Chapter 1

Pathophysiology & Epidemiology

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Perspective

Once upon a time things were simple. Increasing age hardened the brain arteries, causing a slow strangulation of the brain's blood supply, resulting in chronic ischemia and neuronal death. However, in the 1970s a number of studies demonstrated that when vascular disease was responsible for dementia, it most often acted through the agency of cerebral infarcts, which led to the concept of "multi infarct dementia" meaning that it resulted from multiple cerebral infarcts large and small.[1] This stricter definition of vascular dementia contributed to the impression that cerebrovascular disease was an uncommon cause of dementia.

Hitherto, Alzheimer disease had been considered a pre-senile dementia and rare. However, with the waning of "atherosclerotic dementia" as the main cause of cognitive decline and increasing concern about cognitive impairment in the elderly, an expert committee developed criteria for "Alzheimer disease" in the elderly.[2] Although at the time, it was not clear whether the hallmark lesions of pre-senile dementia, namely plaques and neurofibrillary tangles, that also appear in the elderly represented the same process, a controversy that remains to this day.

This chapter provides a brief overview of basic anatomy and physiology of the brain, a description of cognitive abilities and their relevant age-related changes, and finally, the importance of vascular cognitive impairment.

Basic Anatomy and Physiology

Undoubtedly, the brain is by far the most complex organ. It contains 10^{11} neurons and at least 1000 dendrites per neuron, producing an extremely extensive network of billions of nerve cells, enabling human beings to perform a wide range of activities, from autonomic responses to higher cognitive functions of memory and thought.[3] Not surprisingly, the brain is also one of the most metabolically demanding organs in the human body. Due to the lack of long-term substrate storage and a very high rate of metabolic demand, it needs a continuous supply of blood and oxygen.[4,5] Moreover, the optimal function of the brain cells is only possible in a stable microenvironment, independent of the changes in the periphery. Such strict homeostatic control is achieved via a blood-brain barrier (BBB) and in a special unit of neurons, glia, and vascular tissues: the "neurovascular unit."

The Difference between White Matter and Grey Matter

The brain is divided into grey (substantia grisea) and white matter (substantia alba). It is an extremely interconnected organ, where each and every neuron within the grey matter connects between 1000 to 10000 nearby neurons, and at the same time, long-distance

communication between neurons at separate brain locations is mediated via the white matter.[6]

The grey matter consists of nerve cell bodies, their dendrites and local ramifications of axons, glial cells, and blood vessels. On the other hand, the white matter is made up of bundles of myelinated axons, trafficking in and out of the grey matter and connecting mostly separated cortical regions rather than the cortical to adjacent subcortical structures.[7,8] Long-range myelinated axon tracts with relatively few cell bodies in the white matter and numerous cell bodies with relatively few myelinated axons in the grey matter lead to distinctive color of white and grey in the brain.

Not surprisingly, larger brains, such as human's brains, require longer fibers to communicate, and consequently the volume of the white matter that increases disproportionately faster than the volume of the grey matter.[7] However, the brain's white matter, with almost 50 percent of total brain volume, consumes less energy than grey matter. This is partially due to the dramatically lower number of synapses (if any) in white matter, since the highest level of energy in the brain is used to provide appropriate neuronal connections via synapses.

Although traditionally a majority of cognitive functions are attributed to grey matter, it was clearly shown that age-related cognitive decline in healthy older individuals may happen due to characteristic changes in the ultrastructure of myelin coupled with evidence of inflammatory processes in the white matter.[9] The white matter is quite vulnerable to a broad range of neurological diseases, such as cerebral ischemia and dementing processes. The myelin in the white matter is formed by oligodendrocytes, one of the most vulnerable cells in the brain. Moreover, blood flow and cerebrovascular reactivity in the cerebral cortex of young subjects are significantly higher than those for the white matter in the elderly.[10] It varies based on the type of brain tissues and age, ranging from 20ml/100g/min in white matter to 70/100g/min in grey matter, and is higher in neonates and infants than in adults.[4,11] Impaired autoregulation and higher levels of cerebrovascular resistance were also significantly more prevalent in patients with periventricular white matter lesions,[12] increasing substantially the risk of dementia in elderly people.[13]

