3 Preclinical Evidence

Brain functions critically rely on cerebrovascular health, which depends on the integrity of two key functional aspects—blood-brain barrier (BBB) and neurovascular coupling. BBB prevents exposure of the brain parenchyma to potential neurotoxic substances. Neurovascular coupling ensures that the heterogeneous metabolic demands of the different regions of the brain which vary from moment to moment depending on the instantaneous state of information processing (e.g., tactile sensation, visual scene processing) are properly matched. Both BBB integrity and neurovascular coupling are regulated by cells constituting the neurovascular units (NVU), formed by neurons, astrocytes, endothelial cells and vascular mural cells including smooth muscle cells and pericytes [22].

Recent mechanistic studies in animals modeling pathological processes affecting the integrity of NVU have revealed the contribution of neurovascular defects to neurodegeneration in AD. Pericytes play a central role in the maintenance of NVU integrity, regulating both BBB and neurovascular coupling [22–25]. In human postmortem AD brain tissues, pericyte loss is a prominent feature [26]. Transgenic mice with pericyte deficiency induced by loss-of-function mutation or deletion of platelet-derived growth factor receptor-β (Pdgfrβ) exhibit impaired BBB integrity [27, 28], diminished capillary dilation in response to neuronal activation, and reduced brain parenchymal oxygenation [29], alongside extensive white matter dysfunction [30]. In numerous animal models of AD, including the $APP^{sw/0}$, 5xFAD, and other APP transgenic mice, early BBB disruption preceding brain parenchymal β-amyloid deposition, cerebral amyloid angiopathy (CAA), or behavioral deficits is a common feature reported [31–36]. While these findings might be explained by the vasculotoxic and vasoconstrictive effects of β-amyloid oligomer on vascular mural cells [37, 38], it is also becoming evident that pericyte loss also accentuates AD pathology. Knocking out one allele of Pdgfrβ to induce pericyte loss in the $APP^{sw/0}$ mice accelerates amyloid plaque formation and development of CAA [36]. Remarkably, although these mice only carry amyloid precursor protein mutations and typically do not develop tauopathy, the increased pericyte loss is sufficient to trigger increased hyperphosphorylation of tau in the cortex and the hippocampus [36], suggesting a strong role of compromised NVU in augmenting the pathogenesis of AD by favoring development of tauopathy.

The importance of compromised NVU in AD pathogenesis is further exemplified by experiments demonstrating the impacts of different isoforms of Apolipoprotein E (ApoE) on the development of AD pathology and the integrity of pericytes and BBB. ApoE is a class of glycoproteins produced by the liver peripherally and by astrocytes in the brain mediating fat metabolism. In human beings, there are three different isoforms of ApoE, namely, ApoE2, ApoE3, and ApoE4. The ApoE4 isoform is known to be a major AD risk factor. Heterozygous ApoE4 carriers have a 3.7-fold increased risk of AD, while ApoE4 homozygotes are at 12 times risk of AD when compared to ApoE3 homozygotes [39]. Studies replacing murine form of ApoE by different isoforms of human ApoE in mice revealed that ApoE4 can accelerate both amyloid and tau pathologies [40, 41]. In the APP_{SWE}/PS1ΔE9 AD mice model, astrocytic expression of human ApoE4 during the early phase of amyloid seeding results in an acceleration of amyloid plaque pathology development [40]. In double knock-in mice harboring MAPT P301S and human ApoE, ApoE4 significantly exacerbates the neurotoxicity of mutant tau, worsening brain atrophy and neuroinflammation when compared to APOE2 and APOE3 [41]. The effects of ApoE4 on amyloid/tau pathology are partially attributed to neurovascular changes mediated by ApoE4. ApoE itself has an essential role in the maintenance of BBB, as transgenic animals lacking ApoE develop BBB breakdown [42]. On the other hand, ApoE4, but not ApoE2 or ApoE3, leads to activation of a CypA-nuclear factor-κB-matrix-metalloproteinase-9 (MMP-9) proinflammatory pathway in pericytes and results in BBB breakdown, whereas genetic or pharmacological inhibition of this pathway can slow down

neurodegeneration [43]. Accelerated pericyte loss and BBB breakdown, accompanied by increased CypA and MMP-9 accumulation in pericytes in ApoE4 carriers, have also been verified in human brain postmortem brain tissues [44]. Notably, in *APOE* knockout and human ApoE4 transgenic mice, neurovascular deficits occur as early as ages of 2–8 weeks, well before the onset of neuronal dysfunction [42, 43, 45]. It is therefore tempting to speculate that ApoE4-mediated neurovascular dysfunction could be a prominent contributor to both the initiation and subsequent acceleration of amyloid/tau pathology. In fact, other reported risk factors of AD in human, including natural aging, and cardiovascular risk factors such as hypertension, share NVU pathological features such as pericyte degeneration and basement membrane thickening on human autopsy studies [46] and could be explained by their detrimental effects on NVU integrity shown in animal studies [47].

8.4 AD in Poststroke Dementia

Stroke can be seen as a severe "symptomatic" manifestation of cerebrovascular disease. Note that cerebrovascular brain lesions can also be "silent" (e.g., lacunes, microbleeds). Stroke is one of the leading causes of mortality, hospitalization, and disability worldwide. The majority of stroke is secondary to intra-/extracranial large artery atherosclerotic disease, age-related sporadic cerebral small vessel disease (SVD) (including both lacunar infarct and deep intracranial hemorrhage), and cardioembolism (commonly associated with atrial fibrillation) among the elderly. Poststroke early- and delayed-onset dementia is the most recognizable form of vascular cognitive impairment (VCI) or vascular dementia. Poststroke dementia is a prototype of VCI and provides a framework, whereby we can understand and study the complex mechanisms of VCI. Early diagnostic criteria of vascular dementia require the presence of stroke and a clear temporal relationship between stroke and dementia to determine that the dementia is secondary to a vascular cause, rather than to nonvascular causes (e.g., neurodegenerative diseases) [2]. Overall, the prevalence of poststroke dementia is high. A meta-analysis showed that 20% of subjects developed dementia shortly after a stroke, and more than a third will develop dementia after recurrent stroke [48]. Furthermore, if any severity levels of cognitive impairment are considered, as high as 80% of subjects may have some levels of cognitive impairment when assessed 3-month poststroke [49]. Mechanisms of how stroke can cause dementia are complex and are currently hypothesized to be the result of an interplay between the features of the acute stroke lesion (e.g., size, number, and site of lesion), subject's cognitive reserve (e.g., education level), as well as burden of underlying chronic brain pathological changes (e.g., AD pathology, SVD, silent infarcts) [50]. In this section, we will focus on the contribution of AD pathology in the context of stroke. There are other specific forms of VCI, including cerebral amyloid angiopathy (with or without a history of stroke), subclinical cerebrovascular injury (e.g., stroke-free subjects having cognitive impairment associated with lacune, WMH, cerebral microbleeds), or hereditary cerebral SVD (e.g., CADASIL). The potential contribution of AD in these other forms of VCI will not be discussed in this section.

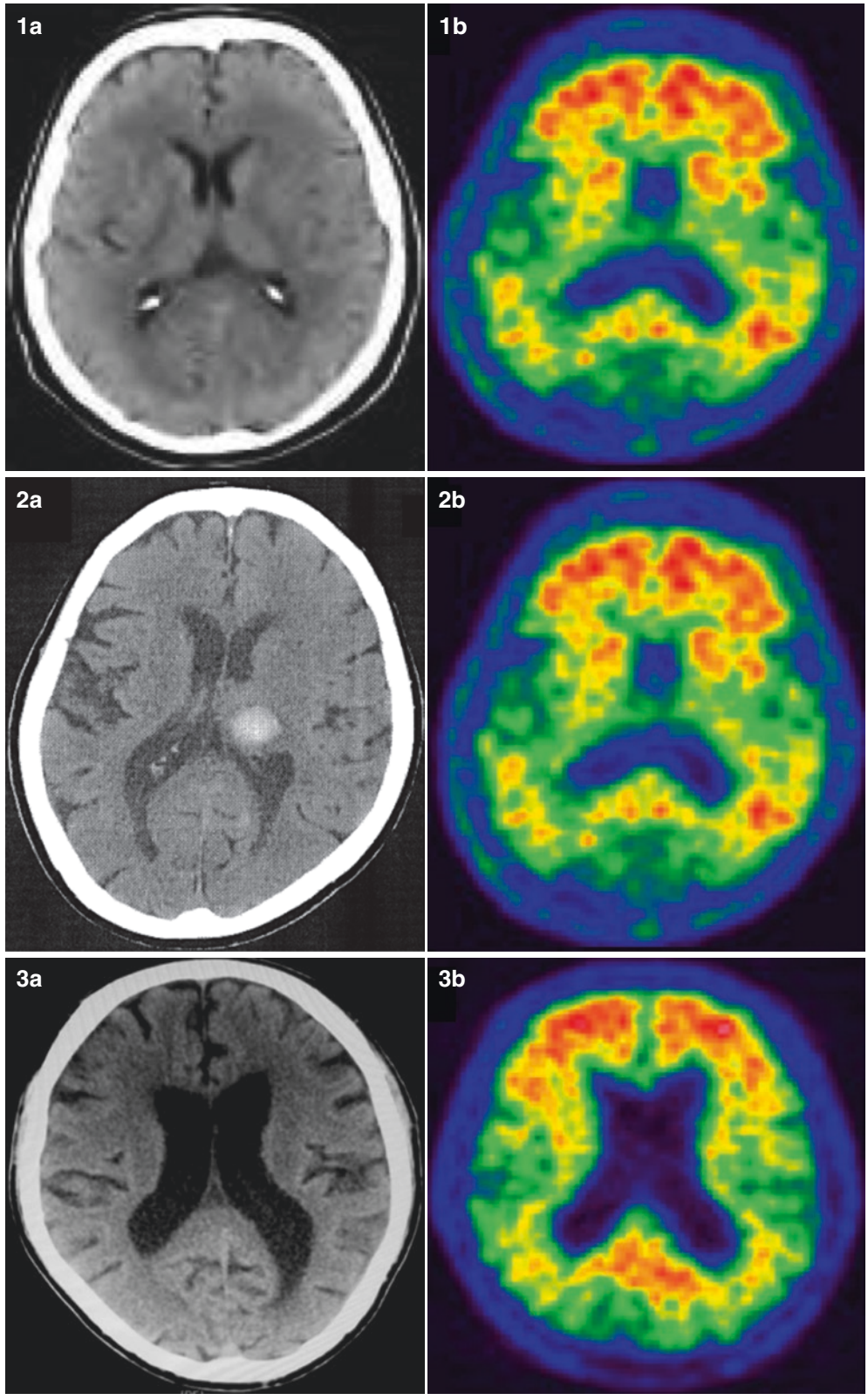
Given the strong clinical and preclinical evidence supporting the association between vascular risk factors and AD, it is natural to assume that AD pathology will also be prevalent in subjects with poststroke dementia [6] given the known strong association between vascular risk factors and stroke. To date, few autopsy studies had investigated particularly the prevalence and relevance of AD pathology in subjects with a history of stroke, poststroke dementia, and/or vascular dementia. Note that many autopsy studies investigating the relationship between AD pathology and cerebrovascular lesions did not provide enough clinical information regarding whether subjects' cerebrovascular lesions were associated with clinically overt stroke or not. In an early study analyzing subjects with a clinical diagnosis of vascular dementia (n = 27), the frequency of subjects with concurrent AD pathology was only

11% [51]. In another population-based autopsy study among subjects with poststroke dementia (n = 15), the frequency of AD pathology was 20% [52]. A more recent autopsy study among a small series (n = 6) of subjects with poststroke dementia diagnosed at 3 months poststroke (subjects with dementia before stroke were not excluded) showed that 50% of patients had concurrent AD pathology [53]. Contrary, in another autopsy study among a subset of subjects recruited from dementia clinic (n = 13) with a clinical diagnosis of vascular dementia, almost half had AD pathology mixed with cerebrovascular lesion (n = 6, 46%), another 6 (46%) had AD pathology only (i.e., without cerebrovascular lesion), while the remaining 1 (8%) had cerebrovascular lesion mixed with Parkinson's disease pathology. In other words, almost all (92%) subjects who were diagnosed to have vascular dementia clinically during life were found to have concurrent AD pathology [54]. Overall, based on the available autopsy studies, the prevalence of AD pathology in subjects with vascular or poststroke dementia varies greatly. Before the advent of amyloid PET in the early 2000s, it is difficult to ascertain the prevalence and relevance of AD pathology in the context of poststroke dementia *in vivo*. This is due to the fact that structural imaging features of AD including medial temporal lobe atrophy or global brain atrophy are also not uncommonly found in subjects with pure vascular dementia [55]. On the other hand, amnestic syndrome resembling that of AD may also be found in vascular dementia [56]. Even the profile of cerebrospinal fluid biomarkers (e.g., β-amyloid 42, tau) of stroke or vascular dementia subjects may resemble that of AD [57]. With the advent of PiB amyloid PET since 2004, [58] it became more feasible to determine the presence of β-amyloid even in the context of stroke. PiB is a carbon-11-labeled ligand with a short half-life of 20 min; hence an on-site cyclotron is needed for its production and administration. Following the discovery of PiB, other longer-lived fluorine-18 based ligands, with a 110 min half-life, were developed (e.g., F-18 florbetapir) and can also be used to study the contribution of β-amyloid in the context of stroke.

Our group conducted the first *in vivo* clinical study exploring the feasibility of using PiB-PET in the study of prevalence and relevance of AD pathology in poststroke dementia [6]. We recruited a convenient sample of ten subjects with new-onset poststroke dementia, four subjects with clinical AD, and three healthy controls to receive PiB-PET. We found that four out of the ten (40%) poststroke dementia subjects had significant amyloid retention (i.e., PiB-positive), while all AD subjects and one out of three subjects were PiB-positive. PiB positivity in this first study was defined by a predominant increase in PiB binding observed visually at the frontal cortex, posterior cingulate, precuneus, caudate, parietal cortex, and/or lateral temporal cortex and by having a global PiB retention standardized uptake value (SUV) at 35–45 min of >1.46. This value was based on the value of the AD subject who had the lowest global PIB retention among our three AD subjects. The mean global PiB retention SUV for PiB-positive stroke subjects was 1.67 (range 1.56–1.82), which was similar to that of the AD subjects (1.65; range 1.46–1.88) and was lower than that of PiB-negative subjects (1.29, range 1.24–1.34). Among the poststroke dementia subjects, we further compared the clinical and imaging profile between PiB-positive and PiB-negative subjects. There was no significant difference in terms of mean age (77 years old) and years of education (4 years) between the two groups. Yet, based on retrospective analysis of the medical records, mean annual mini-mental state examination (MMSE) decline of the PiB-positive subjects (2.9 points) was almost three times as high as the PiB-negative subjects (1 point). In this first in vivo study using amyloid PET in poststroke dementia, we found that significant amyloid plaques deposition mimic that of AD is not uncommon in poststroke dementia (~40%), and its presence is possibly associated with a more rapid cognitive decline. However, given the very small sample size of this study and its non-prospective nature, more conclusive remarks cannot be made regarding the prevalence and relevance of amyloid plaques in poststroke dementia.

Our group further conducted a larger study involving PiB-PET administration among consecutive samples of subjects with early- and delayed-onset poststroke cognitive impairment and dementia [55, 59, 60]. This PiB-PET study was part of a larger study: CU-STRIDE (The Chinese University of Hong Kong-Stroke Registry Investigating Cognitive Decline) [55, 59]. The CU-STRIDE recruited 1013 consecutive subjects with stroke and transient ischemic attack (TIA), aiming to investigate clinical and imaging predictors for early (3–6 months)- and delayed (3–5 years)-onset cognitive decline after stroke or TIA. Yearly cognitive assessment was performed among the recruited subjects. In this study, subjects with prestroke dementia were excluded. In the first phase of this PiB-PET substudy, 50 subjects received PiB-PET, 37 of these had early-onset dementia after the index event, while another 13 subjects who survived stroke/TIA without early-onset dementia and with age, gender, and education matched to those with early-onset dementia were recruited as a comparison. PiB positivity was found in 11/37 (i.e., 30%) and 1/13 (i.e., 7.7%) among those with and without incident dementia, respectively ($p = 0.032$), suggesting that PiB positivity was associated with a significantly higher chance of developing dementia early after stroke/TIA. Further analysis among the 37 subjects who had dementia showed that PiB-positive subjects ($n = 11$) had a higher proportion of subjects having TIA and fewer infarcts when compared with PiB-negative subjects ($n = 26$). These findings suggested that less cerebrovascular burden is needed for the development of dementia in the presence of AD pathology. Of further note is that the prevalence of 7% of amyloid positivity found in CU-STRIDE was lower than that of the estimate of amyloid positivity (~30%) of cognitive healthy controls derived from a large meta-analysis [61]. A similar low rate of amyloid positivity in subjects who survived stroke without dementia was observed in another study, which found that amyloid PET positivity (F-18 flutemetamol) was present in only 5% of individuals who had poststroke mild cognitive impairment no dementia and was lower than that of stroke-free healthy controls (11%) recruited in the same study [62]. A reason explaining the relative low amyloid positivity in subjects who survived stroke without dementia is that majority of subjects harboring concurrent AD pathology will likely develop significant cognitive decline or dementia shortly after stroke because brain reserve in subjects harboring AD pathology is compromised, and the occurrence of cerebrovascular event will easily trigger the manifestation of dementia in these subjects [50]. In the CU-STRIDE PiB-PET substudy, we observed that even a TIA was able to trigger the onset of dementia in subjects harboring AD-like PiB retention (Fig. 8.1). Furthermore, a key finding of the CU-STRIDE main study is that features of acute stroke lesions (e.g., size, site, laterality) were not associated with the development of

Fig. 8.1 Cases on poststroke dementia associated with AD pathology. Case 1. 83-year-old female, with known hypertension, denied prestroke cognitive impairment; she presented with acute aphasia and severe right-sided weakness (power 1/5), CT head was normal upon admission (**1a**), and CT Angiogram showed complete middle cerebral artery occlusion; intravenous tissue plasminogen activator was given and power returned to almost full power shortly after the infusion with improvement in aphasia as well; upon follow-up 5 months poststroke, she complained of progressive cognitive decline since stroke episode, mini-mental state examination score (MMSE) was only 14 with a clinical dementia rating of 2; Pittsburgh compound B (PiB) positron emission tomography (PET) showing Alzheimer's disease (AD)-like PiB retention (**1b**). Case 2. 80-year-old female, illiterate, with known hypertension, living alone, and claimed to have good cognition prestroke; she presented with slurred speech, right-sided weakness (power 2/5), and acute cognitive decline, CT head showed left corona radiata hemorrhage (**2a**); upon follow-up at 3 months poststroke, her cognitive impairment persisted, MMSE score was only 6, clinical dementia rating scale was 1; PiB positron emission tomography showing AD-like PiB retention (**2b**). Case 3. 79-year-old male presented with transient left-sided weakness for 30 min (transient ischemic attack); cerebral computed tomography showed no apparent infarct (**3a**); carotid duplex ultrasound showed 50% stenosis of right internal carotid artery; upon follow-up 3 months after this episode, his wife complained that his cognition had significantly declined since the episode, MMSE was 22 and clinical dementia rating of 1; both wife and patient denied cognitive symptoms before the episode; PiB positron emission tomography showing AD-like PiB retention (**3b**)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early-onset dementia, rather, medial temporal lobe atrophy (an imaging marker of AD) was the strongest risk factor of early-onset dementia. Overall, findings of the above studies suggested that AD pathology significantly compromises brain resilience, and the occurrence of a cerebrovascular event, even if it is mild (e.g., TIA), is able to trigger the onset of dementia.

