Neuroimaging of Vascular Dementia

Sangam Kanekar, MD[a,b,*], Jeffrey D. Poot, DO[a]

KEY POINTS

- Vascular dementia (VaD) is the third leading cause of progressive and irreversible dementia after Alzheimer disease (60%–70%) and dementia with Lewy bodies (10%–25%).
- Because of the high variability of cerebrovascular pathologic conditions and its causative factors, there are no accepted neuropathologic criteria for diagnosing VaD.
- Brain pathology may show diffuse confluent age-related white matter changes, multi-lacunar state (état lacunaire), multiple (territorial) infarcts, strategic cortical-subcortical or watershed lesions, cortical laminar necrosis (granular cortical atrophy), and delayed postischemic demyelination and hippocampal sclerosis.
- Subcortical VaD is the most common subtype of small-vessel VaD and constitutes approximately 50% of VaD cases.

INTRODUCTION

Cerebrovascular disease (CVD) is the second most prominent cause of dementia either alone or in combination with Alzheimer disease (AD).[1] In the past, the term *vascular dementia* (VaD) was used to define the cognitive impairment resulting from CVD and ischemic or hemorrhagic brain injury.[2] The definition and diagnostic criteria of VaD remains unclear and generates much confusion in clinical practice. In addition, it was not able to classify patients who develop a cognitive impairment that does not fulfill the traditional criteria for dementia but that nonetheless has a significant impact on the patients' quality of life and ability to carry out activities of daily living. The term *vascular cognitive impairment* (VCI) was introduced to encompass all of the effects of vascular diseases or lesions on cognition and incorporate the complex interactions between vascular causes, risk factors, and cellular changes within the brain and cognition.[3] VCI refers to "a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain." VCI also includes both pure (CVD alone) and mixed (CVD with other pathologic conditions, such as that of AD). It is important to understand that VCI is not a disease like AD but is rather a syndrome or phenotype that results from CVD, subsequently leading to vascular brain injury that disrupts the brain network for memory and thinking. VaD is a subset of the broader designation VCI.

PREVALENCE

Dementia from all causes has a prevalence of about 8% in individuals aged more than 65 years.[1,3] In the Western literature, VaD is the third leading cause of progressive and irreversible

[a] Department of Radiology, Penn State Milton S. Hershey Medical Center and College of Medicine, The Pennsylvania State University, 500 University Drive, Hershey, PA 17033, USA; [b] Department of Neurology, Penn State Milton S. Hershey Medical Center and College of Medicine, The Pennsylvania State University, 500 University Drive, Hershey, PA 17033, USA
* Corresponding author. Department of Radiology and Neurology, Penn State Milton S. Hershey Medical Center and College of Medicine, The Pennsylvania State University, 500 University Drive, Hershey, PA 17033.
E-mail address: skanekar@hmc.psu.edu

dementia after AD (60%–70%) and dementia with Lewy bodies (10%–25%).[4] The incidence of VaD shows a wide variation in the patient population (age, sex), geographic location, and use of clinical methods. Of all causes of dementia, 13% to 19% are from pure vascular causes, whereas mixed dementia whereby vascular causes are part of the disease is seen in 11% to 43%.[3,4] The proportion of cases caused by VaD decreases with increasing age, but the prevalence of all dementia increases so rapidly with age that the prevalence of VaD also increases, from 0% to 2% in the 60- to 69-year-old age group and up to 16% (3%–6% for men) in individuals aged 80 to 89 years.[5] Globally, VaD seems to be more common in men, especially before 75 years of age. The incidence in women and men aged 85 years and older is around 9.3% and 15.9%, respectively. Epidemiologic studies suggest that the incidence of VaD in Europe accounts for about 15% to 20% of the cases, whereas in Japan it accounts for around 50% of the cases.[1,6] VaD is also more prevalent in populations affected by cerebral small-vessel disease (SVD), such as Asians, African Americans, and Hispanics.

The introduction of the new term *VCI* encompasses all of the effects of vascular disease on cognition leading to a change in the epidemiology. In patients younger than 74 years, VCI may be the single most common cause of cognitive impairment. In those individuals aged 75 to 84 years, cases of pure VCI, VaD, and those with a vascular component in the context of mixed disease outnumber those with pure AD.[7] In a Canadian study, the prevalence of VCI has been estimated at 5% in people older than 65 years.[1,5] The cognitive outcome of patients with VaD may be as severe as in AD, but their morbidity and mortality are usually worse.

DIAGNOSTIC CRITERIA

The concept of CVD leading to cognitive decline and dementia has been recognized since the seventeenth century. In the latter half of the nineteenth century, Kraepelin and colleagues coined the term *atherosclerotic dementia*.[8] In 1974, Vladimir Hachinski and colleagues[9] introduced the term *multi-infarct dementia* (MID). Since then, because of the advances in imaging techniques, our understanding of the disease process has significantly evolved. Unfortunately, because of the high variability of cerebrovascular pathologic conditions and its causative factors, there are no accepted neuropathologic criteria for diagnosing VaD or VCI, as agreed for AD or dementia with Lewy bodies. Unlike AD, vascular lesions are classified based on the morphologic characteristics rather than by their pathogenesis. The criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, (Fourth Edition) (*DSM-IV*) for VaD were proposed by the American Psychiatric Association from a general definition of dementia (**Box 1**).[10] The major limitations for these criteria are the following: They are purely clinical. No neuroimaging findings are incorporated. No criteria are mentioned to establish a causal relationship between dementia and vascular disease. The cross-sectional neuroimaging modalities computed tomography (CT) and magnetic resonance (MR) imaging have significantly improved our understanding of SVD, MID, and VaD. In 1993, the National Institute of Neurologic Disorders and Stroke (NINDS)–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) formulated criteria that incorporated the structural neuroimaging as a crucial element for the diagnosis of VaD (**Box 2**).[11] To enhance their clinical implementation, operational definitions for the radiological part of the NINDS-AIREN's criteria were subsequently modified in 2003.[12] To diagnose VaD, the current criteria require the presence of the syndrome of dementia and a pathophysiologic mechanism.

Box 1
***DSM-IV* criteria for VaD**

a. There are multiple cognitive deficits manifested by both memory impairment and one or more of the following cognitive disturbances: aphasia, apraxia, agnosia, or disturbance in executive functioning.

b. The cognitive deficits cause significant impairment in social or occupational activities and represent a significant decline from a previous level of functioning.

c. There are focal neurologic signs and symptoms (eg, exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicating CVD (eg, multiple infarcts involving the cortex and the underlying white matter) that are judged to be etiologically related to the disturbance.

d. The deficits do not exclusively occur during the course of a delirium.