The Neurovascular Unit

The BBB is a highly selective permeability barrier, separating the central nervous system (CNS) from the peripheral circulation and plays a critical role in the maintenance of CNS homeostasis. This regulatory interface includes three major components, namely the BBB-endothelial cells, astrocyte end-feet, and pericytes (Figure 1.1).[14,15] Tight junctions between endothelial cells (about 50–100 times tighter than peripheral microvessels), the absence of intercellular clefts, lack of fenestrations, minor pinocytic activity, and a high transendothelial electrical resistance contribute significantly in the selective function of BBB and provide a strict homeostatic control over the brain.[16,17] From one side, the BBB is supported by astrocytes and pericytes, and from the other side it is closely connected to microglia and neurons.[18,19] This combination of cerebral microvascular endothelium with astrocytes, pericytes, neurons, and the extracellular matrix constitutes a special "neurovascular unit" that is essential for the health and function of the CNS.[15] Such controlling gates and special units can act as the best safeguard mechanism, efficiently protecting the brain from any harmful substance, and at the same time, can sufficiently maintain the ionic concentrations of the central nervous system within a narrow range. However, it is also a major obstacle to

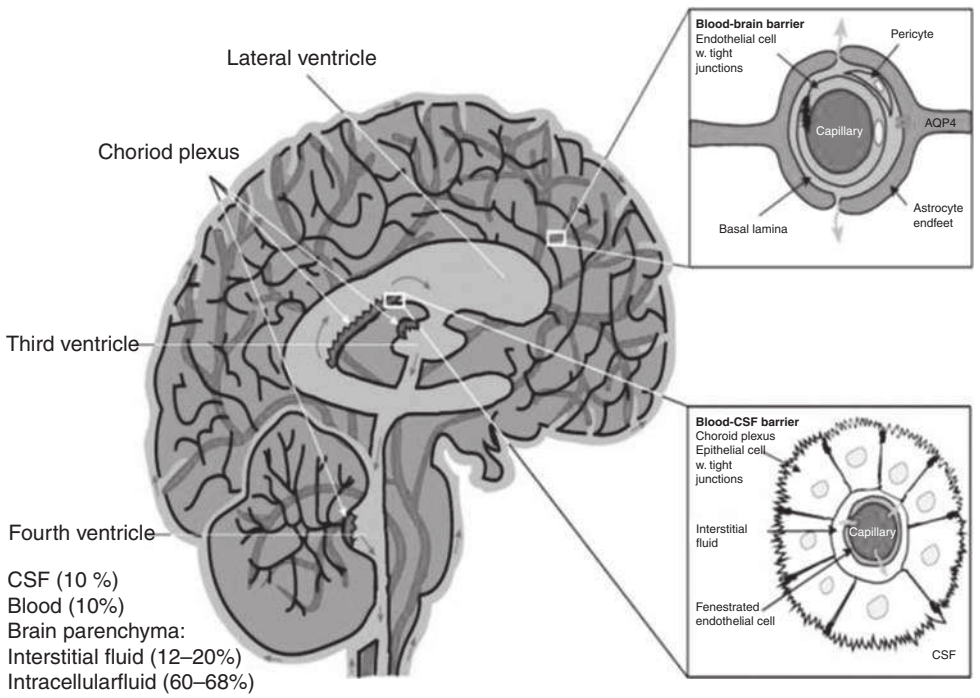

Figure 1.1 Schematic representation of the brain's fluid compartments and barriers. Reproduced by permission of Springer from: Jessen NA, Munk ASF, Lundgaar, I, Nedergaard M. The glymphatic system: a beginner's guide. *Neurochemical Research*. 2015;40(12):1–17.

the delivery of medications to the CNS. Therefore, this barrier can be a friend and simultaneously a foe to clinicians and researchers.[20]

Although the brain has been considered unique due to the lack of a conventional lymphatic system, recently a macroscopic waste clearance system in the brain has been described.[21,22] This is a unique paravascular pathway formed by astroglial cells named the "glymphatic system." This pathway facilitates cerebrospinal flow through the brain parenchyma and the clearance of interstitial solutes and potentially neurotoxic waste products, such as beta amyloid,[21,22] the main component of the amyloid plaques and significant contributors to the pathogenesis of Alzheimer disease.