In the second phase of CU-STRIDE PiB-PET substudy, we administered PiB-PET to 31 subjects who developed progressive cognitive decline over the course of 3 years after baseline assessment (i.e., 3–6 months post-index event). Note that those who developed dementia at baseline (i.e., 3–6 months post-index event) and those who had recurrent stroke/TIA during the follow-up period were excluded from this second phase of the study. We initially hypothesized that concurrent AD was the primary etiology that drive delayed-onset dementia after stroke/TIA. Among these 31 subjects who survived dementia at baseline but later developed cognitive decline of a progressive nature, PiB positivity was found in only six (19%) subjects. A majority of these subjects (19, 61%) had imaging features of severe SVD (i.e., confluent white matter changes and/or ≥3 lacunes) at baseline. Note further that imaging features of severe SVD were found in four of the six PiB-positive subjects as well. A similar finding was observed in an autopsy study showing that delayed-onset dementia after stroke in the elderly is mainly due to cerebrovascular disease, instead of AD [53]. A clinical study involving serial *in vivo* amyloid PET also failed to show any increase in amyloid deposition over a period of ≤18 months after ischemic stroke [63]. In another small case series of stroke patients, ten patients with severe WMH and delayed-onset dementia were administered PiB-PET, but only one patient had AD-like PiB retention [55]. Overall, evidence-based on recent clinical studies using amyloid PET suggested that AD pathology does not play an important role in driving delayed-onset cognitive decline poststroke among subjects who survived stoke/TIA without early-onset dementia.

Finally, we combined all subjects who received PiB-PET during the 3-year follow-up period with serial cognitive assessment [60]. Among the 72 analyzed subjects, 14 were PiB-positive, while 58 were PiB-negative. We found that the rate of cognitive decline was significantly faster in the PiB-positive group compared with the PiB-negative group. The rate of drop in MMSE for the PiB-positive group (2.2 points) was three times faster than the PiB-negative group (0.7 points; $p = 0.023$). In the whole sample, higher PiB SUVR was significantly associated with a greater average annual decline on the total scores of the MMSE and Montreal Cognitive Assessment (MoCA) ($\beta = -0.360$, $P = 0.006$), as well as domain scores of visuospatial and executive functions ($\beta = -0.294$, $P = 0.023$) on the MoCA after correcting for age and years of education.

Findings based on studies showed that concurrent AD pathology is present in about 30% of subjects with new-onset dementia shortly after stroke/TIA. The presence of AD pathology in stroke- and dementia-free subject is associated with reduced brain resilience and increases significantly the risk of developing dementia if a stroke/TIA episode occurs. The presence of AD pathology thus lowers the threshold of dementia after stroke/TIA, and less cerebrovascular burden (or even a TIA) may possibly trigger dementia onset in subjects harboring concurrent AD pathology. Moreover, AD pathology, if present, will enhance a more rapid cognitive decline in the long-term poststroke. However, if the subjects survive stroke without dementia, the prevalence of having significant AD pathology is low among these subjects (e.g., 5–19%) and delayed-onset dementia is mainly driven by vascular and/or SVD pathology in these subjects.

8.5 Conclusion

In this chapter, we provided preclinical and clinical evidence demonstrating the vascular contribution in AD. Vascular risk factors can induce silent cerebrovascular brain lesions that lower the threshold of dementia in subjects with AD pathology, and/or it may directly induce the development of AD pathology mediated by NVU

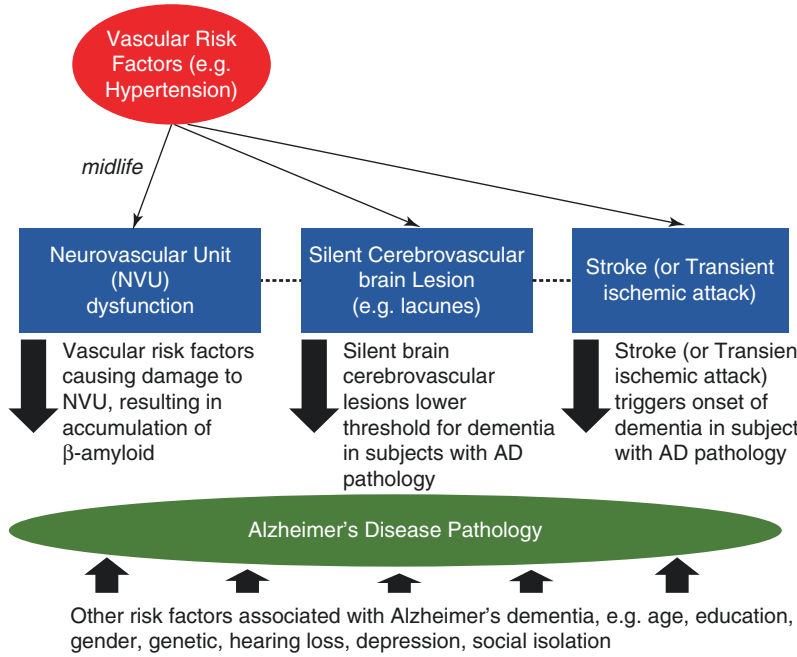

Fig. 8.2 Mechanistic associations between vascular risk factors, Alzheimer's disease, and poststroke dementia

dysfunction. Furthermore, we presented recent data derived from in vivo amyloid PET, showing that AD is also common in poststroke dementia (~30%), its presence significantly lowers the threshold for dementia if stroke/TIA occurs, and it is associated with a more rapid cognitive decline than subjects who have no AD pathology (Fig. 8.2). Overall, evidence to date suggests that vascular risk factors have a causal relationship with AD pathology. Moreover, subjects with concurrent presence of AD or cerebrovascular pathology increase the likelihood of developing dementia via an additive or synergistic effect if the other pathology also exists. These findings highlight the importance of aggressive control of vascular risk factors (to begin at midlife) as well as exploring measures that can prevent amyloid accumulation (i.e., primary prevention). Moreover, in subjects diagnosed with AD-related mild cognitive impairment/dementia, evaluating the presence of concurrent vascular risk factors and cerebrovascular lesions will have prognostic and treatment implications [64]. Vice versa, in subjects presenting with poststroke dementia, evaluating the presence of concurrent AD pathology will also have prognostic and treatment implications. Conventional treatments for AD dementia (e.g., acetylcholinesterase inhibitors) may be used in subjects with poststroke dementia having concurrent AD pathology [64].

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9 Classical Neuroimaging Biomarkers of Vascular Cognitive Impairment

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9.1 Introduction

Vascular cognitive impairment (VCI) can be defined as cognitive disorders related to cerebrovascular diseases despite the variability in its pathogenesis (e.g., cardioembolic, atherosclerotic, ischemic hemorrhagic, or genetic). The term spans a range of cognitive disorders associated with stroke, vascular brain injury, or subclinical diseases [1–3]. The clinical patterns of VCI may differ depending on the vessels involved, the location of vascular lesions, and the stages of disease. Therefore, neuroimaging is critical in the diagnosis and prediction of VCI, due to the direct visualization of ischemic and hemorrhagic injury of gray and white matter [4].

The neuroimaging appearance of VCI can be broadly divided into two subcategories: large vessel disease and small vessel diseases (SVD). VCI associated with large vessel disease can be caused by single or multiple territorial infarctions in cortical or subcortical locations due to occlusions in cerebral arteries and arterioles [5], while the penetrating arterioles in contact with subcortical structures such as deep gray matter (basal ganglia and thalamus) or white matter (periventricular and deep white matter) play a causative role in SVD [3].

In clinical practice, computed tomography (CT) is normally carried out in most acute stroke patients, and as a result, studies using CT have been representative of the whole clinical population. Initially, CT is useful as it can preclude hemorrhage and stroke mimics (such as brain tumors) and can often detect early signs of ischemia (e.g., swelling, hypodensity, and hyperdense vessels) and old stroke lesions. Nowadays, MRI has become more favorable for routine clinical applications as well as for research owing to its heightened sensitivity and specificity for identifying pathological changes as a result of cerebrovascular disease [6]. MRI is very useful for detecting changes of the brain related to SVD including lacunes, white matter hyperintensities (WMH), and cerebral microbleeds (CMB) even before the relevant symptoms are clinically evident [7].

This chapter describes classical neuroimaging markers for VCI based on MRI, their relationships with cognition, and introduces recommended standard MR imaging protocols for image acquisition and analysis for SVD in VCI (Standards for Reporting Vascular Changes on Neuroimaging, STRIVE).

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S.-H. Lee, J.-S. Lim (eds.), *Stroke Revisited: Vascular Cognitive Impairment*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1433-8_9

9.2 Large Vessel Diseases

VCI associated with large vessel disease can be caused by single or multiple territorial infarctions in cortical or subcortical locations (multi-infarct dementia), watershed infarction, single strategic infarct, and chronic hypoperfusion [8].

9.2.1 Multi-Infarct Dementia

The concept of multi-infarct dementia (MID), as outlined in the International Workshop of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) International Workgroup criteria, defines an illness with multiple cognitive deficits and multiple large vessel strokes involving cerebral cortical areas, resulting in a clinical dementia syndrome [9]. Single or multiple infarctions are caused by the occlusion of large and medium-sized arteries such as the internal carotid artery, middle cerebral artery, or proximal perforating arteries [10]. The total lesion volume size, the number of lesions, and the location of each of the individual lesions influence the pathogenesis of MID (e.g., in general, the larger the infarct size, the more severe the dementia) [11, 12]. However, the quantitative correlations between the level of cognitive deficits and lesion volumes or lesion locations have yet to be further elucidated [13]. The NINDS-AIREN criteria known for diagnosing vascular dementia provide a mere limited suggestion that posterior cerebral artery (PCA), bilateral anterior cerebral artery (ACA) distribution, parietotemporal and temporo-occipital association areas, and superior frontal and parietal watershed territories could be the major candidate areas for vascular dementia [9]. Multiple infarctions of any combination of these restricted cortical regions can result in MID [3].

Neuroimaging contributes to identifying the type of stroke (hemorrhagic vs. nonhemorrhagic), localizing the anatomical location of the abnormalities and the condition of large vessels in brain [8]. Diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) is a well-established method for the diagnosis of hyperacute infarction [8]. An infarcted area, which displays decreased Brownian motion, can be shown on the DWI sequence as restricted diffusion with low ADC. Moreover, the subacute-chronic stage of infarction is characterized by local brain atrophy, gliosis, cavity formation, and ex vacuo dilatation of the ipsilateral ventricle in brain imaging [8]. Encephalomalacia and gliosis are seen on T2 and fluid-attenuated inversion recovery (FLAIR) images as a loss of parenchymal tissue with hyperintensity in the infarcted and subjacent tissue with prominence of cerebrospinal fluid (CSF) space (Fig. 9.1a). Laminar necrosis is also detected by signs of hyperintensity in the cortex on T1-weighted and FLAIR images. These changes are visible from 2 weeks after infarction has occurred and are most prominent at 1–3 months. MR angiography (MRA) is one of the important imaging modalities for assessing the status of large vessels of the brain [8, 14], as MRA is highly sensitive in differentiating the size and location of both symptomatic and asymptomatic strokes [10].

9.2.2 Watershed Infarction

Watershed infarctions occur in the distal areas of major cerebral arteries, in the border regions between two or three main cerebral arterial territories [8, 10]. They are classified as external (cortical) and internal (subcortical) watershed infarcts [8, 15, 16]. The external or cortical border zones are located at the junctions of main arterial territories including the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) territories, whereas the internal or subcortical border zones are located at the junctions of the ACA, MCA, and PCA territories with the Heubner, lenticulostriate, and anterior choroidal artery territories [10, 16]. The pathophysiology of watershed infarcts remains controversial. They mostly result from hemodynamic events, usually in patients with severe internal carotid artery (ICA) stenosis or occlusion, systemic hypotension, microemboli, or a combination of the listed causes [14]. There

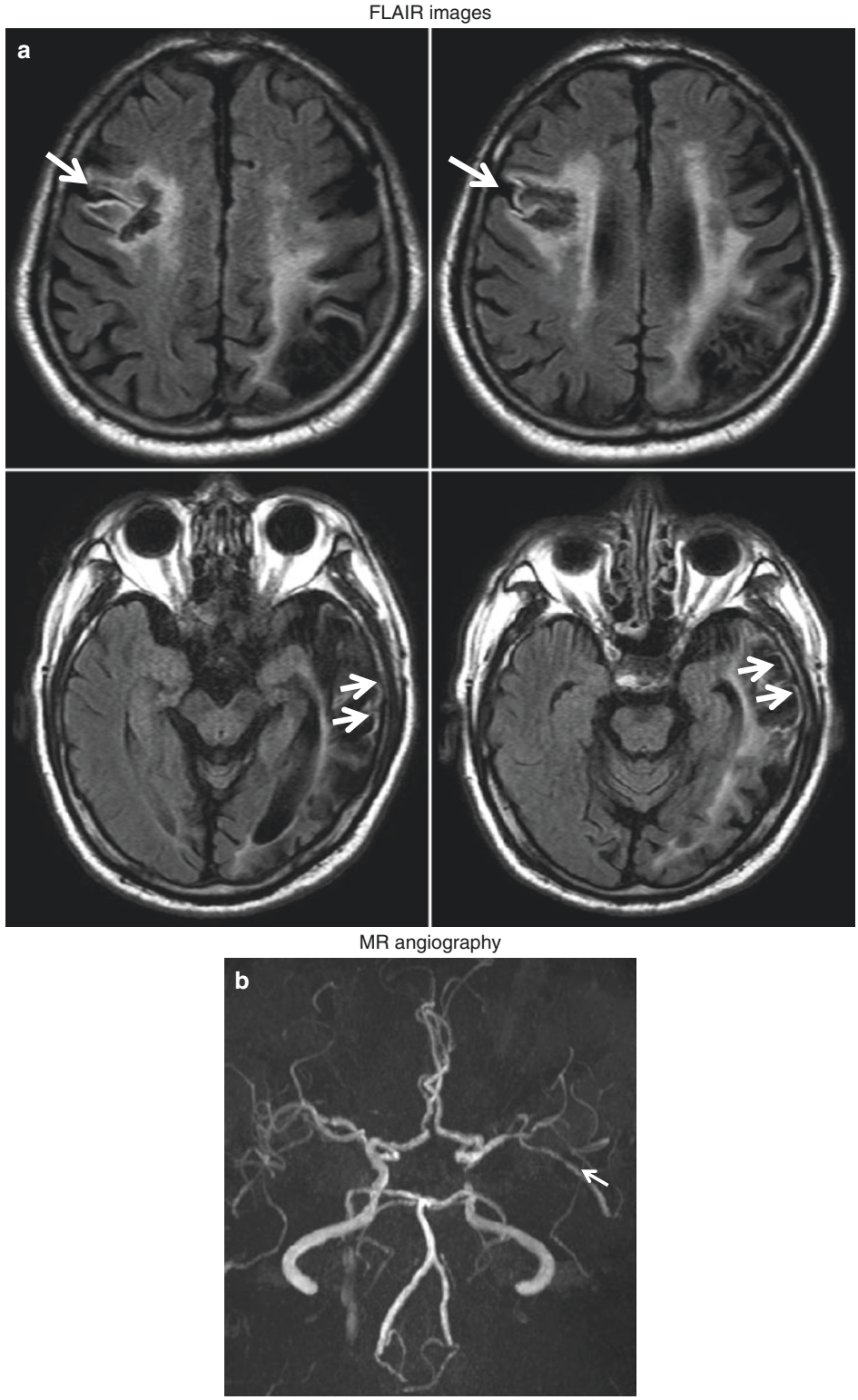


Fig. 9.1 MR images in patients with multi-infarct dementia. (**a**) Axial FLAIR images show chronic right frontal infarction and left MCA territorial infarction with encephalomalacia and surrounding hyperintensities due to gliosis (white arrows). (**b**) MRA shows severe stenosis in left intracranial cerebral artery

is also a consistent association between hemodynamic compromise and internal border zone infarcts, whereas the association between hemodynamic compromise and cortical border zone infarcts is ambiguous [16].

Neuroimaging aims to determine the presence of hemodynamic impairment and assess its severity in patients with border zone infarcts. In the case of acute events, DWI is very sensitive for the diagnosis of both external and internal watershed infarct [16]. External watershed infarcts appear as fan- or wedge-shaped hyperintensities extending from the lateral margins of the lateral ventricle toward the cortex, whereas internal watershed infarcts are seen as hyperintensities running parallel to the lateral ventricles, either confluent or focal, and may be unilateral or bilateral [8, 16]. MRA and perfusion-weighted imaging (PWI) have also been performed in patients with a watershed infarct to evaluate the status of vessels and perfusion.