From American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th edition. Washington, DC: American Psychiatric Association; 1994. p. 9–36; with permission.

Box 2
Operational definitions for the radiological part of the NINDS-AIREN's criteria (2003)

Topography

Large-vessel stroke

- Large-vessel stroke is an infarction defined as a parenchymal defect in an arterial territory involving the cortical gray matter.
  - ○ ACA: Only bilateral ACA infarcts are sufficient to meet the NINDS-AIREN's criteria.
  - ○ PCA: Infarcts in the PCA territory can be included only when they involve the following regions:
    - ■ Paramedian thalamic infarct
    - ■ Inferior medial temporal lobe lesions
- Association areas: MCA infarcts need to involve the following regions:
  - ○ Parietotemporal lobe (eg, angular gyrus)
  - ○ Temporo-occipital cortex
- Watershed carotid territories (between the MCA and PCA or the MCA and ACA)

SVD

- Multiple basal ganglia and frontal white matter lacunes
- Extensive periventricular white matter lesions (leukoaraiosis)
- Bilateral thalamic lesions

Severity

- Large-vessel disease of the dominant hemisphere
- Bilateral large-vessel hemispheric strokes
- Leukoencephalopathy involving at least 25% of the total white matter

Fulfillment of radiological criteria for probable VaD

- Large-vessel disease: Both the topography and severity criteria should be met (a lesion must be scored in at least 1 subsection of both topography and severity).
- SVD: For white matter lesions, both the topography and severity criteria should be met.

Abbreviations: ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.
    Modified from Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–60; with permission.

PATHOPHYSIOLOGY

The risk factors for VCI are the same as that for CVD, stroke, and white matter lesions (WMLs), which include arterial hypertension, atrial fibrillation, myocardial infarction, coronary artery disease, diabetes, generalized atherosclerosis, lipid abnormalities, smoking, family history, and specific genetic features.[13] The pathophysiology of VCI and VaD is thought to be multifactorial and is attributed to causes like CVD, infarcts, diffuse WMLS, atrophy, and host factors. These lesions are either diffuse or in the strategic location and cause interruptions of the various white matter tracts and cortical and subcortical neuronal circuits leading to various cognitive declines and dementia. The neuropathologic changes associated with VaD include multifocal and/or diffuse disease or as a single focal lesion in the strategic location. Brain pathology may show diffuse confluent age-related white matter changes, multi-lacunar state (état lacunaire), multiple (territorial) infarcts, strategic cortical-subcortical or watershed lesions, cortical laminar necrosis (granular cortical atrophy), and delayed postischemic demyelination and hippocampal sclerosis.[14] It is the combinations of these findings seen that often

cause the cognitive decline. Histopathology specimens show cellular processes, such as demyelination, axonal damage, diaschisis or retrograde degeneration, and atrophy.

At the neurotransmitter level, cholinergic dysfunction has been well documented in the experimental animal models of ischemic VaD.[15] Deficits in cholinergic markers and cholinergic receptors have also been documented in human cases of VaD. These changes are most pronounced in the basal forebrain nuclei, which are supplied by penetrating arterioles from the middle cerebral artery (MCA), anterior communicating artery, and anterior cerebral artery (ACA). In addition, vascular insults affecting the white matter and basal ganglia can also interrupt the cholinergic projections from the basal forebrain.

NEUROIMAGING

The imaging appearance of VaD can be broadly divided into (1) large-vessel VaD, (2) small-vessel VaD, and (3) microhemorrhage and dementia (**Box 3**).

LARGE-VESSEL VAD
MID (Poststroke Dementia)

Large-vessel VaD may be either caused by multiple or single cortical or subcortical infarcts or

---

Box 3
Neuroimaging classification of VaD

LARGE-VESSEL VaD

1. Multi-infarct dementia (multiple large complete infarcts involving cortical and subcortical areas)
2. Watershed infarction
3. Strategic single-infarct dementia
4. Hypoperfusion and ischemic encephalopathy

SMALL-VESSEL VaD

1. Subcortical VaD
2. Lacunes
3. Perivascular spaces
4. Silent cerebral infarcts

MICROHEMORRHAGE AND DEMENTIA

CAA, cerebral amyloid angiopathy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; HERNS, hereditary endotheliopathy retinopathy nephropathy and stroke.

---

caused by a cerebrovascular lesion involving the strategic regions like the hippocampus, paramedian thalamus, and thalamocortical networks.[11] The source of these infarcts may be due to atherosclerosis, vasculitis, or embolic phenomenon. Occlusion of the extracranial arteries, the internal carotid artery, the main intracranial arteries including the MCA, medium-sized arteries in the leptomeninges, and proximal perforating arteries can lead to VaD. The damage can be worse depending on the presence of hypertension and related CVD. The NINDS-AIREN's criteria define probable VaD as a cognitive decline from a previously higher level of functioning in memory and 2 or more cognitive domains, with the decline being severe enough to interfere with activities of daily living.[11] For the diagnosis of the VaD, both clinical criteria and neuroimaging evidence of CVD are required. The clinical criteria may have 2 of the following: (1) onset of dementia within 3 months after a recognized stroke, (2) abrupt deterioration in cognition (days to weeks), and/or (3) stepwise deterioration.[16] Imaging plays a supportive role by identifying the type (hemorrhagic vs nonhemorrhagic) and localizing the anatomic site of the abnormality.

VaD largely depends on the site of the blocked vessel and the affected brain parenchyma. Up to one-third of stroke survivors exhibit dementia within 3 months after their stroke, whereby memory loss may not be the primary symptom. In classic poststroke patients, cortical cognitive deficits, such as agnosia, apraxia, alexia, aphasia, and visuospatial or constructional difficulty, are seen, often without motor deficit.