Cerebral Blood Flow (CBF)

The brain tissues and cells are exquisitely sensitive to oxygen deprivation. Consequently, to meet its optimal requirement, although it only represents 2 percent of body weight, the brain receives almost 15 percent of the body's total cardiac output, approximately 50 ml blood/100g brain tissue /min or 700 ml/min. The blood supply of the brain varies based on the type of brain tissues, ranging from 20ml/100g/min in white matter to 70ml/100g/min in grey matter.[4,11] More important, normal brain function and tissues integrity are highly dependent on the "regulation" for constant supply of oxygen and energy to the brain.[23] Brain blood flow regulation is a process in which, despite the change in cerebral perfusion

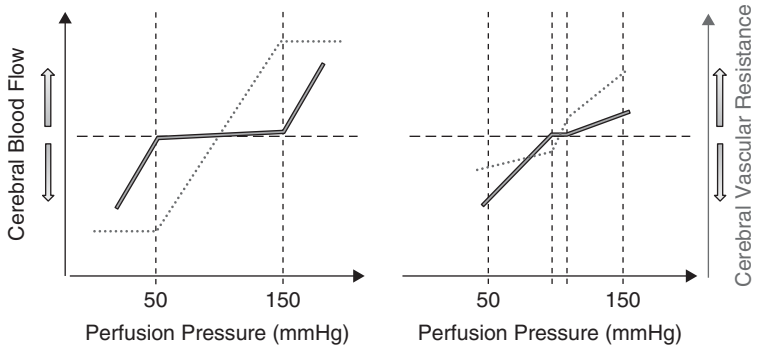

Figure 1.2 The relationship between cerebral blood flow and perfusion pressure. Willie CK., Tzeng Y-C, Fisher J. A, Ainslie PN. Integrative regulation of human brain blood flow. The Journal of Physiology. 2014;592(Pt5):841–859.

pressure (CPP), brain arteries and particularly arterioles, provide a roughly constant amount of CBF to protect the human brain and provide a favorable regional and global oxygen supply to the brain. While autoregulation is also present in other organs of the body, the most developed system is in the brain, where it's regularity maintains a relatively constant amount of blood flow. As shown in Figure 1.2 (left panel), a stable amount of CBF is especially obvious when the mean arterial pressure (MAP) is between ~50 and 150 mm Hg. MAP is a steady component of blood flow during a single cardiac cycle and therefore a better indicator for adequate tissue perfusion, such as the brain than systolic or diastolic pressure. It is calculated as:

$$\text{diastolic pressure} + 1/3\ (\text{systolic pressure} - \text{diastolic pressure})$$

CBF in MAP above and below these levels becomes completely dependent on MAP in a linear fashion. However, a recent study showed that the CBF–MAP relationship may not be linear through a broad range of MAP (Figure 1.2, right panel).[24]

Knowledge about the patterns and age-associated changes in CBF is an important, yet largely unknown step in the differentiation between the normal aging process and cognitive impairments due to vascular or neurodegenerative diseases.[25] While some studies found that total CBF remains unchanged or decreases minimally during normal aging,[26,27] most researchers find a gradual decline, although at different rates, ranging from 3.9 mL/min[28] to 4.8 mL/min (0.52 percent) per year,[29] and in different anatomical localizations, i.e., grey (0.45 percent to 0.74 percent per year) versus white matter (0.3 percent per year), with increasing age.[30,31]

Cognitive Changes with Aging

Our daily lives depend on the close, coordinated and simultaneous interactions between several cognitive abilities. We need to have adequate attention, be able to collect, memorize, and retrieve relevant information, inhibit distracting or irrelevant information in working memory, make correct decisions, design flexible plans, solve problems appropriately, and perform goal-directed activities. These huge series of mental activities, covering almost all aspects of cognitive functions, logically need to be controlled centrally and coordinated adequately to accomplish any specific task, particularly novel ones, and achieve the desired