Cognitive impairment is associated with two types of external watershed infarction: the anterior and posterior watershed infarct. The former is located between the superficial territories of the ACA and MCA, while the latter is located between the MCA and PCA territories. The symptoms of anterior type in the superior frontal area are somnolence and transcortical motor aphasia [3] (Fig. 9.2). The posterior type located in the parieto-temporo-occipital triangle produces Wernicke type of aphasia, hemispatial neglect, anosognosia, transcortical sensory aphasia, cortical hemihypesthesia, sensorimotor hemiparesis, or hemianopia [3].

9.2.3 Single Strategic Infract

Strategic infarct dementia is characterized by focal, ischemic lesions in areas that control or participate in cognition and behavior or higher cortical functions. The strategic cortical sites include the hippocampal formation, angular gyrus, and cingulate gyrus, and the subcortical sites responsible for impairment are the thalamus, fornix, basal forebrain, caudate, globus pallidus, and the genu or anterior limb of the internal capsule [17] (Fig. 9.3).

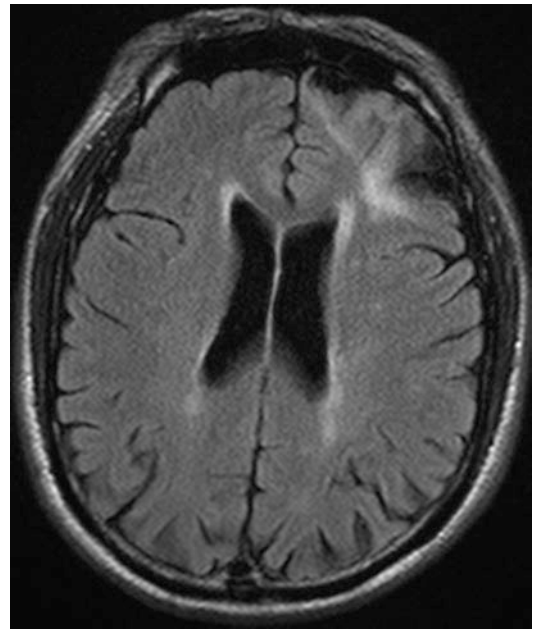


Fig. 9.2 MR images in patients with watershed infarct dementia. Axial FLAIR images show left anterior watershed infarction in a 74-year-old man who showed transcortical motor aphasia and executive dysfunctions

9.2.4 Chronic Hypoperfusion

Diseases of the large arteries and the heart can lead to cerebral hypoperfusion, which can consequently lead to development of cognitive impairment [8]. Since it has been known that the periventricular white matter, basal ganglia [18], and hippocampus [19] are susceptible to chronic ischemic hypoperfusive states, interruption of prefrontal-basal ganglia circuits or hippocampal damage may explain the cognitive decline in these patients [3].

Hypoperfusion can affect both gray matter and white matter. Hypoperfusion may lead to white matter hyperintensities (WMH) and incomplete infarction on FLAIR images [8]. The hippocampus is particularly vulnerable to acute cerebral hypoperfusion [20]. Decrease in size of the hippocampus with increased signal intensity may be visible in T2 and FLAIR images, recurrently accompanied by multiple small infarcts in other brain regions [8]. Cerebral hypoperfusion in patients following cardiac arrest also seems to cause damage to the hippocampus, more so than

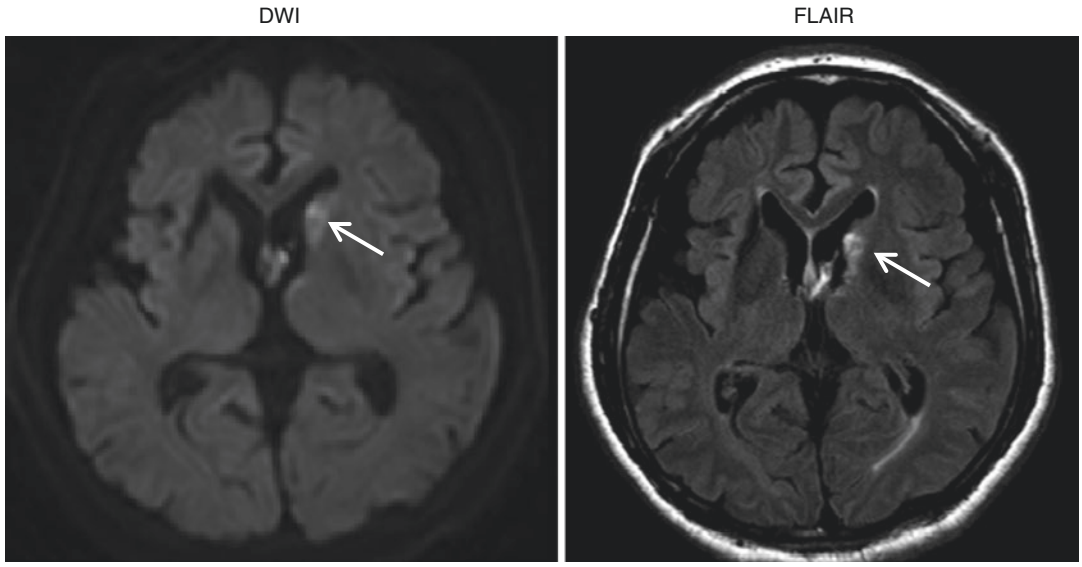


Fig. 9.3 MR images in patients with single strategic infarct dementia. DWI (left) and FLAIR (right) images show left caudate infarction (white arrow) in a 67-year-old man who developed memory impairment and abulia

any other brain regions [21]. One study reported that the hippocampus was 28% smaller in patients 8–21 days after cardiac arrest than in healthy controls matched for age, sex, and body size distribution and it also demonstrated that most of the cell loss occurred in the cornus ammonis (CA) 1 subdivision of the hippocampus [21]. Previous finding also suggests that specific segments of the hippocampus might be particularly sensitive to hypoxia [22]: hippocampus was noticeably reduced in posterior areas of the hippocampus in a cohort of patients following successful resuscitation after cardiac arrest [20].

The association between chronic ischemia and cognitive functions has yet to be further elucidated. However, a few reports suggested that cognitive impairments can be associated with the chronic cerebral hypoperfusion state caused by various medical conditions [23–25]. For example, cognitive impairment is relatively common among the elderly with systolic hypotension due to heart failure [24]. Reduced cerebral perfusion was associated with frontal and memory dysfunctions [26]. Recently, cerebral blood flow velocity predicted deteriorated attention and executive functions as well as more severe depressive symptoms in patients with heart failure [27].

9.3 Small Vessel Diseases

Cerebral small vessel diseases (SVD) refers to a complex of clinical, cognitive, neuroimaging, and neuropathological findings that are thought to arise from a disease affecting the perforating cerebral arterioles, capillaries, and venules and the consequent brain damage in the cerebral white and deep gray matter [28].

Cerebral arterial small vessels originate anatomically from two sources: superficially, they stem from the subarachnoid circulation as the terminal vessels of medium-sized cortical and leptomeningeal arteries, which are derived from larger arteries; and at the base of the brain, they stem directly from the large vessels as small arterial perforators or lenticulostriate arteries [29]. These two structures eventually merge with each other after having passed the cortical layers and the deep gray structures, respectively. They tend to fuse in the deepest areas of the subcortical white matter [29]. The deep penetrating branches are thin, long, and lack of communications, which makes them vulnerable to systemic hypertension [3].

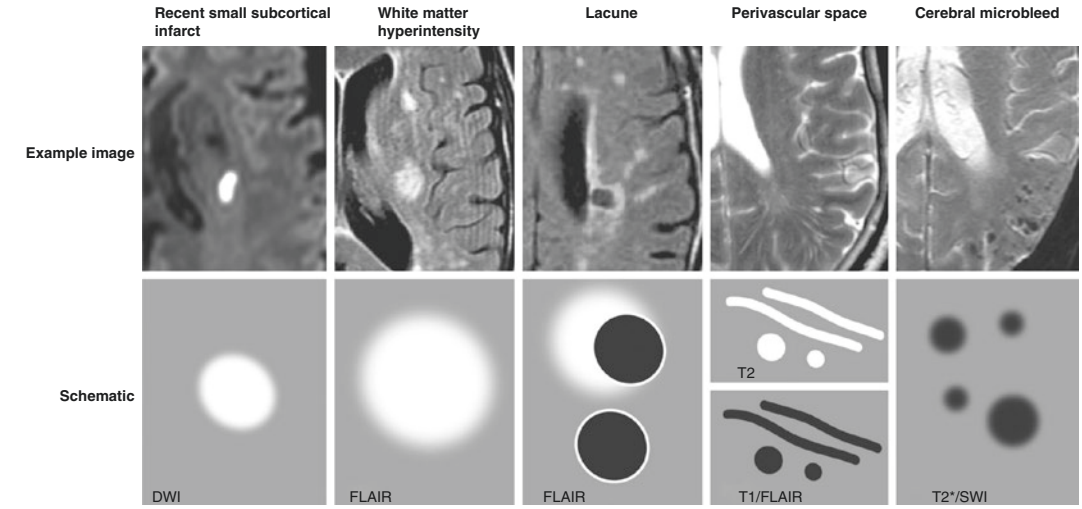
Unlike large vessels, small vessels are hardly visualized in vivo. Hence, the parenchymal

lesions attributed to SVD are epitomized as surrogate markers of the underlying processes for SVD. Recent small subcortical infarcts, lacunes, white matter hyperintensities (WMH), perivascular spaces (PVS), and cerebral microbleeds (CMB) are all distinctive markers of SVD on MRI. Consequently, the term SVD has been applied to describe these features. In addition, clinically SVD usually lack the classic stepwise decline that are typically seen in large vessel disease but rather show a slow progressive course of disease. Neuroimaging, therefore, plays a pivotal role in the diagnosis of SVD, which can detect subtle changes even before the symptoms are clinically manifested in patients with VCI.

Here, this section describes classical neuroimaging characteristics related to SVD seen on MRI according to Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) (Fig. 9.4) [30].

9.3.1 Recent Small Subcortical Infarcts

Recent small subcortical infarct is defined as recent infarction in one perforating arteriole region, with neuroimaging evidence or consistent clinical symptoms relevant to the lesion in the previous few weeks (Fig. 9.4a). The term "recent"



	Recent small subcortical infarct	White matter hyperintensity	Lacune	Perivascular space	Cerebral microbleed
Usual diameter	≤20 mm	Variable	3–15 mm	≤2 mm	≤10 mm
Comment	Best identified on DWI	Located in white matter	Usually have hyperintense rim	Most linear without hyperintense rim	Detected on GRE seq., round or ovoid, blooming
DWI	↑	↔	↔/(↓)	↔	↔
FLAIR	↑	↑	↓	↓	↔
T2	↑	↑	↑	↑	↔
T1	↓	↔/(↓)	↓	↓	↔
T2*-weighted GRE	↔	↑	↔/(↓ if haemorrhage)	↔	↓↓

↑ Increased signal ↓ Decreased signal ↔ Iso-intense signal

Fig. 9.4 MRI findings for lesions related to small vessel diseases, STRIVE criteria. Examples (upper) and schematic representations (middle) of MRI features for changes related to small vessel diseases with a summary of imaging characteristics (lower) for individual lesions are shown. *DWI* diffusion-weighted imaging, *FLAIR* fluid-attenuated inversion recovery, *SWI* susceptibility-weighted imaging, *GRE* gradient-recalled echo. (Reproduced from Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Adapted from Journal of Lancet Neurology [30])

should refer to the lesions with symptoms or imaging features which have occurred in the previous few weeks; the word "recent" is used instead of using "acute" because it includes the first few weeks of the lesion, not just the hyperacute stage only. The word "small" highlights that a lesion should be less than 20 mm in its maximum diameter in the axial plane [30].

Approximately 25% of all ischemic strokes result from clinically evident recent small subcortical infarcts, commonly named lacunar strokes or lacunar syndrome. Occasionally, a silent cerebral infarct is detected under imaging, which is a recent asymptomatic small subcortical infarct. On the contrary, symptomatic lacunar stroke syndromes are not accompanied by visible small subcortical infarcts in up to 30% of patients for reasons as yet unknown [31]. This finding highlights that MRI is not yet entirely sensitive in the detection of such infarcts. Additionally, some studies have shown that different outcomes await the small subcortical infarcts evolving into either a lacunar cavity or hyperintensity without apparent cavitation on T2-weighted sequences or might disappear leaving little visible consequence on conventional MRI (Fig. 9.5). Estimates of the proportion of recent small subcortical infarcts that cavitate range from 28% to 94% [32].

Although further investigation is necessary for accurate definition of upper size limits, lesions in the basal ganglia and internal capsule that are larger than 20 mm should not be classified as small subcortical infarcts but rather as striatocapsular infarcts, a subtype of infarct with a distinct cause [30].

9.3.2 White Matter Hyperintensities (WMH)

White matter hyperintensities (WMH) can be observed as hyperintense areas on T2-weighted sequences and can appear as isointense or hypointense (not as hypointense as CSF) on T1-weighted sequences (Fig. 9.4b). WMH can be depicted as focal or multifocal, and as they become more extensive, they coalesce, and large areas of the white matter may be engaged [33]. WMHs often appear as small "caps" on the frontal and/or occipital horns and as thin "rims" along the walls of the lateral ventricles on transverse sections (periventricular lesions),or as punctuate foci in the subcortical white matter, also referred to as "deep white matter" (deep WMH) at the relatively mild stage. As the severity of the lesions develops, the periventricular WMH may spread into the subcortical white matter, where they can become confluent.

The underlying pathology of WMH is mostly reflective of demyelination and axonal loss due to chronic ischemia caused by cerebral small vessel disease (microangiopathy) [33]. There is a positive correlation between the prevalence and severity of WMH with age and also with arterial hypertension [34]. The pathogenesis of WMH is not yet clearly understood despite their strong association with cerebrovascular disease and vascular risk factors [35], and its nature could be multifactorial including nonvascular pathology such as demyelinating disorders, infections, and neoplastic processes [10, 36]. The term, WMH of presumed vascular origin, was specifically suggested to exclude white matter lesions from other diseases such as multiple sclerosis or leukodystrophies.

In the general population, the prevalence of WMH ranges from 11% to 21% in adults aged around 64 and increases rapidly to 94% at age 82 [35]. Bilateral and mostly symmetrical WMH on T2-weighted MRI are commonly seen in the elderly [30] and could be a nonspecific radiological finding that may be present in both normal and demented populations [10]. However, WMH are also known to be associated with covert neurological and cognitive decline, especially in executive function and information processing speed [33, 37] and physical difficulties such as gait disturbance and urinary incontinence [30, 38, 39]. Some studies have proposed a threshold of 10 cm^2 [40] or white matter lesion load of 25% [41] to have detrimental effects on cognition. Recent study using semiautomated approaches for measuring WMH has suggested that working memory scores were significantly impaired when WMH was present in 3% of the white matter [42]; however, further studies are unavoidable to fully establish the threshold.

The location of WMH also strongly influences the severity of cognitive impairment; some studies have shown that periventricular WMH have

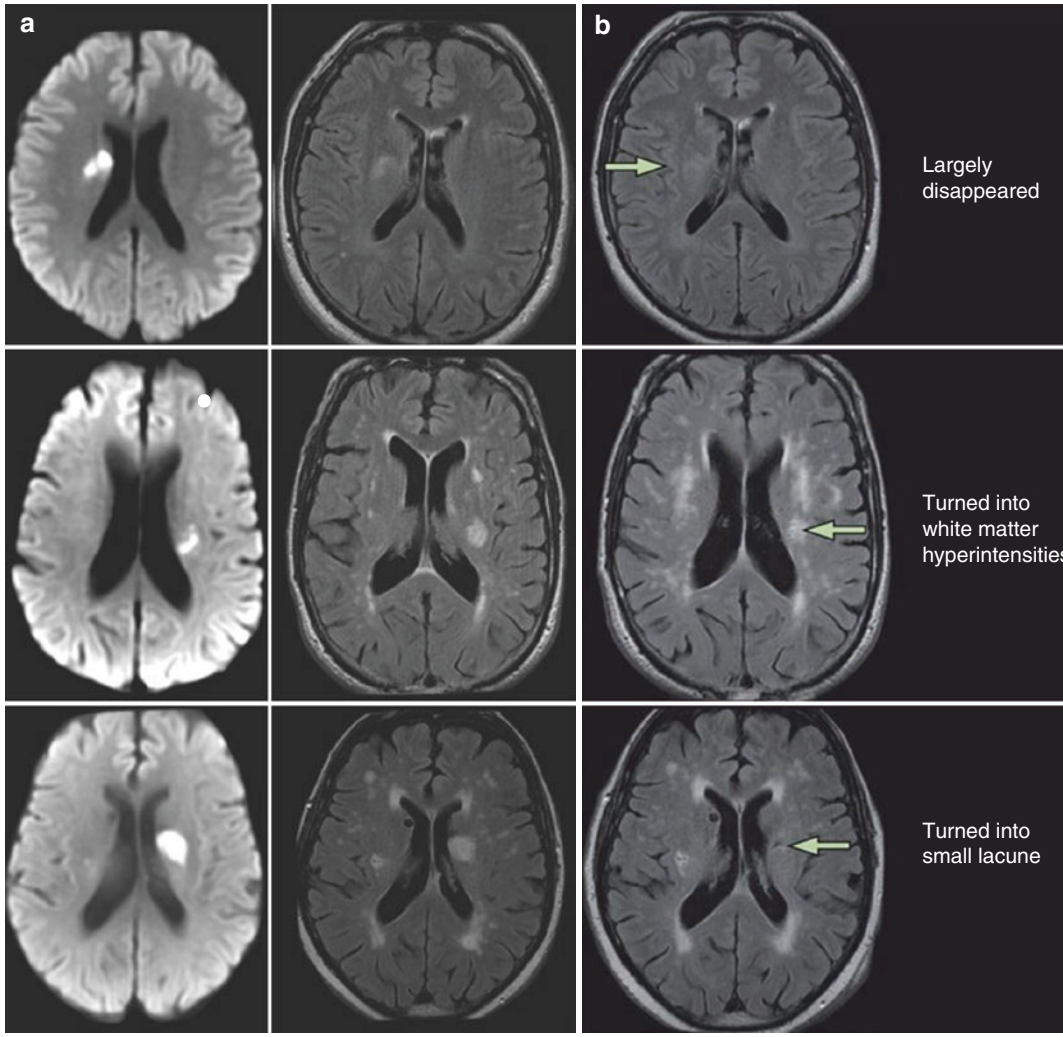


Fig. 9.5 Common late sequelae of acute small deep (lacunar) infarcts. (**a**) Acute stage diffusion-weighted imaging (left column), FLAIR (right column). (**b**) FLAIR images approximately 1 year later. These infarcts can disappear (top), resemble white matter hyperintensities indefinitely (middle), or cavitate to create a lacune (bottom). *FLAIR* fluid-attenuated inversion recovery. (Adapted from Journal of Lancet Neurology [28])

demonstrated greater association with cognitive decline compared to deep WMH [43], which can be supported by the hypothesis that damages to periventricular long association fibers from WMH running close to the ventricles may result in cholinergic denervation in the cerebral cortex [44].