Cross-sectional imaging with CT and MR along with CT angiography or MR angiography have become the imaging modalities to evaluate patients with VaD.[17] These modalities are very sensitive in confirming the size and location of the symptomatic as well as asymptomatic (silent) strokes. MR is also very helpful in the diagnosis of microbleeds, anoxic/hypoxic brain injury, and identifying the changes of gliosis and encephalomalacia. The parenchymal perfusion status may also be obtained using CT or MR perfusion. Diffusion-weighted imaging (DWI)–apparent diffusion coefficient (ADC) has an established role in the diagnosis of hyperacute infarction. An infarcted area, which has a decrease in Brownian motion, is seen on the DWI sequence as restricted diffusion with low ADC. In the subacute-chronic stage of infarction, imaging is characterized by local brain atrophy, gliosis, cavity formation, and ex vacuo dilatation of the ipsilateral ventricle. 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. 1**). Calcification and deposition of blood products (hemosiderin) may be seen on T2 and gradient echo (GRE) sequences. Corticospinal tract degeneration (ie, Wallerian degeneration) is also seen with hemispheric infarction. There is a loss of brain tissue and its corresponding function. Strokes involving the left hemisphere were shown to have a higher incidence of dementia as compared with the right. Also, a strong correlation is seen between dementia and infarctions in the left posterior cerebral artery (PCA) and the ACA and parietal areas (**Fig. 2**).[18] Cortical laminar necrosis, neuronal ischemia accompanied by gliosis, and layered deposition of fat-laden macrophages may be seen in the infarcted region. Gray matter is more vulnerable to hypoxia than white matter. On MR,

laminar necrosis is seen as hyperintensity in the cortex on T1-weighted and FLAIR images (**Fig. 3**). These changes are visible 2 weeks after infarction and are most prominent at 1 to 3 months.

Watershed Infarctions

Watershed infarctions are seen at the junction of the distal fields of the 2 nonanatomizing major cerebral arteries. They are classified into cortical and internal watershed infarcts.[19] Cortical watershed infarcts may occur symmetrically or unilaterally in circular border zones between the deep and superficial branches of ACA, MCA, and PCA. The pathogenesis of watershed infarction remains debatable and is thought to be multifactorial.[19,20] A hemodynamic mechanism, which includes internal carotid stenosis or occlusion, systemic
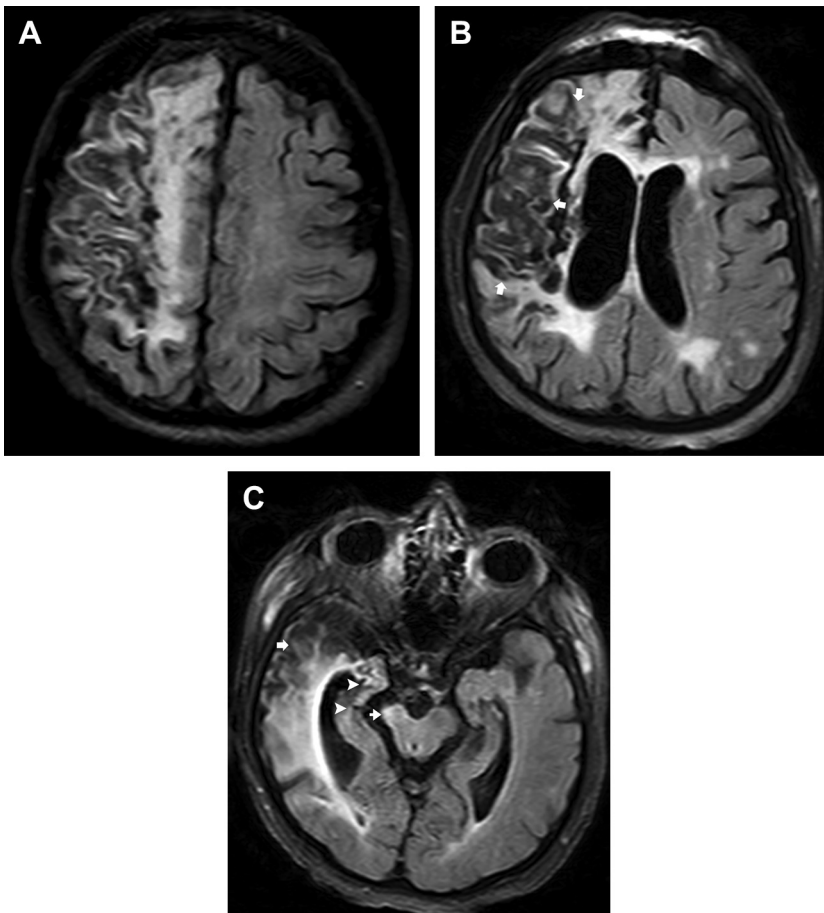
Fig. 1. Chronic right MCA infarction with severe cognitive decline. Axial FLAIR (*A–C*) MR images show large chronic right MCA infarct with encephalomalacia and surrounding hyperintensity caused by gliosis (*fat arrows*). There is ex vacuo dilatation of the ipsilateral lateral ventricle. There is atrophy of the right side of the brainstem with hyperintensity in the cerebral peduncles caused by Wallerian degeneration (*small arrow* in *C*). Also seen is severe atrophy of the head and body of the right hippocampus (*arrowheads* in *C*).
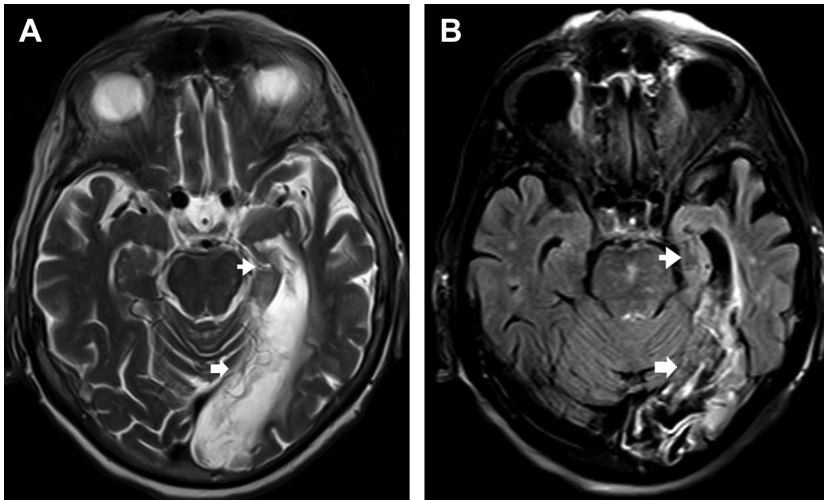
Fig. 2. PCA infarct in a 69-year-old male patient with dementia. Axial T2 (*A*) and FLAIR (*B*) MR images show a large left temporo-occipital chronic infarct with mild ex vacuo dilatation of the temporal horn (*thin arrow*). There is mild volume loss of the head of left hippocampus (*fat arrow*).

hypotension, and embolic events, is a major cause of watershed infarction. They are caused by hypotension with misery perfusion (ie, diminished flow in distal vessels or showers of microemboli).[21] Watershed infarction may affect eloquent areas of the brain and may be associated with a strategic infarct dementia. The superior frontal area, between the distal supply of the ACA and MCA, and the posterior parieto-occipital junction, among ACA, MCA, and PCA, are frequently involved with watershed infarction. Associated hypoxia may also cause alterations in the hippocampal subareas CA-1 and CA-4, the outer half

of the caudate nucleus and putamen, and the anterior and dorsomedial nucleus of the thalamus. Damage to these areas is often associated with the development of cognitive decline and dementia.