Table 1.1 Cognitive domain: classifications, definitions and age-associated changes

	Decline	Remain Stable	Improve
Cognitive functions	Attention Processing speed Short-term memory* Working Memory** (in high demanding tasks) Declarative memory: Episodic memory*** Prospective memory**** Executive function	Decision-making Non-declarative memory: Procedural motor skills† Non-declarative memory: Priming†† Language	Declarative memory: Semantic memory††† (remain stable or improve)

*Ability to process information speedily to execute cognitive tasks efficiently in a limited period of time.
**Ability to maintain and manipulate a critical, yet limited, amount of information with several options, and consequences.
***Ability to consciously remember, recognize, or recollect past experiences.
****Ability to plan, retain, and retrieve an intention as planned in the future.
† Ability to perform a routine daily task unconsciously.
†† Ability to easily identify a stimulus after a previous exposure to a relevant stimulus.
††† Explicit storage of knowledge/categorical information, and word meanings.

goals. The mechanisms of integration and controlling of these neural functions are named "executive control." Along with other higher cognitive functions such as anticipation, judgment, planning, and decision-making, executive functions have a close relationship with the prefrontal cortex.[32]

While age-related cognitive changes are common in the elderly, they are not inevitable outcomes of aging, and are not uniform, with some abilities diminishing more rapidly than others.[33] (See Table 1.1.) For example, despite a decline in the attention and processing speed with aging, decision-making and language functions usually remain stable. Even in memory function, ability to perform a routine daily task (the procedural motor skills memory) may often remain unchanged. It is postulated that age-related declines in many cognitive domains may be due to changes of executive control. Along with other higher cognitive functions such as anticipation, judgment, planning, and decision-making, executive functions have a close relationship with the prefrontal cortex.[32] It was shown that white matter changes, atrophy, and certain forms of neurotransmitter depletion in frontal lobes[34] may lead to executive dysfunctions.

Human Diversity: Inter- and Intra-Individual Variability in Cognitive Abilities

One of the most well-known landmarks in downtown Chicago is a huge 50-foot, 162 ton sculpture with a totally abstract shape resembling a bird, a horse, or a woman. This masterpiece was designed by Picasso and donated by him to the people of Chicago, and named in his honor the "Chicago Picasso" or "Picasso" (Figure 1.3). One interesting fact about this famous sculpture is that Picasso completed a maquette of the sculpture in 1965 and approved the final model in 1966, when he was eighty-five years old.

Figure 1.3 "Chicago Picasso," a landmark in downtown Chicago, was designed by Pablo Picasso at age eighty-five years.
(Photo courtesy of L. Hachinski.)

There are several other examples throughout history, like the Picasso sculpture, where older adults were able to retain their mental abilities and perform well or even better than younger ones. It seems that while aging is an undeniable part of life, cognitive decline is not an inevitable part and that significant inter-individual variability can be observed in mental abilities. This rich diversity in human behavior and cognitive abilities in aging has opened a new window to clinical and neuro-functional imaging research in the field of aging and cognition.[35,36,37] A range of factors from genetic background to socioeconomic and educational status, probably contribute to inter-individual variability. Interestingly, functional imaging studies provide insight into the different patterns of brain activity, and more efficient use of brain networks and/or greater ability to recruit alternative networks in the elderly with better cognitive performance.[35,37]

It has also been demonstrated that there are age-dependent intra-individual inconsistencies in performance in neurocognitive tests, such as reaction times[38] that may change from both moment to moment and from day to day.[39] This intra-individual variability has also a stable pattern across time and occasion, which means individuals with greater levels of inconsistency may have more inconsistency at other tasks and testing occasions.[40,41] Moreover, it may affect long-term cognitive outcomes.[42] It is postulated that aging may be associated with a decrease in the stability of executive control over time, which in turn, may lead to inter-individual variability.[43,44]

Finally, it is also important to know the stability of individual differences in cognitive ability across the life course. In one important cohort study, the Lothian Birth Cohort, the intelligence of almost every child born in 1921 and 1936 attending school in Scotland in the month of June in those years was evaluated. The reassessment of these individuals' cognitive ability at age ninety years, showed moderately high stability from childhood to old-old age.[45] Therefore, in definition, classification, and interpretation of neuropsychiatric tests, the importance of intra-individual inconsistencies should always be considered by clinicians and researchers.