While there are various methods available to gauge presence and severity of WMH on MRI from visual rating to semiautomated and fully automated methods, further research into establishing the gold standard for assessment of WMH is still necessary. Visual rating scales have been adopted in clinical settings when measuring the severity of WMH, owing to their fast speed and reliability when employed by an experience rater. Furthermore, they do not require sophisticated and expensive post-processing facilities. On the other hand, for research purposes, semiautomated and automated methods are favorable for providing exact WMH volumes, which are desirable when subtle association is required. The Fazekas scale, one of the most commonly used visual rating scales [45], is described in Table 9.1 and Fig. 9.6 [33].

Table 9.1 Visual rating of white matter hyperintensities according to Fazekas scale

	Deep white matter		Periventricular white matter
	Number	Extent	
Grade 0	No lesions	No lesions	No lesions
Grade 1	1–4 foci	Punctate foci	Cap or pencil thin lining
Grade 2	5–9 foci	Beginning confluent foci	Smooth halo
Grade 3	More than 9	Confluent	Irregular periventricular caps extending into deep gray matter

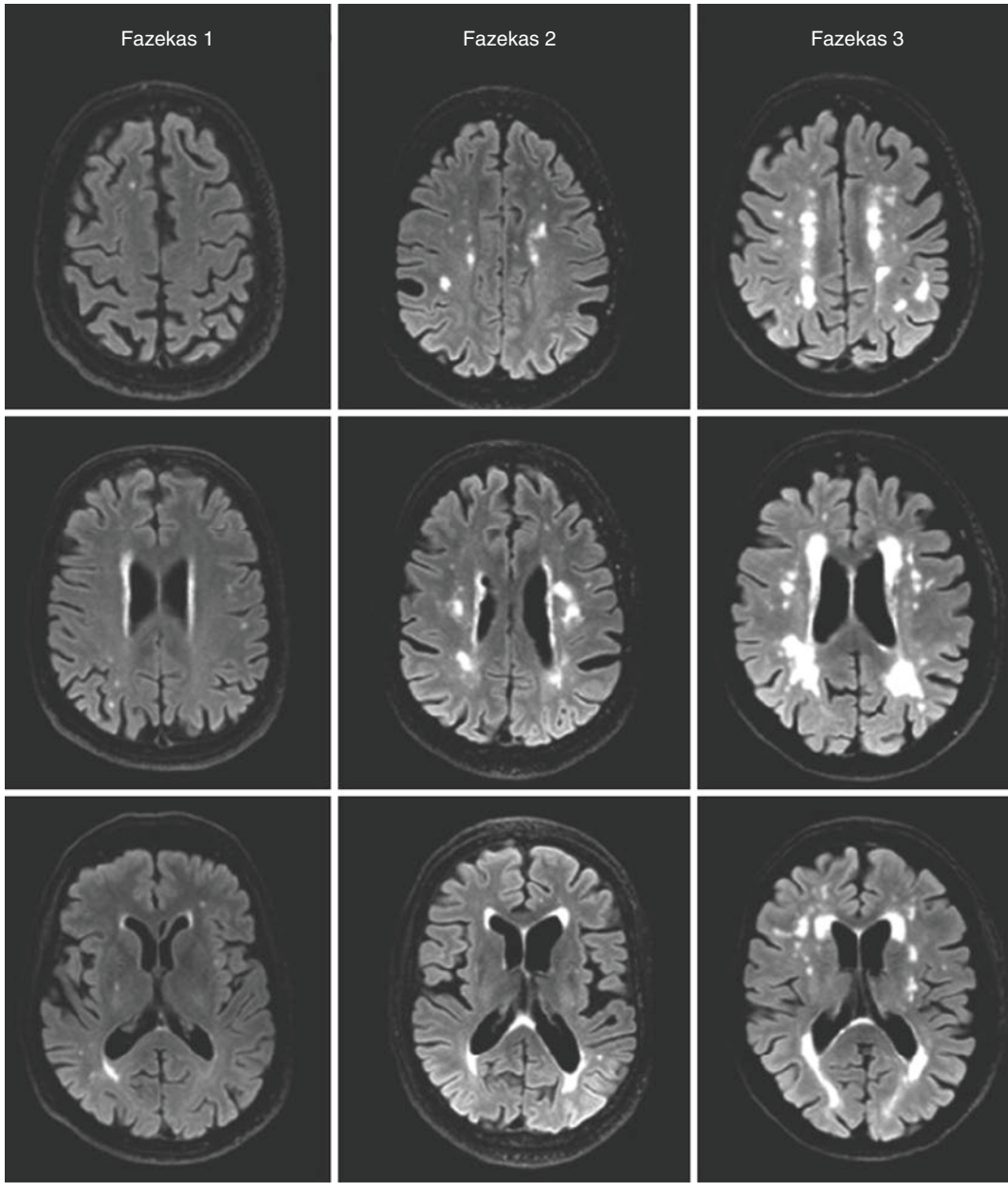


Fig. 9.6 Axial FLAIR images illustrating the Fazekas scales. (Adapted from Journal of Lancet Neurology [33])

9.3.3 Lacunes

According to the STRIVE, lacunes of presumed vascular origin are defined as a round or ovoid, subcortical, fluid-filled (similar signal as that of CSF) cavity, of between 3 mm and about 15 mm in diameter, consistent with a previous acute small deep brain infarct or hemorrhage in the territory of one perforating arteriole.

On FLAIR images, lacunes of presumed vascular origin generally display a central CSF-like hypointensity signals with a surrounding rim of hyperintensity; however, the rim is not always present, and a hyperintense rim can also surround perivascular spaces when they pass through an area of WMH (Fig. 9.4c). In some cases, the central cavity fluid is not suppressed on FLAIR, and the lesion can appear as entirely hyperintense, despite MRI showing a clear CSF-like intensity on other sequences such as T1-weighted and T2-weighted MRI.

Silent lacunes give rise to poorer executive functioning as demonstrated by several studies, suggesting its contributory role in cognitive impairment [46, 47]. This is inevitably consistent with the hypothesis that SVD may disrupt frontal-subcortical circuits [10]. Lacunes may also have important implications for the successful execution of activities critical to the maintenance of an independent lifestyle, due to their association with executive dysfunction [48].

9.3.4 Perivascular Spaces (PVS)

Perivascular spaces (PVS) are branches of the extracerebral fluid space around arteries, arterioles, veins, and venules as they stem from the brain surface into and throughout the brain parenchyma, and they can be followed by sheets of leptomeninges [30]. PVS on MRI are defined as fluid-filled spaces that follow the typical course of a vessel as it goes through gray or white matter, which have signal intensity similar to that of CSF on all sequences (Fig. 9.4d); since they follow the course of penetrating vessels, they appear linear when imaged parallel to the course of the vessel and round or ovoid, with a diameter generally smaller than 3 mm, when imaged perpendicular to the course of the vessel. At high resolution, a central vessel can occasionally be seen in the center of a perivascular space, which could possibly differentiate the spaces from lacunes. PVS are generally most prominent in the inferior basal ganglia and can also be seen coursing centripetally through the hemispheric white matter and in the midbrain; however, the spaces are rarely seen in the cerebellum. PVS can show focal enlargement and can enlarge up to 10–20 mm in diameter, even with mass effect in the inferior basal ganglia.

Recently, the STRIVE described that lacunes of presumed vascular origin should be distinguished from PVS [30]. Although pathological studies have not yet defined an absolute cutoff size, lesions that are less than 3 mm in diameter are more likely to be PVS than lacunes [49]. In addition, PVS usually do not have a T2-hyperintense rim around the fluid-filled space on T2-weighted or FLAIR images, unless they traverse an area of WMH [30]. Additionally, PVS are often described as linear or slit-like, following the course of a blood vessel traveling through the gray or white matter, while lacunes tend to be more ovoid or spherical in nature [50].

In general, enlargement of PVS is associated with other morphological features of SVD such as WMH and lacunes, but not atrophies [51–53]. Some studies have shown that the larger the PVS enlargement, the more impaired the cognitive function. Enlarged PVS were associated with an increased risk of incident dementia, with the highest degree of enlarged PVS on the whole white matter conferring a hazard ratio of 9.8 (95% CI 1.7–55.3) and the highest degree of PVS on basal ganglia resulting in a hazard radio of 5.8 (1.2–28.4) in the healthy elderly [54]. Another study in the healthy elderly investigated that more prominent PVS correlated significantly with impaired performance in tasks of nonverbal reasoning and general visuospatial ability [55]. In addition, prominent basal ganglia PVS were associated with a decrease in information processing speed in patients with hypertension and lacunar strokes, which is independent of age and WMH [56].

9.3.5 Cerebral Microbleeds (CMB)

Cerebral microbleeds (CMB) are recognized as small hypointense lesions that are visible on paramagnetic-sensitive MR sequences such as T2∗-weighted gradient-recalled echo (GRE) or susceptibility-weighted imaging (SWI). On T2∗-weighted MRI or other sequences that are sensitive to susceptibility effects, CMB are well defined, of homogeneous low signal, and have a tendency to manifest as either round or oval in shape, which are visualized as signal void with associated blooming [30] (Fig. 9.4e). The visualized size of CMB depends on MR field strength and sequence due to the blooming artifact. Once imaged with 1.5 T and 3.0 T GRE sequences, CMB are generally 2–5 mm in diameter, but can be up to 10 mm, which most commonly occupy the cortico-subcortical junction, and deep gray or white matter can be found in the cerebral hemispheres, brain stem, and cerebellum. It is debatable to regard hypointensities of less than 2 mm as CMB on 1.5 T MRI, because such minute hypointensities could be classified as artifacts arising from signal loss from only one voxel. Not only this but SWI can also be employed for CMB assessment, and this can be compared to other current MR imaging and outlines of CMB listed in Table 9.2 [57].

Lesions such as calcification, normal vessels seen in cross section, iron deposits from other causes, hemorrhagic metastases (e.g., melanoma), and diffuse axonal injury (e.g., after head trauma) can be easily mistaken for CMB. CMB can be differentiated from an old small deep spontaneous intracerebral hemorrhage because, visually, the intracerebral hemorrhages are larger, irregular in shape with a cystic cavity, and will be detected on T1-weighted and T2-weighted or FLAIR sequences.

If in the past, CMB were regarded as asymptomatic traits of SVD, there has been an increasing positive data which pinpoints toward its association with cognitive impairment. The underlying mechanism of such link between the two requires further research, particularly into justifiable evidence for CMB damaging the brain and leading to dysfunction [2]. Previous studies have shown that CMB load is related to cognitive performance in the healthy elderly as well as patients with cerebrovascular diseases [2, 58, 59]. CMB load tends to have a strong association particularly with executive function, but deficits in global cognition, memory, psychomotor speed, and attention should also be taken into account [2, 58, 59].

Table 9.2 Current consensus of MRI criteria for identification of cerebral microbleeds

• Homogeneous hypointense lesions (black) on T2∗-GRE MRI or SWI
• Well-defined rounded or ovoid in shape (rather than linear)
• "Blooming" effect on T2∗-GRE and SWI compared to T1- or T2-weighted sequences
• Small
• Devoid of signal hyperintensity on T1-weighted or T2-weighted sequences
• Surrounded by brain parenchyma (at least half of the lesion)
• Differentiated from other hypointense lesions or artifacts such as iron or calcium deposits, bone, or vessel flow voids
• Clinical history excluding traumatic diffuse axonal injury

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9.4 Proposed Minimum Standards MR Imaging for Clinical Purpose

The factors which MRI protocol for vascular cognitive impairment should include at least axial DWI and ADC map, FLAIR, T2-weighted, T2∗-weighted GRE or SWI, and T1-weighted imaging. The DWI sequence is particularly very important for identification of recent infarcts, when used in patients with symptoms. In hindsight, MRI with DWI should be considered the reference standard for recent small subcortical infarcts, which could be detected for up to several weeks after cerebrovascular event [30]. Reduced signal on ADC map helps to discriminate recent lesions from old lesions. FLAIR and T2-weighted images are used to identify WMH, lacunes, and cortical infarcts as well as to differentiate WMH from PVS or lacunes. On T2-weighted images,

all these changes are seen as high signal intensities, whereas on FLAIR images, cavities are shown as dark signals. This difference can differentiate lacunes or enlarged PVS from WMH. T1-weighted sequences are obtained to assess regional atrophy. At least one sequence of T1-weighted images with sagittal or coronal plane is helpful to visualize full extent and orientation of lesions. T2∗-weighted GRE or SWI is normally used to detect hemorrhage, CMB, and calcifications [60].

9.5 Conclusion

Neuroimaging plays an important role in identifying vascular lesions of the brain, even before the clinical manifestation of the cognitive decline. Among a variety of neuroimaging modalities, MRI is especially the most frequently used and is widely available in most centers. Although not included in this chapter, modern MRI techniques such as diffusion tensor imaging or arterial spin labeling can help expand our understanding of VCI. Considering that neuroimaging is evolving very rapidly, neuroimaging will continue to play a leading role in the diagnosis of VCI.

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10 Neuroimaging Characteristics of Subcortical Vascular Cognitive Impairment

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Subcortical vascular cognitive impairment (SVCI) refers to the cognitive impairment associated with small vessel diseases (SVD) such as lacunes, white matter hyperintensities (WMH), and cerebral microbleeds (CMB) in the subcortical areas [1], which encompasses both subcortical vascular mild cognitive impairment (svMCI) and subcortical ischemic vascular dementia (SVaD) [2, 3]. Clinically, it is important to detect SVCI as early as possible since early intervention for SVCI can delay the progression of the disease. Therefore, magnetic resonance imaging (MRI) is the most commonly used tool to diagnose SVCI which can detect SVD including lacunes, WMH, and CMB in the subcortical area. In addition, recent methodological advances in MR imaging analysis have enabled further image-based analyses to investigate neuroimaging characteristics related to the mechanisms that underlie cognitive dysfunctions in SVCI.

Although ischemia is regarded as the primary underlying pathology of SVCI, one of the major concerns regarding diagnosis and research for SVCI is that the large proportion of clinically diagnosed SVCI patients often reveal concomitant Alzheimer's disease (AD) pathology [4]. The overlapping clinical manifestations and neuroimaging findings between pure SVCI and mixed AD concomitant with SVD (mixed dementia) have made it difficult to differentiate between the two. With the recent availability of amyloid positron emission tomography (PET) that allows for in vivo detection of cerebral amyloidosis [5], however, it becomes possible to discriminate patients with relatively pure SVCI defined as not having concomitant amyloid (negative amyloid PET scan) from those with mixed pathology (positive amyloid PET scan) [6]. Indeed, a recent study (AMPETIS study) suggests that pure SVCI is more common than expected, which shows that 68.9% of patients with severe WMH compatible with SVCI revealed negative for amyloid PET scan and they were slightly younger and had greater number of lacunes but less severe hippocampal atrophy on MRI than amyloid positive SVaD [6]. Therefore, more recent neuroimaging studies with amyloid PET scan in SVCI have shown that pure SVCI also has distinctive neuroimaging features compared to those in patients with AD or mixed pathology.

Here, this section aims to provide an overview of the structural and functional neuroimaging characteristics of SVCI based on the recent

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S.-H. Lee, J.-S. Lim (eds.), *Stroke Revisited: Vascular Cognitive Impairment*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1433-8_10

neuroimaging studies with MRI, with a special focus on pure SVCI.

10.1 Imaging Criteria for the Diagnosis of Pure SVCI

Criteria for brain imaging requirements by Erkinjuntti et al. were commonly used for diagnosing SVCI [7] (Table 10.1). This brain imaging criteria for SVaD not only cover cases having predominantly WMHs ("the white matter type," Binswanger's disease) but also is applicable for those with predominantly lacunar infarcts ("the lacunar state type"). It is common for both lacunar state and the white matter type to occur together as the underlying pathology involves the lenticulostriate and the penetrating subcortical arterioles of the hemispheric white matter simultaneously [8]. However, these criteria cannot discriminate pure SVCI from mixed dementia.