MR is very sensitive and specific in the diagnosis of watershed infarction. In acute events, DWI is very sensitive for the diagnosis of both cortical watershed infarct and internal watershed infarct. Classically, cortical watershed infarcts appear as fan- or wedge-shaped hyperintensities extending from the lateral margins of the lateral ventricle toward the cortex, whereas internal watershed
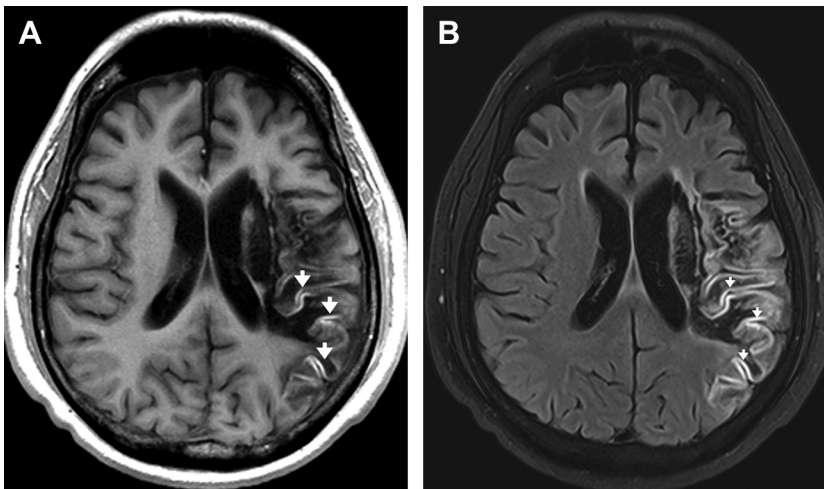
Fig. 3. Laminar necrosis. Axial T1 (*A*) and FLAIR (*B*) MR images reveal large chronic left MCA infarction with encephalomalacia and gliosis. Hyperintensity seen along the gyri on T1 and FLAIR images within the infarcted area is suggestive of cortical laminar necrosis (*arrows*).

infarcts are seen as hyperintensities running parallel to the lateral ventricles, either confluent or focal, and may be unilateral or bilateral (**Fig. 4**).[22]

Strategic Single-Infarct Dementia

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, whereas the *subcortical* sites leading to impairment are the thalamus, fornix, basal forebrain, caudate, globus pallidus, and the genu or anterior limb of the internal capsule.[23] The mechanism by which the strategic single infarct leads to dementia is not completely understood, but it is thought to be caused by the interruption of frontal-subcortical circuits.[11,24] The general organization of these circuits includes the frontal lobes, striatum, globus pallidus/substantia nigra, and the thalamus.

Cognitive decline and the clinical symptoms largely depend on the strategic area involved. *Caudate nucleus infarctions* can lead to abulia, restlessness and hyperactivity, language deficits, and poor memory. The cognitive domains mostly affected in caudate infarcts are decreased problem-solving ability, impaired recent and remote memory with preservation of recognition memory, and decreased attention. Ischemic stroke or a subarachnoid hemorrhage from ruptured aneurysms involving the *mesial temporal lobe* and thalamus may cause memory and other
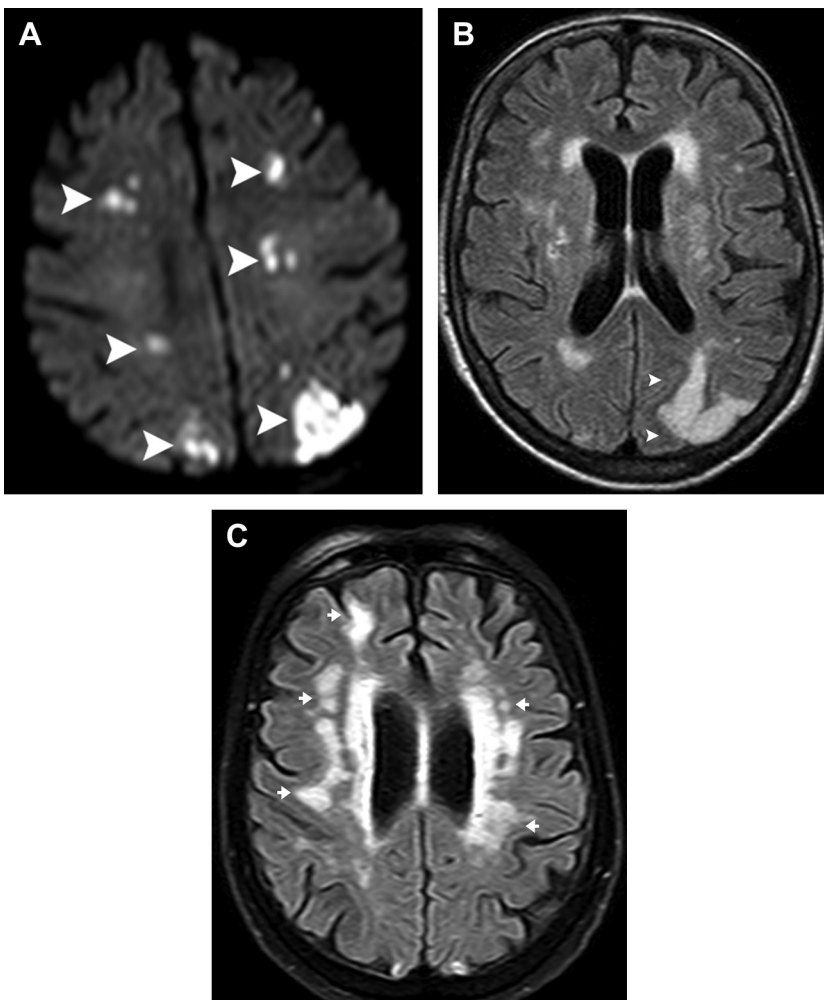