Differences in Brain Structures of Men and Women

The lifetime prevalence rates, symptoms and final outcomes of several neuropsychiatric disorders vary significantly between the sexes.[46,47] Understanding the neuroanatomical and functional differences between the male and female brains may help to elucidate the reasons for gender-specific differences among diseases. A combination of genetic,[48,49] steroid hormones, immune systems,[50] and postnatal factors can lead to sex differences in brain structure.[51] Interestingly, these differences emerge as early as the prenatal period and continue throughout the lifespan.

The brain size of male neonates is approximately 6 percent larger than those of female.[52] A result of a recent meta-analysis showed that differences in overall brain volumes are sustained between males and females from newborns to individuals over eighty years old. The most striking differences were reported in limbic and language systems. While in men, volume increases and higher densities were mostly reported in bilateral limbic areas, left posterior cingulate gyrus, and to the left side of the limbic system respectively, larger volumes in females were more frequently seen in special areas in the right hemisphere related to language and to several limbic structures such as the right insular cortex and anterior cingulate gyrus.[53] In addition, women exhibited greater total percentage brain volume loss than men during midlife. While the more extensive volume reduction occurs on the lateral edge of women's brains, it is more significant in midline structures in men.[54] Interestingly, although the results of studies regarding cerebral blood flow in men and women vary, several researchers have shown a higher (about 11 percent or 5 ml/100 g/min) global blood flow in women than in men.[30,55–57].

Finally cognitive performances vary between men and women. Women often show a relatively better performance in working memory,[58] episodic memory, and verbal fluency tasks,[59] whereas men are better in spatial tasks and mathematical problem solving.[60]

Alzheimer-Prone Bias in the Definition and Classification of Dementia

Although in the early twentieth century, vascular disease with hardening of arteries was considered as the main culprit for dementia, several factors have contributed to an "Alzheimerization" bias in favor of neurodegenerative causes of dementia (Figure 1.4).

First and foremost, considering "memory loss" as a core symptom for diagnosis of dementia is the leading source of bias in dementia research. Since cognitive impairment of vascular origin is a heterogeneous group of brain disorders, it may present with a range of cognitive dysfunctions, and in particular, executive dysfunctions. Such definition can dramatically exclude cases of vascular cognitive impairment. Secondly, ideal population-based studies regarding dementia, and in particular cognitive impairment associated with vascular diseases, are scant,[61] and it is not possible to compare many studies since their inclusion criteria and definition for vascular cognitive impairment are not usually interchangeable.[62,63] Therefore, the reported prevalence of vascular cognitive impairment may significantly vary in population-based studies.[62] Different methods of study design and follow up in epidemiological studies on one hand, and restrictive inclusion criteria for vascular cognitive impairment and finally sensitivity and specificity of applied clinical criteria on the other hand, have led to underestimation of the actual rate of vascular origins in dementia studies.[64–66] In addition, the higher rate of death of dementia with

Source of Bias toward AD		Suggestive soloution to decrease the bias		
Rule out Pathological method for Vascular diagnosis	AD	VCI	Revised pathological criteria	Lesser importance
Clinic based studies	AD	VCI	Population based studies	
MMSE	AD	VCI	MoCA and reaction time, development of new tests	Greater importance
Memory based definition of dementia	AD	VCI	Assessment of executive function	

AD: Alzheimer's Disease; VCI: Vascular Cognitive Impairment; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment.

Figure 1.4 Source of bias toward Alzheimerization and suggestive solution to decrease the bias.
AD: Alzheimer Disease; VCI: Vascular Cognitive Impairment; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment.

cerebrovascular diseases, probably due to comorbid coronary artery diseases, in comparison to Alzheimer disease[67] can also be another reason for the perceived lower prevalence of the former.