Recently, a new criterion that could help characterize pure SVaD from mixed dementia has

Table 10.1 Brain imaging criteria for subcortical vascular dementia proposed by Erkinjuntti et al. [7]

A. Computed tomography
• Extending periventricular and deep white matter lesions: patchy or diffuse symmetrical areas of low attenuation (intermediate density between that of normal white matter and that of intraventricualr cerebrospinal fluid) with ill-defined margins extending to the centrum semiovale *and* at least one lacunar infarct
• Absence of cortical and/or cortico-subcortical non-lacunar territorial infarcts and watershed infarcts, hemorrhages, signs of normal pressure hydrocephalus, and specific cause of white matter lesions (e.g., multiple sclerosis, sarcoidosis, brain irradiation)
B. Magnetic resonance imaging
• To include predominantly "white matter cases": extending periventricular and deep white matter lesions, extending caps (>10 mm as measured parallel to ventricle) or irregular halo (>10 mm broad, irregular margins and extending into deep white matter) *and* diffusely confluent hyperintensities (>25 mm, irregular shape) or extensive white matter change (diffuse hyperintensity without focal lesions) *and* lacune(s) in the deep gray matter
• To include predominantly "lacunar cases": multiple lacunes (e.g., >5) in the deep gray matter and at least moderate white matter lesions, extending caps or irregular halo or diffusely confluent hyperintensities or extensive white matter change
• Absence of cortical and/or cortico-subcortical non-lacunar territorial infarcts and watershed infarcts, hemorrhages, signs of normal pressure hydrocephalus, and specific causes of white matter lesions (e.g., multiple sclerosis, sarcoidosis, brain irradiation)

Table 10.2 New operational criteria for pure SVaD[a] [9]

A. Meet the DSM-VI criteria for vascular dementia
1. Development of multiple cognitive deficits manifested by both
(a) Memory impairment (impaired ability to learn new information or to recall previously learned information)
(b) One or more of the following cognitive disturbances:
• Aphasia
• Apraxia
• Agnosia
• Disturbance in executive functioning
2. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from the previous level of functioning
3. Focal neurologic sign and symptoms of laboratory evidence indicative of cerebrovascular disease, which are judged to be etiologically related to the disturbance
4. The deficits do not occur exclusively during the course of an episode of delirium
B. Severe white matter hyperintensities on MRI (cap or band ≥ mm and deep white lesion ≥ 25 mm)
C. Age ≤75 years
D. Number of lacunes ≥5
E. Visual rating scale of temporal atrophy ≤3
F. Exclusion criteria
1. Only patients with SVaD or AD with small vessel diseases are included. Thus, patients with other than AD or SVaD are excluded. These include frontotemporal lobar degeneration, dementia of Parkinson's disease, Lewy body dementia, corticobasal degeneration, and progressive supranuclear palsy
2. Patients with territory infarction, hemorrhage, or high signal abnormalities on MRI that are associated with etiologies other than ischemia, such as radiation injury, multiple sclerosis, vasculitis, or leukodystrophy

AD Alzheimer's disease, *DSM-IV* Diagnosis and Statistical Manual Disorders, Fourth Edition, *SVaD* subcortical vascular dementia

[a]A, B, and F are essential for pure mixed SVaD alike; C, D, and E should be fulfilled to differentiate pure SVaD from mixed SVaD

been proposed using a combination of clinical and MRI findings, based on the data from SVaD patients with amyloid PET imaging [9] (Table 10.2). According to these criteria, among patients who met the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria for vascular dementia [10] and also had severe WMH with a cap or band ≥10 mm and a deep white matter lesion ≥25 mm, the cut-off values of clinical and MRI variables to discriminate pure SVaD from mixed dementia were age ≤75, ≥5 lacunes, and visual rating scale of medial temporal atrophy ≤3, which in total yielded an accuracy of 67.5% [9].

10.2 Characteristics of Structural Neuroimaging in SVCI

10.2.1 Diffusion Tensor Imaging

The subtle change of microstructural integrity of white matters is one of the earliest manifestations of SVCI, although the most prominent manifestations of SVCI on MRI include WMH and lacunes in subcortical areas [11]. Such early changes could not be detected by conventional MRI but can be noticed by diffusion tensor imaging (DTI) [12], and abnormal DTI parameters can identify axonal or myelin disruption in the white matter tracts [13].

Previous studies using DTI analysis indicate that patients with SVCI display reduced fractional anisotropy (FA) in the anterior corpus callosum, frontal and parietal white matter regions [14], and mean FA values of the whole brain [15, 16] compared to controls. This finding suggests that SVCI may have extensive microstructural abnormalities of white matters, although it often appears to be normal on conventional MRI [3].

One of the recent methods for DTI analyses is tract-based spatial statistics (TBSS) that can localize microstructural alterations by mapping diffusion parameters onto a white matter skeleton [17]. This method confirmed decreased FA in the bilateral frontal, temporal, and parietal white matters of AD patients with positive [^{11}C] Pittsburgh compound B (PiB) PET scan compared to the healthy controls (Fig. 10.1a). On the other hand, microstructural changes were seen in all of the white matters in the brain of patients with pure SVaD (characterized as PiB PET negative) when compared to normal controls [18] (Fig. 10.1b). Furthermore, direct comparison between patients with PiB(+) AD and PiB(−) SVaD also showed decreased FA in the anterior and posterior white matter regions of PiB(−) SVaD groups (Fig. 10.1c), unlike the PiB(+) AD group. Such results among the clinically diagnosed SVCI patients may stem from a combination of AD pathology [3]. However, this study based on PiB PET demonstrated that even pure SVCI patients also showed microstructural alterations in posterior white matter regions without amyloid pathology in the brain [18], although the pathophysiology of posterior involvement of white matters in SVCI patients remains unclear.

A more recent study using tract-specific statistical analysis (TSSA) based on 14 major white matter tracts also found that SVCI patients showed focal deficits in the bilateral anterior thalamic radiation, cingulum, superior longitudinal fasciculus, uncinate fasciculus, corticospinal tract, and the left inferior longitudinal fasciculus relative to normal controls, which suggests that SVCI patients might have significant deficits in the tracts that traverse frontal and parietal white matter regions [19]. This finding could support the idea that ischemia in SVCI may preferentially affect the white matter in frontal and parietal regions rather than in the temporal and occipital regions [20–22].

It is well known that cognitive impairments in SVCI are related to ischemic interruption of frontal cortical circuits or disruption of cholinergic pathways that traverse the subcortical white matter [23, 24]. DTI measurement can also be used as one of the markers that correlate with cognitive functions in SVCI once age and other SVD markers are adjusted [25]. It has been suggested that white matter integrity at specific locations in SVCI was related to specific cognitive performance [25]. For example, the low FA and high mean diffusivity (MD) in the genu and splenium of the corpus callosum were associated with lower scores in the global cognitive function and

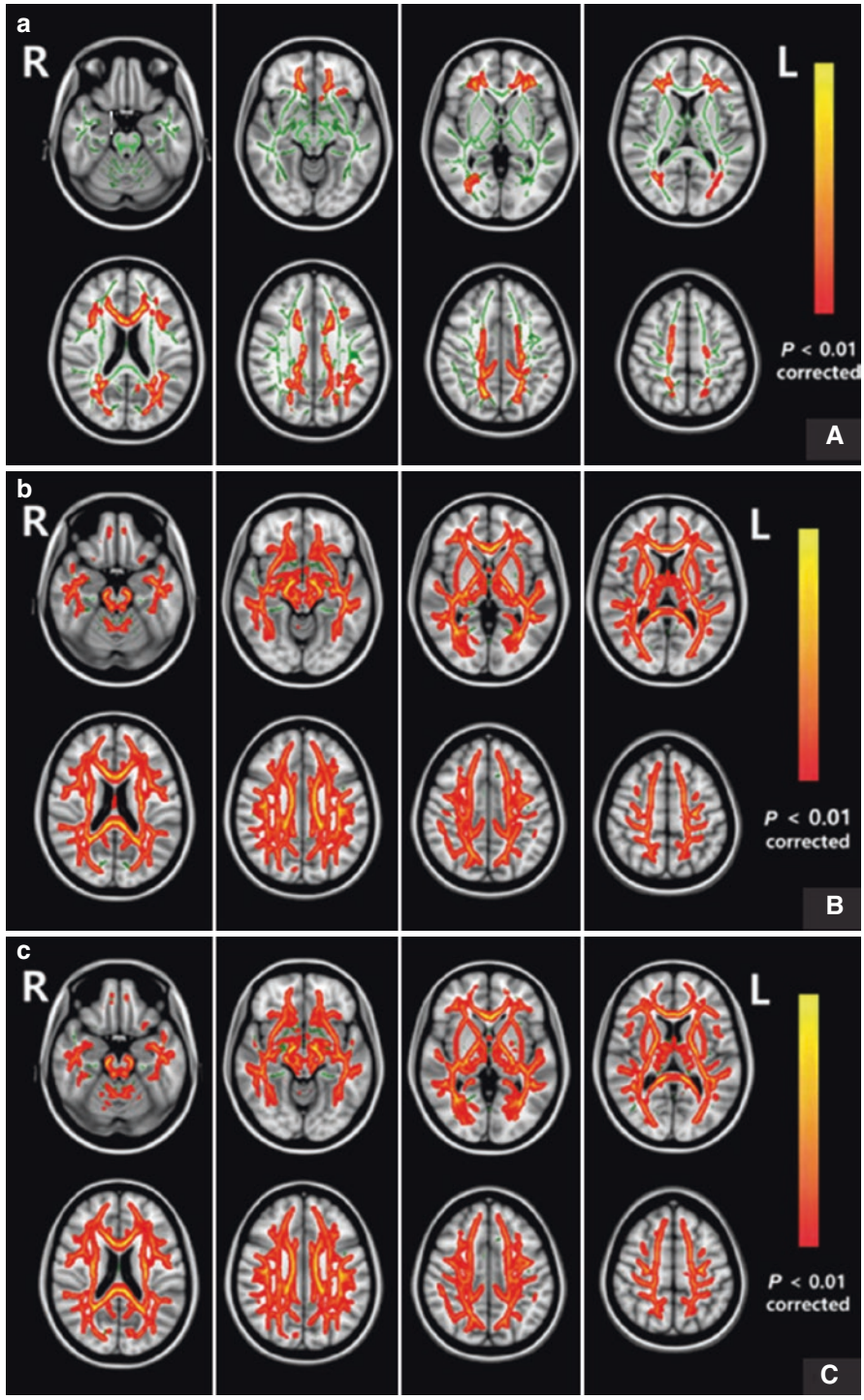

Fig. 10.1 Tract-based spatial statistics results of FA images. Green represents the MNI152 standard brain and the skeleton image. Red-yellow color represents decreased FA (**a**) in PiB(+) AD patients compared with normal controls, (**b**) in PiB(−) SVaD patients compared with normal controls, and (**c**) in PiB(−) SVaD patients compared with PiB(+) AD patients. $P < 0.01$, FWE corrected for multiple comparisons. *AD* Alzheimer's disease, *PiB* Pittsburgh compound-B, *SVaD* subcortical vascular dementia. (Adapted from European Journal of Neurology [18])

executive functions, whereas those in the cingulum bundle correlated with poorer verbal memory performance [25]. An approach with TSSA also indicated that FA values in the cingulum were associated with the scores in language, visuospatial, memory, and frontal functions, while those in the anterior thalamic radiation were associated with scores in attention, language, memory, and frontal functions [19].

It is also noteworthy that microstructural changes in SVCI were also correlated with motor symptoms such as gait disturbances [3, 26, 27]. A previous study showed that gait disturbance in SVCI was associated with decreased FA and increased MD values in the frontal and parietal white matter including anterior thalamic radiation, superior longitudinal fasciculus, cingulum, inferior fronto-occipital fasciculus, corticospinal tract, and corpus callosum [27].

10.2.2 Cortical Thickness

The term "subcortical" vascular cognitive impairment is used by researchers due to prominent WMH and lacunes within white and deep gray matter and their characteristic clinical features associated with this particular anatomic location [1, 28, 29]. Increasing evidence has highlighted that the impacts of SVD on subcortical areas may extend into the cerebral cortex, manifesting both as microscopic vascular lesions and cortical atrophy [30–32]. Therefore, cortical changes have now been considered as clinically relevant characteristics of SVCI [11, 30, 33].

Relative to normal controls, recent cortical thickness measurement revealed widespread cortical thinning in patients with SVCI, especially in the frontal areas including dorsolateral prefrontal cortex, superior medial frontal region, and orbitofrontal gyrus, which are known to be associated with the frontosubcortical circuits [34]. This is contrary to the previous findings showing that patients with AD demonstrated cortical thinning in temporoparietal association cortices including the medial temporal lobe [34–36]. Interestingly, more recent studies based on PiB PET showed that compared to controls, cortical thinning in PiB(−) SVCI was most profound in the perisylvian area, medial prefrontal area, and posterior cingulate gyri, while the precuneus and medial temporal lobes were relatively spared (Fig. 10.2b) [37, 38]. When the cortical thickness of AD and PiB(−) SVaD was directly compared, PiB(−) SVaD demonstrated significant cortical thinning in the bilateral inferior frontal, superior temporal gyri, and right medial frontal and orbitofrontal lobes, while AD showed significant cortical thinning in the right medial temporal region (Fig. 10.2c) [37]. Although the exact mechanisms underlying secondary cortical atrophy are poorly elucidated, it has been believed that cognitive impairments in SVCI arise when the subcortical ischemic vascular lesions demonstrated by WMH and lacunes disrupt the subcortical axonal damage and interrupt the white matter circuits that connect the various cortical regions and subcortical structures, especially the frontal subcortical circuits and the long association fibers, through which the cholinergic pathways pass [23, 39–41]. These lesions also result in a cascade of secondary neuronal degeneration in connected cortical regions via processes known as "dying back" and Wallerian degeneration [42, 43], manifesting as cortical atrophy which may also contribute toward cognitive impairment. In addition, impaired blood flow causes ischemia, and infarction in the gray matter such as cortical microinfarcts may lead to direct cortical neuronal damage and atrophy [37, 44].

Interestingly, the perisylvian cortical area was one of the characteristic areas that was primarily affected in PiB(−) SVaD. It is plausible that cholinergic circuits may participate in cortical thinning in the perisylvian region. Cholinergic pathways penetrate through the anterior cap and into the perisylvian division of the lateral cholinergic pathway which are joined by the opercula and insular cortex [45]. Hence, the cholinergic pathway by the ischemic lesions in SVaD may contribute toward cortical thinning in the perisylvian area. A study which found impaired subinsular cholinergic fibers in dementia with SVD is in support of the cortical thinning in the perisylvian region [46]. Another possible interpretation could be that subcortical WMH or lacunes might affect

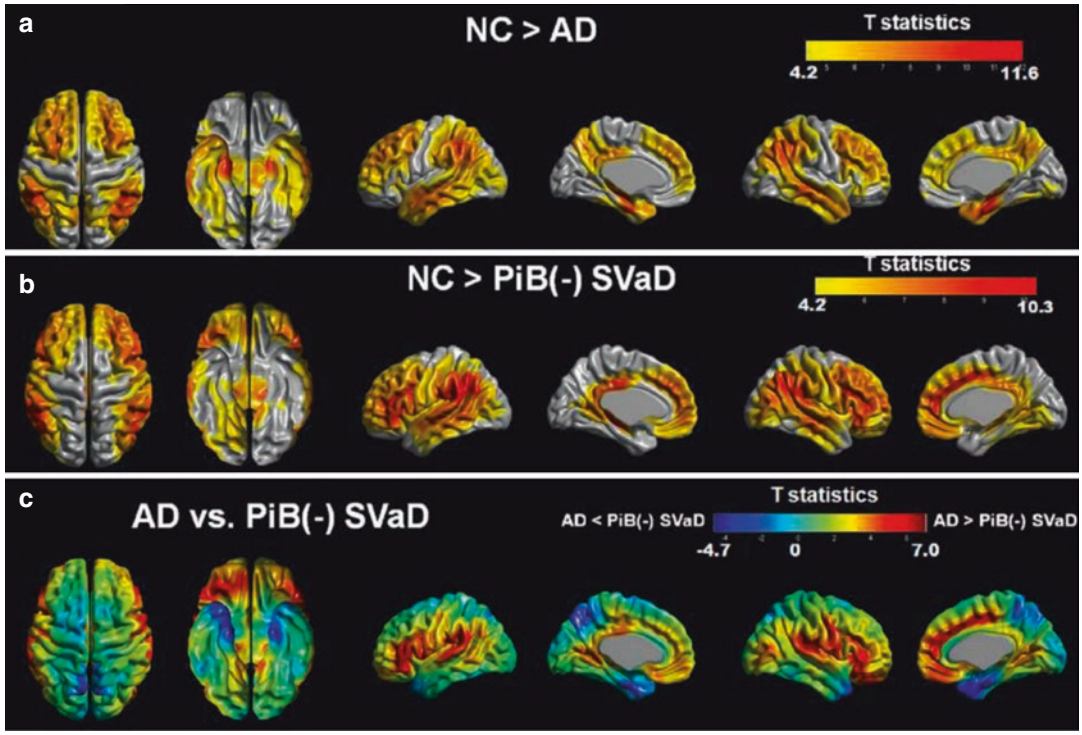

Fig. 10.2 Cortical thickness in PiB(−) SVaD. (**a**) Relative to NC, AD patients showed significant cortical thinning in widespread regions of the temporoparietal and frontal cortices, most prominently in the medial temporal lobes and the inferior parietal lobules. (**b**) PiB(−) SVaD patients showed cortical atrophy in the frontal, temporoparietal, medial frontal, and posterior cingulate cortices and the lingual gyri, while relative sparing in the medial temporal lobe and precuneus. (**c**) The bottom row shows a general trend of cortical thinning between AD (in blue) and PiB(−) SVaD (in red), in particular, statistically meaningful thinning was noted in right temporal lobe in AD and bilateral perisylvian, right medial frontal, and orbitofrontal regions in PiB(−) SVaD. *NC* normal controls, *AD* Alzheimer's disease, *PiB* Pittsburgh compound-B, *SVaD* subcortical vascular dementia. (Adapted from Journal of Alzheimer's Disease [37])

the arcuate fasciculus, which consecutively results in cortical thinning in the adjacent perisylvian region, if there was a strong interrelation between perisylvian cortical thickness and fractional anisotropy of the arcuate fasciculus according to the previous study [47].

10.2.3 Hippocampal Volume and Shape

Although hippocampal atrophy is a key hallmark of AD patients [48, 49], previous studies reported that hippocampal atrophy is also present in patients with SVCI. Hippocampal atrophy in SVCI has been suggested whether it stems from the accumulating burden of ischemia or combined AD pathology [50–52].

Recent studies have demonstrated that pure SVaD defined as the absence of amyloid deposition in PiB PET also had significant hippocampal atrophy compared to normal controls [38, 53] but less than that of AD [53]. Not only this, but hippocampal shape analysis from the same study also showed that both PiB(+) AD (Fig. 10.3a) and PiB(−) SVaD (Fig. 10.3b) patients displayed deflated shape of the cornus ammonis (CA) 1 and subiculum compared with normal controls but more inward deformity in the subiculum of the left hippocampus in PiB(+) AD compared to PiB(−) SVaD (Fig. 10.3c) [53]. Such results all support the idea that cumulative ischemia without amyloid pathology could lead to hippocampal atrophy and shape changes in SVaD.