Fig. 4. Watershed infarct with dementia. Axial DWI (*A*) and FLAIR (*B*) MR images show bilateral deep cortical watershed infarctions bilaterally (*arrowheads*). Sixteen months following the event, the patient presented with gradual cognitive decline. Axial FLAIR (*C*) MR image shows mild global atrophy with diffuse white matter changes (*arrows*) suggestive of chronic microangiopathic changes.

cognitive deficits because of the interruption of the cholinergic projections to the cholinergic nuclei in the basal forebrain (**Fig. 5**). These patients may present with severe anterograde amnesia for verbal or visuospatial material, along with severe apathy, lack of initiative and spontaneity, and executive dysfunction. These patients are also unable to encode and consolidate new verbal material, such as facts, events, short stories, names, and concepts. This inability may be difficult clinically to differentiate from AD. A *thalamic stroke* produces a peculiar form of thalamic VaD (**Fig. 6**). These patients show a depressed level of consciousness impairments in attention, motivation, initiative, executive functions, and memory, as well as dramatic verbal and motor slowness and apathy. Thalamic lesions may cause thalamic amnesia because of the damage to the mammillothalamic tract; even small and/or unilateral damage to this structure may affect memory,

executive functioning, and attention. *PCA infarcts* may cause damage to the hippocampus, isthmus, entorhinal and perirhinal cortex, and parahippocampal gyrus (see **Fig. 2**). Therefore, patients may present with amnesia.

Hypoperfusion and Ischemic Encephalopathy

Diseases of the large arteries and the heart can lead to cerebral hypoperfusion and have been associated with the development of dementia after stroke. Hypoperfusion may affect both gray and white matter. Hypoperfusion affecting white matter may lead to leukoaraiosis and incomplete infarction, which comprises zones of partial neuronal or axonal loss with demyelination, increased perivascular spaces, reactive astrocytosis, and gliosis.[25] Damage to the cerebral cortex with laminar necrosis may be seen at the arterial border zones following hypoxia. These zones are
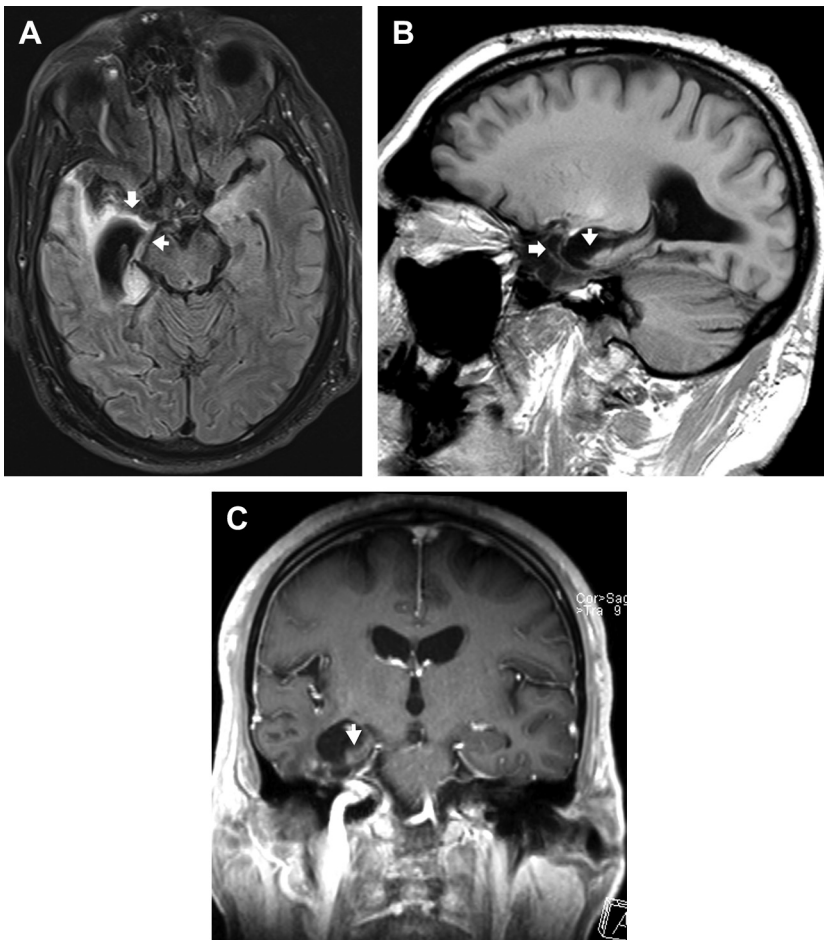
Fig. 5. Chronic right temporal lobe infarction with severe memory loss. Axial FLAIR (*A*), sagittal T1 (*B*), and coronal T1 (*C*) MR images show chronic infarction of the anterior temporal lobe with ex vacuo dilatation of the right temporal horn. There is striking atrophy of the right amygdala (*fat arrow*) and hippocampus (*thin arrow*).
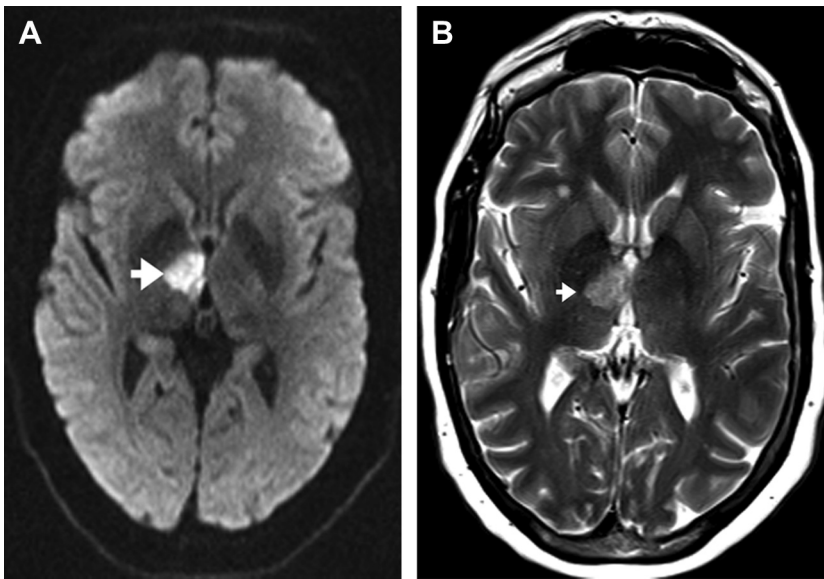
Fig. 6. 61-year-old man with acute-onset amnesia. Axial DWI (*A*) and T2 (*B*) MR images show hyperintensity in the anteromedial aspect of the right thalamus (*arrows*) caused by acute thalamic stroke.