Moreover, most epidemiological and clinical studies use the mini mental state examination (MMSE) for screening.[68] This instrument is sensitive to memory impairment, the hallmark of Alzheimer disease, but insensitive to impairments of executive function[69] that may be a hallmark of cerebrovascular disease. Consequently, since executive dysfunction goes undetected, many cases of cognitive impairment due to vascular disease are excluded and ignored (Figure 1.5). The same source of bias can be also observed in many epidemiological studies, where reaction time, as a symptom due to vascular lesions in the frontal lobes or cortico-basal ganglionic–thalamic circuits[70] has not been evaluated. It is important to know that there are still no accurate neuropsychological tests to diagnose vascular cognitive impairment and differentiate it from other common causes of neurodegenerative dementia, largely in part because all major dementias have a vascular component, ranging from 60 percent in frontotemporal dementia to 80 percent in Alzheimer disease.[71]

Although the Montreal Cognitive Assessment (MoCA) has been increasingly used for detecting post-stroke cognitive impairment, even MoCA cannot thoroughly assess all cognitive domains affected following stroke.[72] This is a major obstacle to an accurate clinical diagnosis and consequently preventive strategies and new research. Therefore, it is quite important to develop common standards to identify subjects with cognitive impairment, particularly in the early stages, and especially those with vascular origins of dementia.[73]

The other contributing factor was the creation of Alzheimer centers. Most of these run memory clinics. Patients going to memory clinics, if they have memory impairment not due to depression, are likely to have Alzheimer disease, thus creating a tremendous ascertainment bias in favor of those who have Alzheimer pathology in their brains. In addition, many

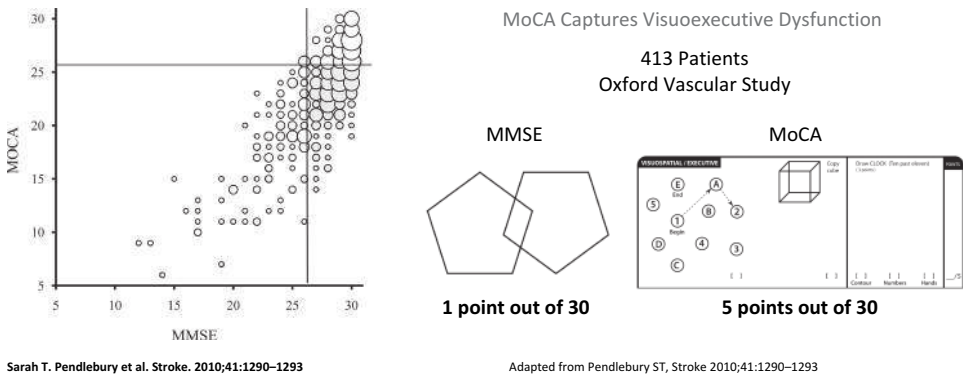

Figure 1.5 Underestimation of cognitive impairment by MMSE vs. MoCA in patients with stroke and TIA. Pendlebury ST, Cuthbertson FC, Welch SJV, Mehta Z, Rothwell PM. Underestimation of cognitive impairment by Mini-Mental State Examination versus the Montreal Cognitive Assessment in patients with transient ischemic attack and stroke: a population-based study. *Stroke: A Journal of Cerebral Circulation*. 2010;41(6):1290–1293.

cases with stroke are followed in stroke outpatient clinics or stroke centers. As a result, non-population-based memory clinic studies can easily underestimate this large group of patients. Physicians also have a tendency to ignore vascular cognitive impairment in their daily practice.

While early signs of memory impairment in the elderly due to medial temporal lobe lesions may easily lead to diagnosis of possible Alzheimer disease, the different localization of vascular pathology and more heterogeneous clinical manifestations, particularly in executive function,[74,75] may unintentionally be ignored and lead to this false, yet common belief that vascular cognitive impairment is an uncommon medical condition. In addition, in the preclinical phases of dementia due to Alzheimer or vascular diseases, similar patterns of cognitive deficits may be observed,[76,77] partially explained by the atrophy in the medial part of the temporal lobe in both conditions.[78] It is also important to know that the underlying pathologies in the majority of community-based demented individuals are a combination between Alzheimer disease and vascular changes.[79] This pattern differs in clinic-based cohorts where atypical forms of dementia and uncommon types such as Lewy body dementia can be seen more frequently,[80] which is another source of bias for underestimation of vascular pathology. In addition, most of the clinical pathological reports of patients are from Alzheimer centers, and they do not take into account that about one-fifth of patients initially diagnosed with having Alzheimer disease do not progress.[81] Typically, clinical pathological studies only include those subjects who deteriorate and die. However, if one adds the denominator of those who do not progress, the accuracy rates of the initial diagnosis of Alzheimer disease is much less than reported in the literature.