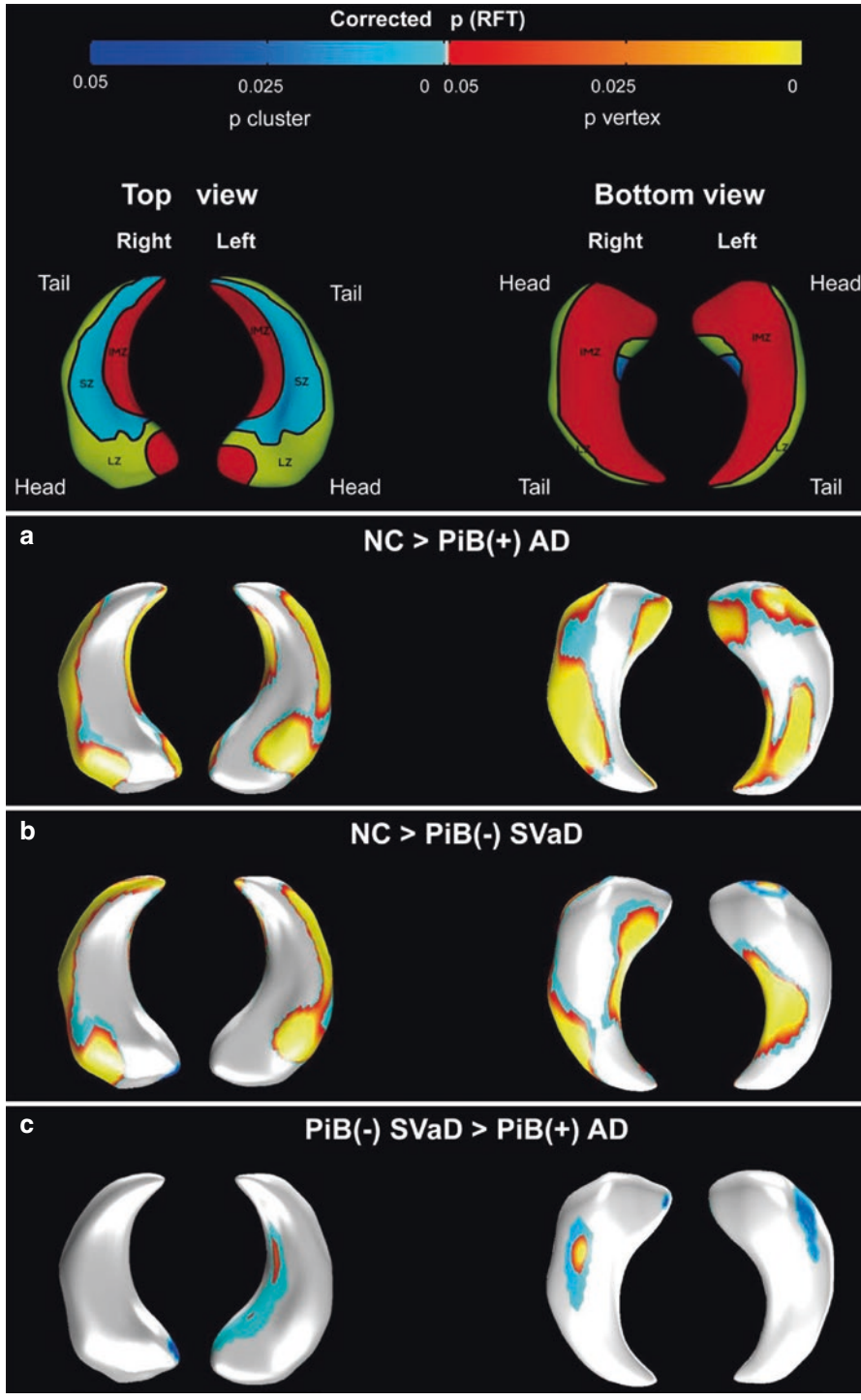

Fig. 10.3 Hippocampal shape comparison. (**a**) Compared with NC, PiB(+) AD patients demonstrate inward deformity in the lateral zones (LZ) containing CA 1 and inferior medial zones (IMZ) approximating subiculum. (**b**) In PiB(−) SVaD patients, the regional inward deformity appears most evident in the LZ and IMZ. (**c**) Compared with PiB(−) SVaD, PiB(+) AD patients show more inward deformity especially in left IMZ. Nonsignificant differences are colored in white. (Adapted from Neurobiology of Aging [53])

Another recent study using an incremental learning method has shown notable results on discriminating mixed dementia from pure SVaD by hippocampus and amygdala shape, with the sensitivity of 95.7%, specificity of 75.6%, and accuracy of 82.4% [54], with pure SVaD highlighted by nonexistence of amyloid deposition on brain confirmed with negative PiB PET scan.

10.3 Structural and Functional Network Analyses in SVCI

A myriad of evidence has suggested that the human brain is a large-scale network with "small-world" topology [55–57], which represents an optimal balance between the integration and segregation of information for efficient use [58]. Therefore, it is known that human cognitive functions depend on the efficient function of the brain networks that consist of cortical gray matter (hubs), subcortical brain regions, and white matter tracts [11, 59].

It has been noted that SVD pathologies in SVCI patients may disrupt the balance in structures and functions of brain network [11]. Undoubtedly, recent neuroimaging studies have shown that the effects of vascular lesions on cognitive functions are mediated through alterations in structural connectivity, which have consistently found an association between the burden of SVD-related brain lesions and reduced network efficiency [59, 60]. Some studies have investigated regional structural connectivity and cognitive functions in SVCI patients [61, 62], which found that reduced network efficiency mediates the effects of SVD-related lesions on frontal gray matter loss, as well as on executive dysfunction [62]. Given that the lower network efficiency predicts conversion to dementia along with older age and lower hippocampal volume [63], structural network disruptions in SVCI may play a pivotal role in the development of cognitive dysfunctions and dementia. In hindsight, these findings emphasize the importance of the network analysis of the structural connectivity as a potential predictive marker in SVCI [63].

Recently, resting-state functional MRI (rs-fMRI) has emerged as an effective, noninvasive imaging technique that is used to study the intrinsic functional architecture of the human brain when subjects are not engaged in external tasks. The rs-fMRI can measure the correlated spontaneous activity within cortical and subcortical regions that are functionally related as well as intrinsic functional organization of the human brain [64]. Although functional connectivity has been less well explored in SVCI, there is some evidence showing that the effects of vascular lesions on SVCI are influenced by altered functional connectivity to some degree [65–68], especially in the frontal brain regions [69, 70].

Recent analysis of resting-state default mode network (DMN) or central executive network (CEN) highlights some distinctive patterns among patients with PiB(−) SVaD, PiB(+) AD, and mixed dementia [70]. When the resting-state DMN of PiB(+) AD and PiB(−) SVaD patients were compared, the PiB(+) AD patients displayed lower functional connectivity particularly in the inferior parietal lobule, whereas the PiB(−) SVaD patients show lower functional connectivity in the medial frontal and superior frontal gyri. Mixed dementia patients, on the other hand, exhibits lower functional connectivity within the DMN specifically in the posterior cingulate gyrus compared to those in the PiB(−) SVaD or PiB(+) AD. In addition, when the resting-state CEN connectivity of PiB(+) AD and PiB(−) SVaD patients were compared (Fig. 10.4), the PiB(−) SVaD patients displayed lower functional connectivity especially in the anterior insular region compared to normal controls. Furthermore, it should be noted that the mixed dementia patients displayed lower functional connectivity within the CEN especially in the inferior frontal gyrus, compared to the PiB(−) SVaD or PiB(+) AD patients. Such accumulative findings point toward the fact that the DMN disruption occurs in both PiB(+) AD and PiB(−) SVaD patients in a disease-specific pattern, while the CEN disruption is more unique in PiB(−) SVaD. Additionally, more profound disruption of DMN and CEN is seen in patients

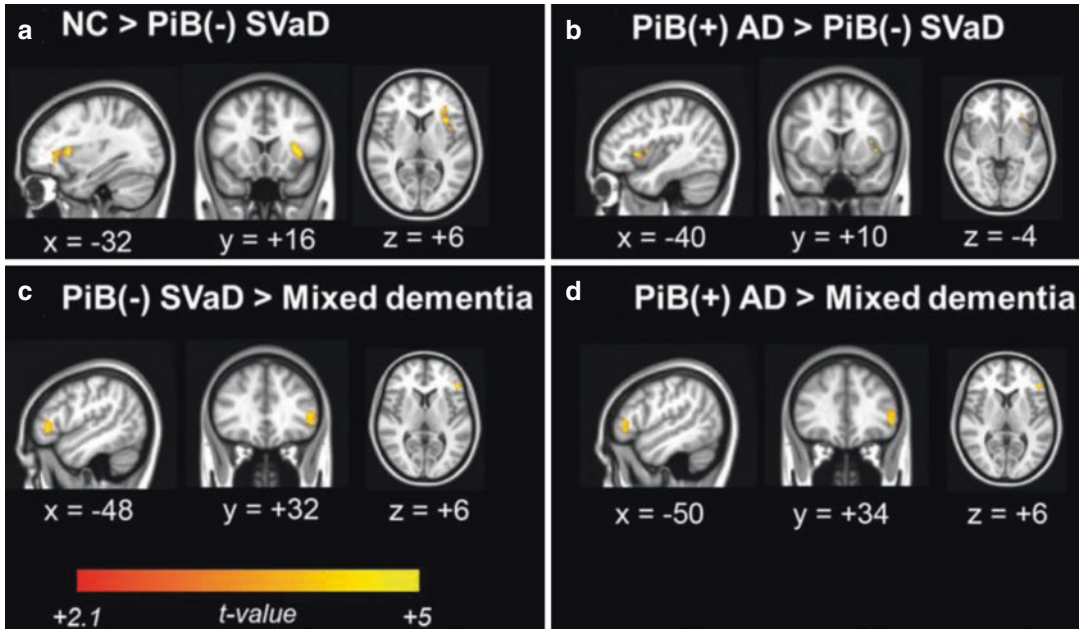

Fig. 10.4 Brain regions with significant differences in resting-state functional connectivity within the central executive network (CEN). Colored areas indicate significantly lower connectivity in the latter group in each comparison. >120 voxel size after post hoc tests with age, gender, and education adjusted. (**a**) Compared to the normal controls, the PiB(−) SVaD patients displayed lower functional connectivity within the CEN in the left insular area. (**b**) In the direct comparison between the PiB(+) AD and PiB(−) SVaD patients, the PiB(−) SVaD patients displayed lower functional connectivity within the CEN in the left insular area, while there was no region where the PiB(+) AD patients displayed lower functional connectivity. (**c**) Compared to the PiB(−) SVaD patients, the mixed dementia patients displayed lower functional connectivity within the CEN in the left inferior frontal gyrus, while there was no region where the PiB(−) SVaD patients displayed lower functional connectivity compared to the mixed dementia patients. (**d**) Compared to the PiB(+) AD patients, the mixed dementia patients displayed lower functional connectivity within the CEN in the left inferior frontal gyrus, while there was no region where the PiB(+) AD patients displayed lower functional connectivity. (Adapted from Journal of Alzheimer's Disease [70])

with mixed dementia that combined AD and SVD burdens. All in all, a growing body of evidence suggests that disturbances in large-scale functional brain networks play a decisive role in cognitive decline [11].

10.4 Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) Findings in SVCI

Functional neuroimaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) techniques are known to provide quantitative information on the possible functional changes which can occur in the early course of disease [71, 72]. SPECT, in particular, is advantageous to investigate cerebral blood flow (CBF), whereas PET can measure regional oxygen (^{15}O isotope) and glucose (^{18}F isotope) metabolism besides CBF and cerebral blood volume [73].

It is well known that the variations in CBF can be compensated with autoregulatory mechanism under normal condition, which means that blood vessels can dilate to maintain regional CBF when cerebral perfusion pressure decreases. With further decline of regional CBF, oxygen extraction fraction (OEF) increases to sustain regional cerebral oxygen metabolism ($CMRO_2$) [1]. Therefore, increased OEF is a characteristic of ongoing ischemia and impending infarction [1].

The compromised autoregulatory reserve in patients with SVCI can increase the risk of isch-

emia if blood pressure should be abruptly lowered (e.g., orthostatic hypotension, aggressive antihypertensive treatment or cardiac failure, etc.) [1]. Several studies have shown that decreased CBF in SVCI may be directly linked to the compromised vascular reserve [74, 75]. A study using ^{15}O PET discovered that resting CBF in patients with Alzheimer's and Binswanger's diseases both decrease within a similar range, with only the latter having a vasoreactive response to hypercapnia [74]. Such adjustment in vasoreactivity in response to acetazolamide is found only in SVaD, not in multi-infarct dementia [75]. Other ^{15}O PET studies also support the above results showing that CBF and $CMRO_2$ were notably reduced in both the white matter and parietal, frontal, and temporal cortices in patients with Binswanger's disease [76, 77], which suggests patients with SVaD had misery perfusion and impaired cerebral vascular reserves.

In patients with Binswanger's disease, the pattern of cerebral perfusion measured by SPECT using *N*-isopropyl-*p*-^{123}I-iodoamphetamine (IMP) as a tracer revealed that regional perfusion was decreased in the thalamus, basal ganglia, and frontal areas, whereas perfusion in AD dementia patients was lowered in the parietal and temporal areas compared to normal controls [78]. Another SPECT study using the same tracer also demonstrated similar results showing that patients with Binswanger's disease had greater CBF reduction in frontal and anterior cingulate cortices, whereas patients with AD dementia had greater CBF reduction in temporoparietal and posterior cingulate cortices compared to normal controls [79]. Similarly, statistical parametric mapping analysis of SPECT using ^{99m}Tc-ethyl-cysteinate dimer(^{99m}TCD) as a tracer showed that reduced regional CBF was noted in the right thalamus, left caudate nucleus, and cingulate, bilateral superior temporal, and left ventral subcallosal gyri in patients with SVaD compared to normal controls [80] (Fig. 10.5). A more recent SPECT study showed that there were no differences in the regional patterns of CBF between the Binswanger's and the lacunar type [81].

In addition to oxygen metabolism, the pattern of glucose metabolism using [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) is also commonly applied to differentiate various types of dementia, which is one of well-established methods to reveal impaired function that usually precedes atrophy [71, 82]. With FDG-PET, SVaD patients showed decreased glucose metabolism in the frontal lobe and deep nuclei, whereas AD dementia patients revealed decreased metabolism in temporoparietal regions [83–85]. Even in patients with svMCI, FDG-PET shows hypometabolism in the subcortical areas especially in the thalamus, cerebellum, and brain stem, which is a distinctive feature compared to that of amnestic mild cognitive impairment [86] (Fig. 10.6). Frontal executive dysfunction in SVaD can also be explained by the FDG-PET study, which revealed that white matter lesions lead to impaired glucose metabolism in the frontal lobe regardless of their location [87].

10.5 Conclusions

MRI has a great potential for diagnosing and differentiating SVCI from various diseases, by providing disease-specific features in cortical, subcortical, and white matters that may occur before the onset of cognitive decline in SVCI. Modern MRI techniques such as DTI or rs-fMRI provide a good opportunity to investigate ischemic vascular lesion as well as detect early changes that are predictive of individual's risk for developing dementia or progression of disease [88] in SVCI as a preventative measure. In addition, SPECT and PET can also be considered as a complement to characterize SVCI from other types of dementia, although there is little consensus on a specific brain perfusion pattern in SVCI. Furthermore, with the aid of amyloid PET, the identification of pure SVCI has provided further insights into the understanding of neuroimaging characteristics of pure SVCI, which may help choose proper management for SVCI according to the presence of amyloid deposition [71]. In the near future, the advancement of neuroimaging will in all likelihood broaden our knowledge of the development of cognitive decline in patients with SVCI.

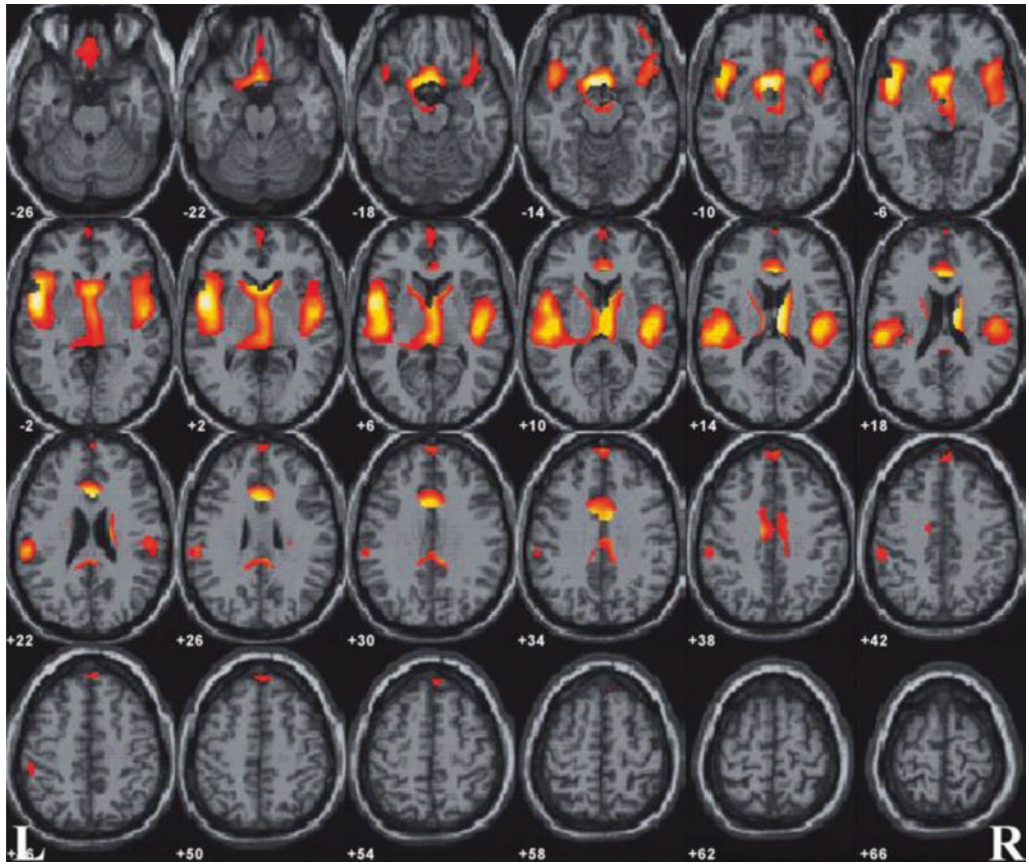

Fig. 10.5 SPM analysis of SPECT results in SVaD. Areas with decreased regional cerebral blood flow in patients with SVaD in comparison to the healthy controls are presented in red and yellow colors (corrected $P < 0.05$). In patients with SVaD, reduced regional CBF was noted in the right thalamus, left caudate nucleus, and cingulate, bilateral superior temporal, and left ventral subcallosal gyri compared to normal controls. (Adapted from Journal of the Neurological Sciences [80])

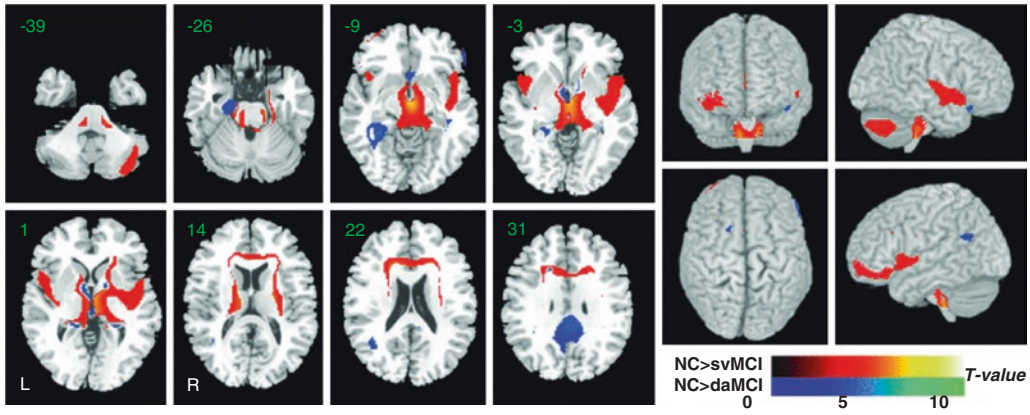

Fig. 10.6 Cerebral glucose metabolism in subcortical vascular MCI. The areas in red represent the brain regions that were more hypometabolic in subcortical vascular mild cognitive impairment (svMCI) than in normal controls (NC), and those in blue represent brain regions that were more hypometabolic in amnestic MCI (aMCI) than in NC. (Adapted from Journal of Neuroimaging [86])

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11 Pharmacological Treatment: Current Evidence for Clinical Uses of Alzheimer's Disease Drugs

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11.1 Introduction

Vascular dementia (VaD) is the second most common form of dementia after Alzheimer's disease (AD). The prevalence of VaD ranges from 1.2% to 4.2% in people over 65 years old and rises linearly with age [1]. VaD is more prevalent in Asians, Blacks, and Hispanics relative to Whites [2, 3]. VaD has been reported to account for 10–50% of dementia cases, depending on the diagnostic criteria and study population [4]. Despite the relatively high prevalence of VaD, no effective medication is currently approved for VaD, so its treatment is limited to the control of known vascular risk factors.