often associated with diffuse white matter damage and cerebellar atrophy. Hypoperfusion can also produce hippocampal neuronal loss or severe white matter changes leading to hippocampal sclerosis. There is severe gliosis and neuronal loss in the CA-1 region of the hippocampus and in the subiculum, which present as cognitive decline often with marked memory impairment.[26] It predominantly co-occurs with AD but is also seen associated with frontotemporal lobar degeneration and tauopathies. Dedicated coronal T2 and FLAIR images show decreased size of the hippocampus with increased signal intensity (**Fig. 7**). There may be bilateral atrophy of the temporal lobes with associated T2 hyperintensity changes in the white matter. It is often accompanied by multiple small infarcts in other brain regions, leukoencephalopathy, or both.
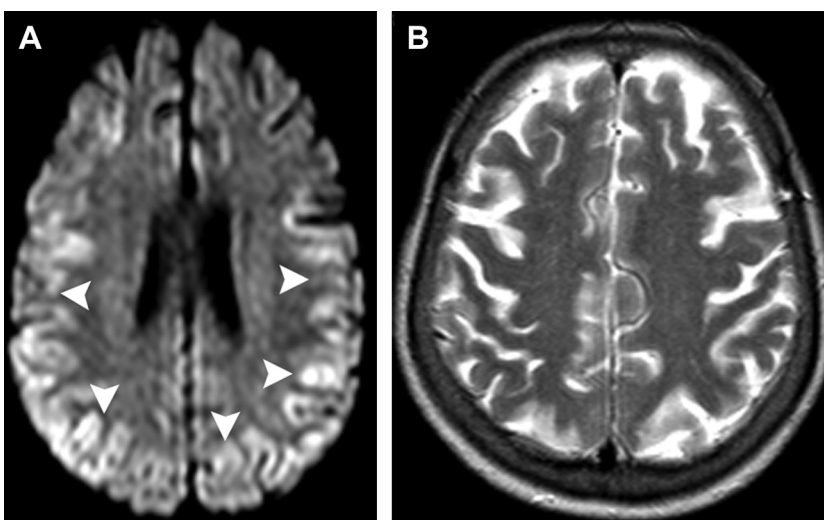
Fig. 7. Dementia caused by global hypoxia in a 54-year-old man. Axial DWI (*A*) MR image shows restricted diffusion in the cerebral cortex bilaterally (*arrowheads*), suggestive of diffuse hypoxic injury from hypotension. Follow-up scan performed 2 years later for early signs of dementia shows advanced cortical atrophy for the age of the patient on T2 MR image (*B*).

SMALL-VESSEL VAD (WMLS AND DEMENTIA)

With the advent of MR imaging, diffuse or focal WMLs are detected with higher sensitivity. These lesions are also related to various cognitive decline and VaD. In neuropathology literature, these lesions are described under various synonyms, such as subcortical arteriosclerotic encephalopathy or Binswanger disease, diffuse white matter disease, WMLs, leukoaraiosis, periventricular arteriosclerotic (leuko) encephalopathy or leukomalacia, subcortical vascular encephalopathy, and periventricular lucency.

Subcortical VaD

As per the NINDS–AIREN's diagnostic criteria, small-vessel VaD is classified into 2 types: *subcortical and cortical* forms.[11,12,27] The subcortical form is a classic subcortical VaD (SCVD), whereas the cortical SVD is mostly cerebral amyloid angiopathy (CAA). SCVD is the most common subtype of small-vessel VaD and constitutes approximately 50% of VaD cases.[27,28] SCVD is attributed to SVD and is characterized by focal and diffuse ischemic WMLs, lacunar infarcts, and incomplete ischemic injury. All of these disease conditions may coexist.

The risk factors for the SCVD are similar to stroke (smoking, hypertension, diabetes, cholesterol). Cerebral arterial small vessels arise superficially from the subarachnoid circulation as terminations of medium-sized arteries and deeply as arterial perforators from larger vessels at the base of the brain. These vessels supply deep white matter structures. Like the rest of the organs of the body, these cerebral blood vessels also undergo progressive age-related changes. These changes include perivascular collagen deposits, also referred to as *microvascular fibrosis* and *basement membrane thickening*, which are mainly seen in the end-arteries and arterioles. The primary target is the small vessels of the white matter; however, the gray matter vessels are affected. Small-vessel changes of fibrohyalinosis in the white matter and angionecrosis and lipohyalinosis in the gray matter, including the basal ganglia and the thalamus. These vessel changes lead to small-vessel cortical microinfarcts, infarcts of the perforating deep small vessels, état criblé (multiple enlarged deep gray matter Virchow–Robin spaces [VRS]), microbleeds, and diffuse WMLs (incomplete infarctions).[27,28] Histopathology shows focal areas of white matter demyelination, loss of axons, gliosis, widening of perivascular spaces, and loss of blood-brain–barrier integrity.[27] These changes are found mainly in the frontal, parietal, and occipital white matter and in the periventricular areas. Various parenchymal changes lead to a loss of neural integrity and retrograde neuronal dysfunction in the basal ganglia and the cerebral cortices, thereby resulting in vascular parkinsonism and dementia.

Because SVD is a slowly progressive disease, it usually lacks the classic stepwise decline more typical of large-vessel VaD. They commonly present with *subcortical cognitive syndrome,* which includes executive dysfunction, mental slowness, decision-making problems, poor organizational ability, adaptability difficulties, attention deficit, and apathy. It is attributed to preferential damage to the prefrontal subcortical circuits.[27] Because the primary anatomic target of SCVD and AD are different, their clinical cognitive and mental profiles are different. Memory loss is relatively mild in SCVD, but the loss of executive control function is prevalent.