The diagnosis of pure Alzheimer disease is accurate only 38 percent of the time,[81] a proportion that has not significantly improved with sophisticated PET brain imaging and cerebrospinal fluid (CSF) biomarkers (only 4 pure Alzheimer disease cases out of a consecutive series of the first 22 presumed Alzheimer disease).[71]

Finally, despite the fact that pathological findings are the gold standard for the majority of diseases, neuropathological criteria for diagnosis of vascular dementia are still a matter of debate,[82,83] and pathological diagnosis of dementia due to vascular disease is based on the exclusion of other causes of dementia (default diagnosis). While such approach seems to be

rational due to the high rate of vascular pathology in the elderly, this type of definition may also cause an underestimation of the prevalence of pure/mixed type of vascular cognitive impairment.

The Resurgence of Cerebrovascular Disease

The rise of Alzheimer disease made things simple again. Alzheimer disease became near synonymous with dementia as "atherosclerosis" of the brain arteries had been. However, with the advent of brain imaging, computed axial tomography (CAT) scanning, and Magnetic Resonance Imaging (MRI) in the 1980s and 1990s, vascular disease regained a part in the diagnostic repertoire again, through the demonstration of white matter changes in cognitively impaired patients.

These white matter changes were immediately attributed with profligate ease to "Binswanger disease," "vascular encephalopathy," "microvascular disease," and "chronic ischemia." The same facile thinking used to explain deterioration by chronic ischemia affecting grey matter was now applied to white matter with no more evidence for the latter than the former. It was suggested that the white matter changes were non-specific and until we sorted out the multiple etiologies it was best to use a descriptive term such as "leukoaraiosis," meaning white matter rarefication.[84] It is also observed that while white matter changes are a prevalent finding among patients suffering from vascular cognitive impairment,[85] these findings can also be frequently seen in asymptomatic elderly patients.[86] In symptomatic individuals, besides cognitive problems and especially executive dysfunction, symptoms include depression,[87,88] and movement disorders such as parkinsonism,[89–91] which may be explained by the disruption in pre-frontal sub-cortical circuits due to white matter lesions or stroke.[92–94]

The Vascular Cognitive Impairment Approach

It was slowly realized that while Alzheimer disease is often progressive and fatal, vascular lesions are not necessarily progressive and that the cognitive impairment spans a whole spectrum between mild cognitive impairment to dementia and hence the term "vascular cognitive impairment" was suggested to describe the whole range of any cognitive impairment due to or associated with vascular disease.[95,96] To date, this remains the only treatable and preventable component. It was also discovered that for each clinical stroke there are probably five so-called silent strokes where upon closer examination, patients exhibit subtle neurological signs and cognitive impairment.[97]

It was also suggested that if we are to be successful, prevention should start early, perhaps at the "brain at risk stage" when there are no clinical manifestations, but risk factors are present to try to prevent or delay subsequent strokes and/or cognitive impairment.[98] For example, it was clearly shown that chronic hypertension can affect small end arteries located in the brainstem and the center of the brain. The medial and basal portions of the brain and brainstem are supplied by relatively short arteries penetrating the brain in the basal dorsal direction. Since these arteries arise from large basal trunks, the gradation between arterial and capillary pressure occurs over a relatively short distance, requiring the arteries to withstand high pressure. Functionally, arteries in the upper brainstem and diencephalon (centrecephalon) are end arteries without substantial collateral supply from adjacent vessels. Therefore, occlusion of a centrecephalon artery usually leads to a small infarct, because it supplies a limited cylinder of tissue (Figure 1.6).[99] Due to