The mainstay of therapy for patients with AD, the other most common form of dementia, is the use of centrally acting cholinesterase inhibitors including donepezil, galantamine, and rivastigmine. Memantine, a partial antagonist of *N*-methyl-D-aspartate (NMDA) receptors, is also approved for the treatment of moderate and severe AD. A number of studies have been designed to determine the efficacy and tolerability of these AD drugs in patients with VaD. However, at the present time, the regulatory approval for the treatment of VaD with these AD drugs has not been acquired in most parts of the world, despite some positive but small effects observed in clinical trials. This chapter will review the background and results of the available clinical trials of AD drugs in VaD.

11.2 The Rationale for the Use of AD Drugs in VaD

11.2.1 Cholinergic Deficits in VaD

Growing evidence for cholinergic deficits in VaD has provided the rationale for the use of cholinergic agents in VaD and led to clinical trials of cholinesterase inhibitors in VaD. Animal models attempting to reproduce VaD exhibit decreases in cholinergic markers. Region-specific decreases in choline acetyltransferase (ChAT) activity, acetylcholine (Ach) levels, and synthesis and release of ACh have been observed in several animal models of cerebral ischemia [5–7]. For example, studies in spontaneously hypertensive stroke-prone (SHSP) rats, a validated animal model for VaD, demonstrated significant reductions in the levels of ACh and choline in the cortex, hippocampus, and cerebrospinal fluid (CSF) of SHSP rats compared with normal control rats [8].

Several postmortem and clinical studies in VaD patients also suggest cholinergic deficits are associated with VaD. Patients with VaD showed decreased brain ChAT activity located in the cortex, hippocampus, and striatum [9, 10]. Compared

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S.-H. Lee, J.-S. Lim (eds.), *Stroke Revisited: Vascular Cognitive Impairment*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1433-8_11

with controls, Binswanger or multi-infarct VaD patients had significantly lower CSF ACh concentrations in postmortem measurements [11]. Cholinergic fibers pass through the white matter and carry widespread cholinergic input to the cerebral cortex, hippocampus, and amygdala [12]. Cerebral ischemia may interrupt these cholinergic pathways. Cholinergic denervation was observed even in a young patient with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a genetic model of pure VaD without AD pathology [13].

11.2.2 Glutamate Toxicity and Neurodegeneration in VaD

Glutamate is the primary excitatory amino acid neurotransmitter in cortical and hippocampal neurons [14]. Excessive stimulation of glutamate receptors triggers an influx of Ca^{2+} through the receptor-controlled channels and subsequently leads to cell death. One of the receptors activated by glutamate is the NMDA receptor [15]. Because of the critical role of excessive glutamate release and over-activation of neuronal NMDA receptors in the pathophysiology of nerve cell death [16], NMDA receptor antagonists might be expected to protect against neurodegeneration.

Memantine, an uncompetitive NMDA receptor antagonist, is approved for the treatment of AD. In animal models, memantine has proved to be effective against ischemic nerve cell injury [17, 18]. The rationale for memantine trials in VaD patients has been based on the expected role of NMDA receptor antagonists which may reduce neuronal damage caused by cerebral ischemia [19, 20].

11.3 Clinical Trials of AD Drugs for VaD

Currently, there are eight published randomized controlled studies (three donepezil, two galantamine, one rivastigmine, and two memantine trials) that investigated the efficacy and safety of AD drugs in VaD. Table 11.1 summarizes these clinical trials.

11.3.1 Donepezil

Donepezil is the most commonly used cholinesterase inhibitor developed for the treatment of AD. It reversibly inactivates cholinesterase, thus inhibiting hydrolysis of ACh. This results in an increased ACh concentration at cholinergic synapses. Two large-scale randomized controlled trials (RCTs) of donepezil enrolled patients with probable or possible VaD according to the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria [21, 22]. A total of 1219 subjects were recruited for a 24-week, multinational, multicenter, randomized, double-blind, placebo-controlled study divided in two identical trials, 307 [21] and 308 [22]. All patients had brain imaging prior to the study (CT or MRI) with demonstration of relevant cerebrovascular lesions. The patients were randomized to one of three groups: placebo, donepezil 5 mg/day, or donepezil 10 mg/day. Patients in the donepezil 10 mg/day treatment arm received donepezil 5 mg/day for the first 4 weeks and 10 mg/day thereafter. The endpoints included cognition measured with the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Mini-Mental State Examination (MMSE), global function measured with the Clinician's Interview-Based Impression of Change-Plus version (CIBIC-plus) and the Sum of Boxes of the Clinical Dementia Rating (CDR-SB), and activities of daily living (ADL) measured with the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS). The primary efficacy outcome measures were ADAS-cog and CIBIC-plus.

In the study 307 [21], at week 24, both donepezil groups showed significant improvement in cognition versus placebo on the ADAS-cog; the mean changes from baseline score were as follows: donepezil 5 mg/day, −1.90 ($p = 0.001$), and donepezil 10 mg/day, −2.33 ($p < 0.001$). The

Table 11.1 Randomized controlled trials of cholinesterase inhibitors and memantine for vascular dementia

Medication	Trial	Trial duration (weeks)	Participants				Outcomes	
			Number	Inclusion criteria	Mean age (years)	Sex (% men)	Primary	Secondary
Donepezil	Donepezil 307	24	Total 603 Placebo 199 5 mg/day 198 10 mg/day 206	Probable or possible VaD (by NINDS-AIREN) MRI or CT evidence of VaD MMSE 10–26	73.9	55%	ADAS-cog[a] CIBIC-plus[b]	MMSE[a] CDR-SB[c] ADFACS[a]
	Donepezil 308	24	Total 616 Placebo 193 5 mg/day 208 10 mg/day 215		75.0	60%	ADAS-cog[a] CIBIC-plus[a]	MMSE[a] CDR-SB[c] ADFACS
	Donepezil 319	24	Total 974 Placebo 326 5 mg/day 648	Probable or possible VaD (by NINDS-AIREN) MRI or CT evidence of VaD	73.0	59%	VADAS-cog[a] CIBIC-plus	ADAS-cog[a] MMSE[a] CLOX 1/2 EXIT-25 CDR-SB DAD
Galantamine	GAL-INT-6	24	Total 592 Placebo 196 Galantamine 396 (VaD subgroup 252 Placebo 81 Galantamine 171)	Probable VaD (by NINDS-AIREN) or Possible AD (by NINDS-ADRDA) combined with CVD MRI or CT evidence of VaD MMSE 10–25, ADAS-cog ≥12	75.1	53%	ADAS-cog[a] CIBIC-plus[a]	ADAS-cog/13[a] DAD[a] NPI[a]
	GAL-INT-26	26	Total 788 Placebo 391 Galantamine 397	Probable or possible VaD (by NINDS-AIREN) MRI evidence of VaD MMSE 10–26, ADAS-cog ≥12	72.3	64%	ADAS-cog[a] ADCS-ADL	ADAS-cog/13[a] ADAS-cog/10[a] ADAS-cog/memory[a] EXIT-25[a] CIBIC-plus NPI

(continued)

Table 11.1 (continued)

Medication	Trial	Trial duration (weeks)	Participants				Outcomes	
			Number	Inclusion criteria	Mean age (years)	Sex (% men)	Primary	Secondary
Rivastigmine	VantagE	24	Total 710 Placebo 345 Rivastigmine 365	VaD (by DSM-IV and NINDS-AIREN) MRI evidence of VaD MMSE 10–24	72.9	61%	VADAS-cog[a] ADCS-CGIC	ADAS-cog[a] MMSE[a] ADCS-ADL GDS NPI
Memantine	MMM 300	28	Total 321 Placebo 156 Memantine 165	Probable VaD (by NINDS-AIREN) MRI or CT evidence of VaD Modified Ischemic Score ≥ 5 MMSE 12–20	76.4	53%	ADAS-cog[a] CIBIC-plus	MMSE[a] GBS[a,d] CGIC NOSGER
	MMM 500	28	Total 579 Placebo 284 Memantine 295	Probable VaD (by NINDS-AIREN) MRI or CT evidence of VaD Hachinski Ischemic Score ≥ 4 MMSE 10–22	77.4	51%	ADAS-cog[a] CGIC	MMSE GBS NOSGER

VaD vascular dementia, *NINDS-AIREN* National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences, *MMSE* Mini-Mental State Examination, *ADAS-cog* Alzheimer's Disease Assessment Scale-cognitive subscale, *CIBIC-plus* Clinician's Interview-Based Impression of Change-Plus version, *CDR-SB* Sum of Boxes of the Clinical Dementia Rating, *ADFACS* Alzheimer's Disease Functional Assessment and Change Scale, *VADAS-cog* Vascular Dementia Assessment Scale cognitive subscale, *CLOX1/2* Executive Clock-Drawing Task 1 and 2, *EXIT-25* Executive Interview, *DAD* Disability Assessment for Dementia, *AD* Alzheimer's disease, *NINDS-ADRDA* National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorder Association, *CVD* cerebrovascular disease, *NPI* Neuropsychiatric Inventory, *ADCS-ADL* Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, *ADCS-CGIC* Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change, *GDS* Global Deterioration Scale, *CGIC* Clinical Global Impression of Change, *GBS* Gottfries-Brane-Steen Scale, *NOSGER* Nurse's Observational Scale for Geriatric Patients

[a]Significant benefit in the treatment group

[b]Significant benefit only in the donepezil 5 mg/day group

[c]Significant benefit only in the donepezil 10 mg/day group

[d]Significant improvement only on the intellectual function subscore of the GBS scale

MMSE also showed statistically significant improvement versus placebo. Significant improvement in patients' global function, as assessed by the CIBIC-plus, was seen only in the donepezil 5 mg/day group ($p = 0.014$), but not in the 10 mg/day group ($p = 0.27$). CDR-SB showed nonsignificant benefits in the 5 mg/day group, but was significant in the 10 mg/day group ($p = 0.022$). Donepezil-treated patients showed significant benefits in ADL compared to placebo on the ADFACS total scores ($p < 0.05$). Withdrawal rates due to adverse events were relatively low (placebo 11.1%; donepezil 5 mg/day 11.1%; donepezil 10 mg/day 21.8%).

In the study 308 [22], the donepezil treatment group showed statistically significant improvement in cognitive function measured with the ADAS-cog; the mean changes from baseline score were as follows: donepezil 5 mg/day, −1.65 ($p = 0.003$); donepezil 10 mg/day, −2.09 ($p = 0.0002$). The MMSE also showed statistically significant improvement compared to placebo. Greater improvements on the CIBIC-plus were observed in both donepezil groups compared to the placebo group (overall donepezil treatment versus placebo, $p = 0.008$); 25% of the placebo group showed improvement compared with 39% ($p = 0.004$) of the 5 mg/daily group and 32% ($p = 0.047$) of the 10 mg/daily group. The CDR-SB showed nonsignificant benefits in the 5 mg/day group but was significant in the 10 mg/day group ($p = 0.03$). The ADFACS scores were more improved in the donepezil-treated patients over placebo in both treatment groups, but not significantly. Withdrawal rates due to adverse events were low (placebo 8.8%; donepezil 5 mg/day 10.1%; donepezil 10 mg/day 16.3%).

Following these two donepezil studies, another large study (study 319) with some methodological changes was undertaken to further evaluate the potential benefits of donepezil in VaD [23]. The methodological changes incorporated into this trial included the exclusive use of low-dose donepezil (5 mg/day) to reduce withdrawals due to adverse events and the use of the Vascular Dementia Assessment Scale cognitive subscale (VADAS-cog) to better assess executive function, an area particularly affected in VaD. As in prior studies, VaD was diagnosed according to NINDS-AIREN criteria. Patients were randomized 2:1 to receive donepezil 5 mg/day or placebo. The coprimary outcome measures were scores on the VADAS-cog and CIBIC-plus. Secondary efficacy endpoints included the ADAS-cog, MMSE, executive clock-drawing task (CLOX1/2), Executive Interview (EXIT-25), Disability Assessment for Dementia (DAD), and CDR-SB.

Compared with placebo, donepezil-treated patients showed significant improvement from baseline to endpoint on the VADAS-cog (least-squares mean difference, −1.156, $p < 0.01$) but not on the CIBIC-plus. Interestingly, hippocampal size modified the effect of donepezil on cognition. Patients with hippocampal atrophy who were treated with donepezil demonstrated stable cognition versus a decline in the placebo-treated group; in those without atrophy, cognition improved with donepezil versus relative stability with placebo. Results on secondary efficacy measures were inconsistent. Significant treatment differences favoring donepezil were demonstrated at endpoint for the ADAS-cog ($p = 0.0464$) and MMSE ($p = 0.0301$). The DAD scores showed significantly greater improvement in the donepezil group at week 24 ($p = 0.02$) and a trend at endpoint ($p = 0.06$). The incidence of adverse events was similar across groups. Eleven deaths occurred in the donepezil group (1.7%), whereas no deaths occurred in the placebo group.

11.3.2 Galantamine

Galantamine is a reversible competitive cholinesterase inhibitor that also acts as an allosteric modulator of nicotinic receptors. There have been two large studies with galantamine in patients with VaD [24, 25]. The first galantamine RCT, named *GAL-INT-6*, included patients with a diagnosis of probable VaD or AD combined with cerebrovascular disease (CVD) [24]. Eligible patients met the clinical criteria of probable VaD of the NINDS-AIREN or possible AD according to the National Institute of Neurological and Communicative Disorders

and Stroke and Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA). They also showed significant radiological evidence of CVD on CT or MRI. Evidence of CVD on a recent (within 12 months) scan included multiple large-vessel infarcts or a single, strategically placed infarct (angular gyrus, thalamus, basal forebrain, territory of the posterior or anterior cerebral arteries), or at least two basal ganglia and white matter lacune, or white matter changes involving at least 25% of the total white matter. Eligible patients were randomly assigned galantamine 24 mg/day or placebo. Primary endpoints were cognition as measured using the standard 11-item ADAS-cog (ADAS-cog/11) and global function as measured using the CIBIC-plus. Secondary endpoints included the 13-item ADAS-cog (ADAS-cog/13), which includes two additional items (comprehension and concentration/distractibility), assessments of ADL using the DAD, and behavioral symptoms using the Neuropsychiatric Inventory (NPI).

Galantamine demonstrated greater efficacy than placebo on all outcome measures. Galantamine showed greater efficacy than placebo on the ADAS-cog (galantamine change −1.7 versus placebo 1.0; treatment difference 2.7 points; $p < 0.0001$) and CIBIC-plus (74% versus 59% of patients remained stable or improved, $p = 0.001$). ADL and behavioral symptoms were also significantly improved compared with placebo ($p = 0.002$ and $p = 0.016$, respectively). Galantamine was well tolerated.

Probable VaD was diagnosed in 81 (41%) of the placebo patients and in 171 (43%) of the patients on galantamine. In the subgroup of patients with probable VaD, the ADAS-cog scores improved from baseline by 2.4 points in those assigned galantamine, where those of patients assigned placebo did not differ significantly from baseline at 6 months (treatment difference 1.9 points, $p = 0.06$). More patients treated with galantamine than with placebo maintained or improved global function as assessed by the CIBIC-plus (31% versus 23%); however, it was not statistically significant. The subgroup of patients with AD plus CVD on galantamine ($N = 188$, 48%) showed greater efficacy than placebo ($N = 97$, 50%) at 6 months on the ADAS-cog ($p = 0.0005$) and CIBIC-plus ($p = 0.019$).

The second study, named GAL-INT-26, evaluated flexible-dose galantamine in patients with VaD [25]. In this multinational, randomized, double-blind, placebo-controlled clinical trial, 788 patients with probable VaD as defined by the NINDS-AIREN were randomized to receive galantamine or placebo. Primary efficacies were cognition, as measured using the ADAS-cog/11, and daily function as measured using the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL) total score. Secondary outcomes included the CIBIC-plus, NPI, ADAS-cog/13, ADAS-cog/10, ADAS-cog/memory, and EXIT-25.