Neuroimaging plays an important role in the diagnosis of SCVD, especially because it is a very slow progressive disease. MR can show changes before the symptoms are evident clinically. The most commonly seen abnormality on MR is a *diffuse hyperintensity* on T2-weighted imaging (T2WI) primarily in the centrum semiovale and around the ventricles.[27,29] Confluent areas of hyperintensities (leukoaraiosis) may also be commonly seen in occipital, periventricular, and sometimes frontal white matter (**Fig. 8**). On T1WI, corresponding areas may or may not show hypointensity. If these areas are isointense on T1WI, then they represent areas of incomplete infarctions; if they show hypointensity, then they are caused by complete infarction and represent tissue destruction. Ex vacuo dilatation of the ventricles may be seen because of softening of the periventricular white matter. Newer imaging techniques, such as CT or MR perfusion, may show a diffuse decrease in the cerebral blood flow and volume in the cerebral white matter. For the diagnosis of Binswanger disease, it is important to have associated clinical cognitive decline from a previously higher level of functioning in memory and 2 or more cognitive domains, in addition to the white matter changes on neuroimaging (**Fig. 9**).[30,31] The decline must at least be severe enough to interfere with activities of daily living. Without clinical findings, such findings on imaging are to be termed *leukoaraiosis*.

The second most common imaging finding seen with SVD is focal WMLs. WMLs have been found in 22% of patients younger than 40 years and in 27% to 60% of those patients older than 65 years, whereas in patients with AD and VaD, they are detected by MR in almost 100% of patients.[32] The WMLs can be categorized into *periventricular WMLs* (PVWMLs), which are attached to the
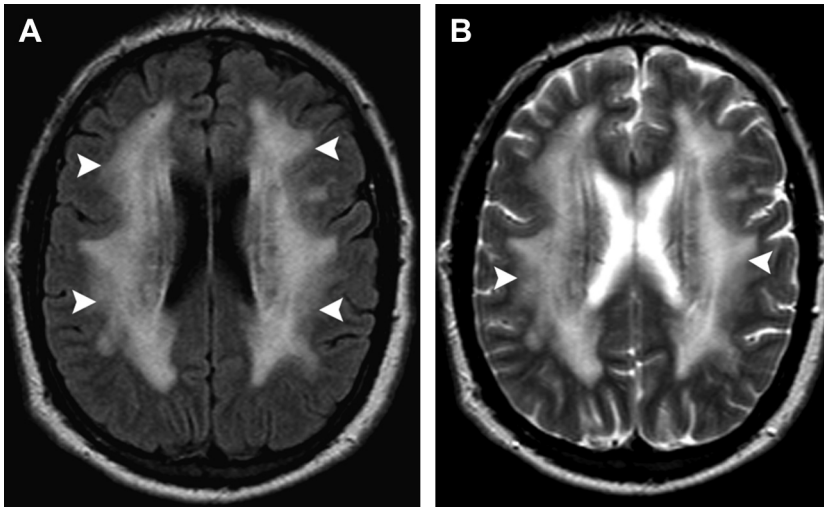
Fig. 8. Diffuse SVD with subcortical dementia. Axial FLAIR (*A*) and T2 (*B*) MR images reveal diffuse confluent hyperintensity in the white matter (*arrowheads*) in a 71-year-old man with hypertension, hyperlipidemia, and long-standing diabetes.

ventricular system, and *deep WMLs* (DWMLs), which are located in subcortical white matter. On T2/FLAIR images, PVWMLs may be further differentiated into smooth, well-defined hyperintensities versus irregular PVWMLs.[32,33] DWMLs and irregular PVWMLs are more likely to be caused by microcystic ischemic lesions. Irregular PVWMLs are more frequently seen with atherosclerosis and thought to be more hemodynamically determined, whereas DWML might be more attributed to SVD, which is seen more commonly with hypertension. Studies have shown that the risk of dementia and the severity of cognitive impairment is preferentially associated with PVWML (**Fig. 10**), whereas mood disorders were more likely seen with DWML (**Fig. 11**).[32,33]

Lacunes

Lacunes are defined as focal complete infarcts of deep small vessels that are less than 2 cm in size.[22] They are the second most common imaging finding seen in patients with subcortical dementia. Lacunae result from SVD with lumen occlusion secondary to arteriolosclerosis caused by microatheroma and lipohyalinosis or embolism, usually in patients with arterial hypertension.[34] These changes are mostly seen in the deep perforators, such as lenticulostriate, thalamoperforating, and long medullary arterioles. Therefore, lacunae are mostly seen in the basal ganglia, the upper two-thirds of the putamen, the internal capsule, the thalamus, the paramedian and lateral regions of the brain stem, the corona radiata, and the centrum semiovale. These regions play an important role in

several aspects of cognition. On histopathology, lacunes are often scattered within the areas of pallor in the white matter. They show cavitary and noncavitary infarctions or areas of vacuolation, with a loss or pallor of myelin, loss of axons and oligodendroglia, and areas of reactive astrocytosis, with or without macrophage reaction.

MR imaging is more sensitive than CT for the diagnosis of acute and chronic lacunar infarctions. Signal intensity of a lacunar infarct largely depends on the stage of the infarct. Acute lacunes show a small area of restricted diffusion with corresponding low ADC signal changes. In the chronic stages, these lesions are seen as round, oval, or slitlike, small cavitated infarcts ranging from a few millimeters to 1.5 cm. These lesions are hyperintense on T2 and FLAIR images and remain hypointense on T1WI (**Fig. 12**). In very late stages, lacunes may be hypointense on FLAIR with an irregular rim of hyperintensity around. A common differential diagnosis includes VRS, which follow CSF signal on all MR imaging sequences. In practice, the 2 forms of subcortical ischemic VaD, lacunae and deep WMLs, are often seen together, presumably because of their common origin.

