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Vascular Dementia The term vascular dementia has traditionally been used to describe a subset of dementia cases due primarily to one or more symptomatic strokes. Considered as such, vascular dementia is usually ranked the second most frequent cause of dementia, exceeded only by Alzheimer's disease (Chap. 442), and is especially common in populations with limited access to medical care, where vascular risk factors are under treated. More recently, this relatively narrow definition of vascular dementia has been substantially broadened to encompass the full impact of cerebrovascular disease on age-related cognitive decline. The term vascular contributions to cognitive impairment and dementia (VCID) reflects the observation that pathologic changes involving the cerebral vasculature are highly prevalent in the elderly and contribute to cognitive impairment, whether occurring in isolation or—more commonly—in conjunction with other neurodegenerative processes. The concept of VCID is one facet of the contemporary understanding of age-related cognitive decline as due to cumulative effects of distinct and overlapping neuropathologic changes. Multifactorial or "mixed" dementias appear to be more prevalent than single-etiology dementias and thus represent the rule rather than the exception. Symptomatic stroke and asymptomatic vascular lesions, most com monly detected with brain magnetic resonance imaging (MRI) scans, both contribute importantly to cognitive impairment. At least some cognitive impairment is present in approximately half of stroke sur vivors and progressively increases with longer periods of follow-up. Population-based studies also demonstrate substantially increased risk of cognitive impairment among individuals without symptomatic stroke but with MRI evidence of cerebrovascular disease. The high risk for subsequent cognitive impairment or dementia conferred by MRI markers of otherwise silent vascular brain injury highlights the cumu lative impact of small distributed brain injuries—often associated with small-vessel brain disease—on compromising brain function. Further support for this framework comes from the correlation of cognitive performance during life with postmortem neuropathology. Analysis of large community-based samples demonstrates independent contri butions to cognitive dysfunction and decline from both grossly vis ible infarcts and pathologic markers of overall cerebrovascular disease severity such as atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy scores. The Religious Orders Study and Memory and Aging Project analysis of 1079 community-based participants, for example, found each of these cerebrovascular entities to be moderate to severe in >30% of postmortem brains and, when present, to each account for ~20% of an individual's premortem cognitive decline. Recent epidemiologic evidence of a decline in age-adjusted dementia incidence hints at the potential public impact of improving vascular health. The population-based Framingham Study reported 5-year age- and sex-adjusted cumulative hazard rates for dementia of 3.6 per 100 persons during the late 1970s to early 1980s, 2.8 in the late

1980s to early 1990s, 2.2 in the late 1990s to early 2000s, and 2.0 in the late 2000s to early 2010s. These time intervals coincide with parallel trends in hypertension control and stroke prevention, though the associations do not prove causation. Evidence supporting a potential causative effect of blood pressure control came from the SPRINT-MIND trial target ing systolic blood pressure (SBP) of <120 mmHg versus 140 mmHg in hypertensive individuals aged ≥50 years. The study ended prematurely because of effective prevention of cardiovascular outcomes in the lower SBP target group but nonetheless demonstrated that SBP reduction reduced rates of mild cognitive impairment (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.69–0.95) and combined mild cogni tive impairment or probable dementia (HR, 0.85; 95% CI, 0.74–0.97), although not dementia alone (HR, 0.83; 95% CI, 0.67–1.04). It is nota ble that both these studies measured all-cause cognitive impairment rather than just a vascular dementia subset, underlining the potential importance of VCID as a target for dementia prevention.

■ ■GLOBAL CONSIDERATIONS A review of data from across the globe indicates good evidence for vari ability in vascular dementia. Intracranial atherosclerosis, for example, is higher in Asians, Hispanics, and American blacks than it is in European and American whites, while whites may have more extracranial dis ease. The causes of these disparities remain under investigation but likely include access to health care, lifestyle factors such as diet, and possible genetic influences.

■ ■SUBTYPES OF CEREBROVASCULAR DISEASE ASSOCIATED WITH VCID Large Cerebral Strokes Symptomatic strokes, whether ischemic (Chap. 438) or hemorrhagic (Chap. 439), reflect irreversible injury to discrete areas of cerebral cortex, subcortical white matter, or other subcortical and infratentorial structures and produce cognitive impair ment as a function of their size and location. Rare individual infarcts in specific strategic locations such as thalamus, medial temporal cortex, anterior corpus callosum, or dominant-side angular gyrus can suffi ciently impair episodic memory and functional skills to meet memorybased criteria for dementia. More commonly, strokes occur outside these strategic territories and affect various other aspects of cognition such as executive function, processing speed, and visuospatial perfor mance that fall under the broader VCID concept. Multiple strokes and larger volumes of infarcted territory are associated with a higher likeli hood of poststroke cognitive dysfunction. CHAPTER 444 Vascular Dementia Stroke patients who make good cognitive recovery nonetheless demonstrate accelerated poststroke cognitive decline. Communitybased individuals in the longitudinal Reasons for Geographic and Racial Differences in Stroke study, for example, changed trajectory from an average prestroke cognitive gain of 0.021 points/year to post stroke cognitive loss of –0.035 points/year on the six-item screener global cognitive function scale. Mechanisms for poststroke cognitive decline likely include ongoing effects of the cerebrovascular disease that gave rise to the index stroke as well as loss of cognitive reserve that makes the brain less resilient to any additional age-related disorders. Cerebral Small-Vessel Disease Diseases of the brain’s small ves sels (Chap. 438) can also cause symptomatic ischemic or hemorrhagic stroke but are more often clinically asymptomatic and recognized only during evaluation for cognitive decline or other symptoms. The two common age-related cerebral small-vessel pathologies are arteriolo sclerosis and cerebral amyloid angiopathy. Arteriolosclerosis represents thickening of arterioles due to infiltration of plasma proteins into the vessel wall. The primary risk factors for this process are age, hyper tension, and diabetes mellitus. Cerebrovascular arteriolosclerosis can present as a cause of ischemic or hemorrhagic symptomatic stroke, both most commonly centered in territories supplied by deep penetrat ing vessels such as thalamus, basal ganglia, or brainstem. Cerebral amy loid angiopathy is defined by deposition of the