Patients treated with galantamine had a greater improvement in the ADAS-cog/11 after 26 weeks compared with placebo (galantamine change −1.8 versus placebo −0.3; $p < 0.001$). Galantamine treatment resulted in a significantly higher response rate and improvement in the ADAS-cog/13, ADAS-cog/10, and ADAS-cog/memory. There was no difference between galantamine and placebo at week 26 on the ADCS-ADL score (0.7 versus 1.3; $p = 0.783$). In a global clinical assessment using the CIBIC-plus, treatment with galantamine showed a numerical, but not significant, improvement versus placebo ($p = 0.069$). A difference between two groups for EXIT-25 favoring galantamine was detected ($p = 0.041$). Safety data revealed that 13% of galantamine and 6% of placebo patients discontinued treatment because of adverse events.

11.3.3 Rivastigmine

Rivastigmine is a dual inhibitor of acetylcholinesterase and butyrylcholinesterase. The Vascular Dementia trial studying Exelon (VantagE) was a 24-week, multicenter, double-blind study to evaluate the efficacy, safety, and tolerability of rivastigmine capsule in VaD patients [26]. Patients were

men or women aged 50–85 years with a diagnosis of VaD according to the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) and a diagnosis of probable VaD according to the NINDS-AIREN criteria. They were randomized to rivastigmine capsules (3–12 mg/day) or placebo. Primary efficacy measures were the VADAS-cog and the Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC). Secondary efficacy outcomes were the ADAS-cog, ADCS-ADL, NPI, MMSE, and Global Deterioration Scale (GDS).

Seven hundred and ten patients were randomized. Rivastigmine demonstrated significant superiority over placebo on the VADAS-cog (mean 0.7 point improvement on rivastigmine versus 0.6 point decline on placebo; $p = 0.028$, intent-to-treat [ITT] population) and the two other measures of cognitive performance (ADAS-cog and MMSE; $p = 0.029$ and $p = 0.007$, respectively). No significant differences between the rivastigmine and placebo groups were seen on measures of global performance, ADL, or neuropsychiatric symptoms. The rivastigmine group had higher rates of nausea and vomiting. Exploratory analyses indicated that older patients (≥75 years), assumed more likely to have concomitant AD pathology, had greater efficacy on cognitive outcomes and safety. Younger patients, assumed less likely to have concomitant AD pathology, showed no efficacy and were associated with slight elevations of blood pressure, cerebrovascular accidents, and mortality.

11.3.4 Memantine

Memantine, a noncompetitive NMDA receptor antagonist, blocks the effects of excessive levels of glutamate that may lead to neuronal dysfunction. Cerebral ischemia in VaD may lead to excessive release of glutamate that activates postsynaptic NMDA receptors. Based on the hypothesis of glutamate-induced neurotoxicity in cerebral ischemia, memantine has been tested in two RCTs, MMM 300 and MMM 500 [19, 27].

MMM 300 was carried out to examine the efficacy and tolerability of memantine in the treatment of mild to moderate VaD [19]. Male and female patients ≥60 years of age with symptomatic mild to moderate VaD of 6 months duration were enrolled. VaD was defined by the NINDS-AIREN criteria for probable VaD and a Modified Ischemic Score (MIS) of ≥5. The diagnosis of dementia of mild to moderate severity was established by participating investigators using the criteria of the DSM (3rd edition, revised) and by MMSE total scores of 12–20 at inclusion. The primary endpoints were the ADAS-cog and CIBIC-plus. Secondary efficacy variables included assessments of dementia severity by another cognitive test, the MMSE at baseline and at week 28; a composite instrument, the Gottfries-Brane-Steen (GBS) scale; and another global rating, the Clinical Global Impression of Change (CGIC), by the investigator at baseline and at weeks 12 and 28 and by the caregiver at week 28. Functional aspects were investigated with the Nurse's Observational Scale for Geriatric Patients (NOSGER).

Three hundred and twenty-one patients received 10 mg/day memantine or placebo twice a day; 288 patients were valid for ITT analysis. After 28 weeks, the mean ADAS-cog scores were significantly improved relative to placebo. In the ITT population, memantine-treated patients had improved by a mean score of 0.4, while the placebo group had declined by 1.6 points. The response rate for CIBIC-plus, defined as improved or stable, was higher with memantine (60%) compared with placebo (52%), although this difference did not reach statistical significance ($p = 0.227$). Among the secondary efficacy parameters, which were analyzed in the per-protocol subset, the MMSE was significantly improved with memantine compared with deterioration with placebo ($p = 0.003$). The GBS scale showed a statistically significant difference, favoring memantine for the intellectual function subscore ($p = 0.04$), but there was no significant difference in the motor function, emotional function, or different symptoms subscore. One NOSGER item,

disturbing behavior, showed a trend ($p = 0.07$) in favor of memantine at 28 week. Memantine was well tolerated with a frequency of adverse events comparable to placebo (76% versus 74%).

MMM 500 was conducted in 54 centers in the UK [27]. This was a 28-week RCT to investigate the safety and efficacy of memantine in mild to moderate VaD. VaD was defined by the NINDS-AIREN criteria for probable VaD and a Hachinski Ischemic Score (HIS) of ≥4. MMSE total scores between 10 and 22 were eligible for inclusion. Primary efficacy parameters were the ADAS-cog and CGIC. Secondary efficacy variables were the MMSE, GBS, and NOSGER.

A total of 579 patients were randomized, and 548 patients with at least one post-baseline efficacy assessment qualified for the ITT analysis. At endpoint, memantine was shown to improve cognition relative to placebo in VaD based on the ADAS-cog (treatment difference 1.75 points, $p < 0.05$). The CGIC, MMSE, GBS, and NOSGER were not different between the groups. No differences between the two groups were found in dropout rates or the number of those suffering at least one adverse event, suggesting that memantine is well tolerated. A total of 77% of all memantine-treated patients experienced adverse events, versus 75% of the placebo-treated patients. Dizziness was the most frequent adverse event (11% versus 8%, respectively).

11.4 A Summary of Current Evidence for the Use of AD Drugs in VaD and Future Needs

Kavirajan and Schneider published a meta-analysis of RCTs of cholinesterase inhibitors and memantine in VaD that included the three donepezil, two galantamine, one rivastigmine, and two memantine trials reviewed earlier in this chapter [4]. In the assessment of cognitive function, the cholinesterase inhibitors produced significant differences in mean ADAS-cog change scores between drug and placebo (Fig. 11.1), ranging from −1.10 points (95% CI −2.15 to −0.05) in the rivastigmine trials to −2.17 (95% CI −2.98 to −1.35) in the 10 mg daily donepezil group. In the galantamine trials with only VaD patients, the difference by meta-analysis was −1.60 (95% CI −2.39 to −0.80). In the memantine trials, the difference was −1.86 (95% CI −2.79 to −0.94). For global measures, only 5 mg daily donepezil was associated with a significant likelihood for improved or no change versus worsened condition with the CIBIC-plus by meta-analysis in two of the three trials that provided that information (odds ratio [OR] 1.51 [95% CI 1.11–2.07]) (Fig. 11.2). ORs for discontinuation from the trials for any reason were significantly greater in patients treated with 10 mg daily donepezil, galantamine, and rivastigmine than with placebo (Fig. 11.3). Compared with placebo, more adverse events (anorexia, nausea, vomiting, diarrhea, and insomnia) occurred with the cholinesterase inhibitors, but not with memantine.

According to this meta-analysis, cholinesterase inhibitors and memantine produce small benefits in cognitive function but without corresponding effects on global function in patients with mild to moderate VaD. Although the ADAS-cog effect was consistent across the trials, the absence of supporting effects on the global outcomes undermines its clinical significance. Thus, data are insufficient to support widespread use of these drugs in VaD.

In addition, there are several important limitations of previous trials. First, VaD patients who were diagnosed by NINDS-AIREN criteria varied widely in the type, locations, and extent of CVD. VaD involves heterogeneous subtypes (e.g., strategic infarct, multi-infarct dementia, and subcortical VaD) that may respond differently to treatment. However, no trials focused on specific subtypes among heterogeneous VaD. Therefore, previous trials could not identify subgroups of patients with VaD who might benefit from a treatment. Further studies in patients with more narrowly defined subtypes of VaD are required.

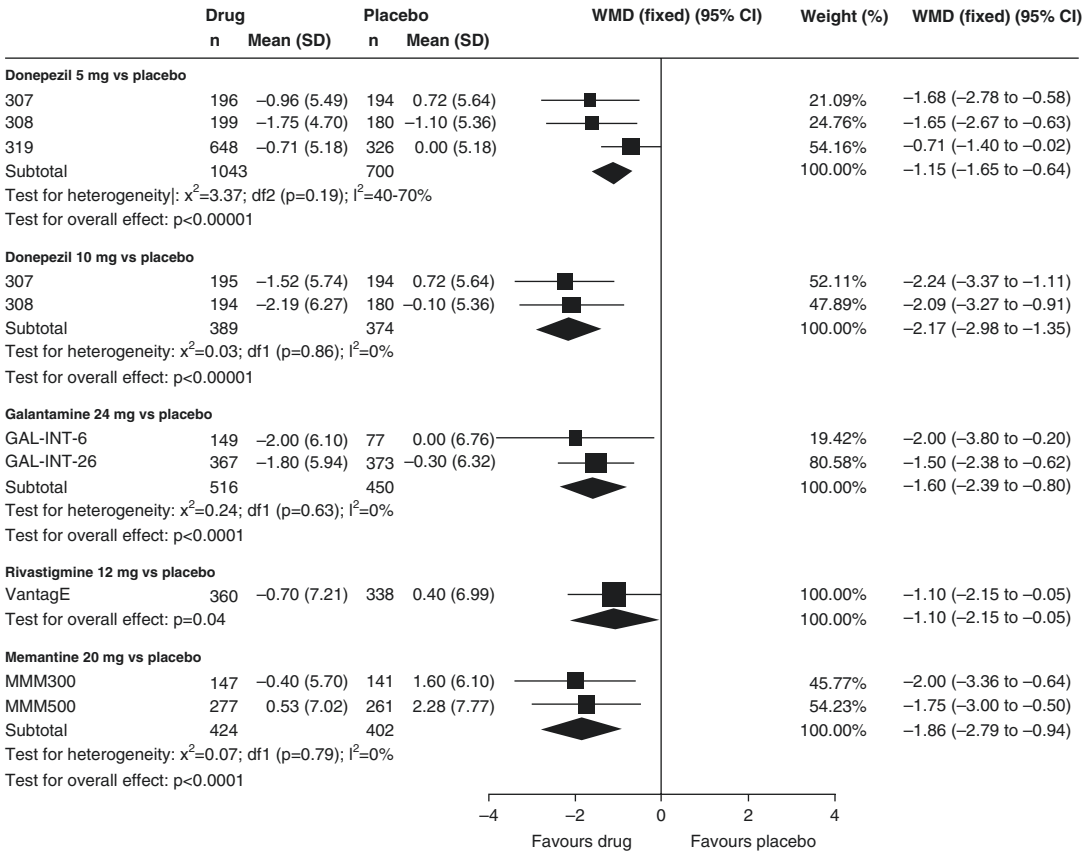

Fig. 11.1 Cognitive outcomes on the ADAS-cog subscale (change from baseline) in vascular dementia patients in cholinesterase inhibitors and memantine trials by drug and dose (last observation carried forward sample). *WMD* weighted mean difference. (Adapted from Lancet Neurology [4])

The second concern is concurrent AD pathology. Because of the high prevalence of AD especially in the elderly, VaD patients may have coexisting AD. Biomarkers for AD pathology including amyloid PET imaging or CSF biomarkers may be helpful for differentiation of patients with pure VaD from those with mixed dementia.

Third, the assessment instruments commonly used in previous trials may not be sufficiently sensitive to detect clinical changes in VaD, because these scales were developed for use specifically in AD. The ADAS-cog is relatively insensitive to frontal dysfunction, which is a prominent symptom of VaD. The CIBIC-plus also may have limited use for patients with VaD, a condition with diverse subtypes and disease courses. VaD-specific outcome measures should be developed and validated.

Finally, the 6-month duration of the trials may be too brief. Relatively short duration, along with the relative stability of placebo patient groups in previous trials, may have made it more difficult to assess treatment benefits. Longer trials would be more appropriate to show the meaningful data on efficacy and safety.

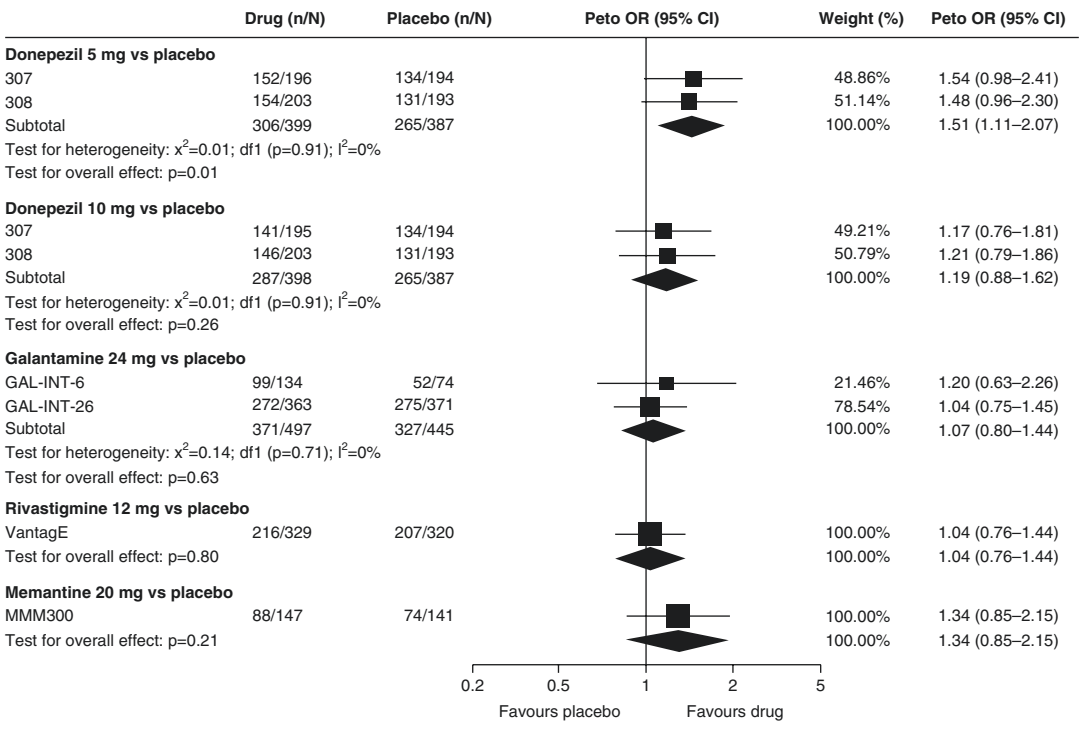

Fig. 11.2 Global change outcomes in vascular dementia patients in cholinesterase inhibitors and memantine trials based on CIBIC-plus or CGIC improvement or no change versus worsening compared to baseline by drug and dose (last observation carried forward sample). Data were not provided for donepezil trial 319 or memantine trial MMM500. Fixed-effects models were used. *OR* odds ratio. (Adapted from Lancet Neurology [4])

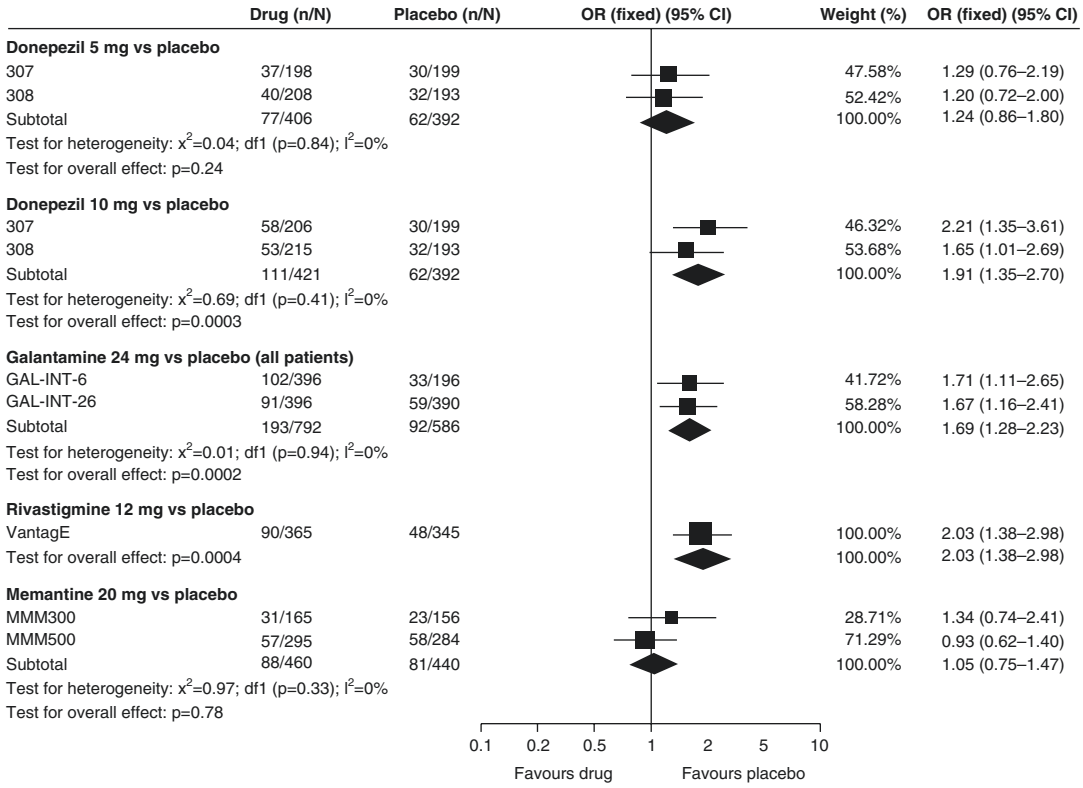

Fig. 11.3 All-cause dropouts in trials of cholinesterase inhibitors and memantine in vascular dementia trials by drug and dose. Data were not provided for donepezil trial 319. *OR* odds ratio. (Adapted from Lancet Neurology [4])

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