β-amyloid peptide in the walls of small cerebral arteries, arterioles, and capillaries, with conse quent loss of normal wall structure. Its primary risk factor is advancing age. Cerebral amyloid angiopathy is most often recognized symptom atically as a cause of intracerebral hemorrhage (Chap. 439), commonly located in cerebral cortex, subcortical white matter (collectively known as lobar hemorrhages), or the cerebral convexity subarachnoid space. This small-vessel pathology also appears to confer increased risk for the adverse amyloid-related imaging abnormalities (ARIA) associ ated with recently approved immunotherapies for Alzheimer's disease (Chap. 442). The distinction between the deep penetrating territories most commonly affected by arteriolosclerosis and superficial lobar brain regions affected by cerebral amyloid angiopathy often allows the two small-vessel diseases to be radiographically distinguished. Despite differences in their underlying pathogenic mechanisms, the two cerebral small-vessel diseases produce a similar range of ischemic and hemorrhagic brain lesions detectable by histopathology at autopsy or MRI scan during life (Fig. 444-1). Small (lacunar) infarcts are a common feature of arteriolosclerosis and less commonly of cerebral amyloid angiopathy. Chronic lacunar infarcts can appear on MRI fluidattenuated inversion recovery (FLAIR) sequences as a hyperintense rim surrounding a hypointense cavitated core with diameters typically

B A PART 13 Neurologic Disorders D FIGURE 444-1 Magnetic resonance imaging (MRI) markers of cerebral small vessel disease. A. Lacunar infarct: fluid-attenuated inversion recovery (FLAIR) sequence showing hyperintense rim surrounding a hypointense cavitated core in the left thalamus (arrowhead). B. Acute microinfarct: diffusion-weighted sequence showing small hyperintense lesion in the left centrum semiovale (arrowhead). C. Cerebral microbleeds in deep penetrating brain region: T2*-weighted sequence showing multiple small hypointense lesions in the pons (arrowheads). D. Cerebral microbleeds in lobar brain regions: T2*-weighted sequence showing multiple small hypointense lesions lobar brain regions (arrowheads). E. White matter hyperintensities: FLAIR sequence showing confluent diffuse hyperintensities in white matter. 3–15 mm (Fig. 444-1A), but this characteristic appearance evolves in only a subset of small infarctions, and many cannot be readily identi fied in the chronic stage. Microinfarcts <3 mm are characteristic of both small-vessel diseases. They are substantially more numerous than lacunar infarcts but less easily visualized. Acute microinfarcts may be visible as punctate hyperintensities on diffusion-weighted MRI images (Fig. 433-1B), whereas a small subset of chronic microinfarcts is detectable on high-resolution T2-weighted MRI sequences as hyper intense lesions in the cerebral cortex. Cerebral microbleeds are less numerous than lacunes or microinfarcts but readily detected in their chronic stage because of the paramagnetic effects of iron products. These appear as round hypointense lesions on T2∗-weighted MRI, pri marily in deep penetrating brain regions if caused by arteriolosclerosis (Fig. 444-1C) or lobar regions if caused by cerebral amyloid angiopathy (Fig. 444-1D). Other MRI markers of small-vessel disease identify diffuse injury of the white matter. White matter hyperintensities on T2-weighted or FLAIR MRI sequences (Fig. 444-1E) are an almost ubiquitous feature of aging. Although these lesions are readily visible on clinical MRI, they represent a nonspecific marker of white matter gliosis, demyelination, or increased water content. Extremely severe diffuse white matter vas cular injury is commonly referred to as Binswanger's disease or subcor tical arteriosclerotic encephalopathy, recognized as a clinical syndrome with gradual cognitive deterioration and notable white matter changes of small-vessel ischemic disease. On neuroimaging, a progressive confluent subcortical and periventricular white matter disease is seen

C E (see Fig. 31-2), with hypoperfusion and hypometabolism. More subtle alterations in white matter structure can be sensitively and quantita tively detected by diffusion tensor MRI (Chap. 434) as increased water diffusivity or decreased diffusion directionality. Diffusion tensor mea sures of white matter structural integrity show a consistent association with cognitive performance and gait speed, reflecting the central role of disconnection of key brain networks in mediating the effects of cere bral small-vessel disease. These diffusion tensor–based methods often require complex processing and are typically used in research rather than clinical settings. A relatively simple diffusion tensor–based metric defined by the peak width of the skeletonized mean diffusivity (PSMD) histogram has emerged as a candidate method for quantifying white matter disconnection. Functional MRI measurement of cerebrovascu lar reactivity to physiologic stimuli is generally not performed in clini cal practice, but it may become abnormal decades before appearance of structural brain injury and therefore represents a promising outcome marker for identifying disease-modifying interventions aimed to slow or prevent vascular brain injury. Role of Accompanying Brain Pathologies The concept of VCID posits that large strokes and small-vessel disease often occur in combination with neurodegenerative brain diseases, most commonly Alzheimer’s disease (Chap. 442). Many clinicopathologic correlation studies have established that the co-occurrence of cerebrovascular and neurodegenerative lesions produces more cognitive and functional impairment than expected from the effects of each disease mechanism

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