Perivascular Spaces

Perivascular spaces (PVS) or VRS represent subpial interstitial spaces surrounding the penetrating arteries and arterioles.[35] They are seen most commonly along the path of lenticulostriate arteries entering the basal ganglia or along the perforating medullary arteries entering the cortical gray matter. Prominent VRS may occur in all age
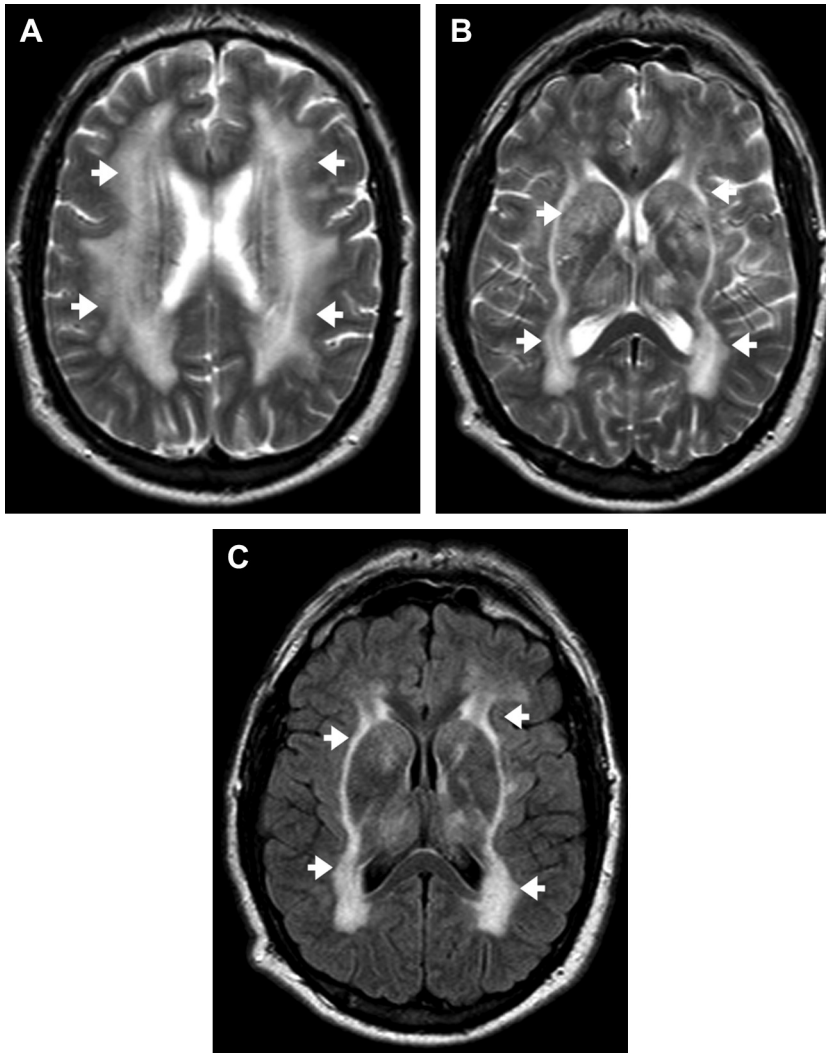
Fig. 9. Binswanger disease in a 67-year-old male patient with cognitive decline. Axial T2 (*A, B*) and FLAIR (*C*) MR images show extensive symmetric hyperintensity in the white matter sparing the U fibers (*arrows*). Increased signal intensity is also noted in the deep gray matter nuclei bilaterally.

groups and are regarded as incidental findings without much clinical significance. However, when they are prominent in elderly patients, they indicate the shrinkage of the surrounding white matter. On histopathology, there is no evidence of necrosis, macrophages, or tissue debris in the VRS. Dilated PVS may contain an insignificant and dispersed population of lipid-rich or iron pigment-laden macrophages. Dilatation of the VRS is common in disorders associated with microvascular diseases, and they are as important as periventricular hyperintensity in the scoring of cognitive deficiency. Multiple enlarged VRS in the basal ganglia is called *état criblé* and may present clinically, either with movement disorders or cognitive decline (**Fig. 13**).[36]

On MR, the PVS appears oval, with a well-defined, smooth margin that is isointense to CSF on all pulse sequences and demonstrates no enhancement after contrast administration. They are usually bilateral but may be unilateral and are localized at the level of anterior commissure, basal ganglia, cerebral convexity, midbrain, or inferior putamen. The most common differential diagnosis is lacunar infarcts, which are hyperintense on FLAIR and proton-density images.

Silent Cerebral Infarcts

Infarcts are defined as silent if they lack strokelike symptoms. Although they are termed *silent strokes*, they do present as subtle deficits in
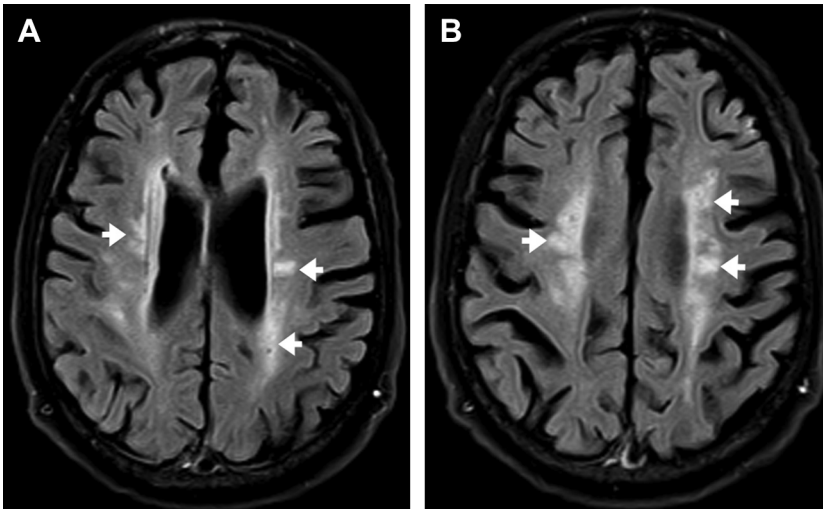
Fig. 10. Periventricular white matter lesions in a female patient with mild cognitive decline. Axial FLAIR (*A, B*) MR images show multiple focal hyperintensities in the periventricular white matter (*arrows*). Most of these lesions are seen abutting the lateral margin of the lateral ventricle.

physical and cognitive function that commonly go unnoticed. Moreover, the presence of silent infarcts more than doubles the risk of subsequent stroke and dementia. The relationship between silent brain infarcts and the risk of dementia and cognitive decline in the general population has been well established following the Rotterdam Scan study.[37] The study showed that the presence of silent brain infarcts more than doubles the risk of dementia, including AD. Silent brain infarcts were also shown to be the risk factor for mild cognitive impairment in the Cardiovascular Health Study. Silent brain infarcts are common among the general population. They are far more common than strokes, both with respect to prevalence and incidence. The overall prevalence of silent infarct ranges from 8% to 28% and increases with age.[38] Their risk factors are similar to infarction, with hypertension being, by far, the strongest modifiable risk factor.

The cumulative effect of this silent infarct can give rise to deficits in cognitive function. The symptoms totally depend on the area and the white matter connections disrupted, with memory performance being most affected by silent thalamic lesions. WMLs and cortical microinfarcts
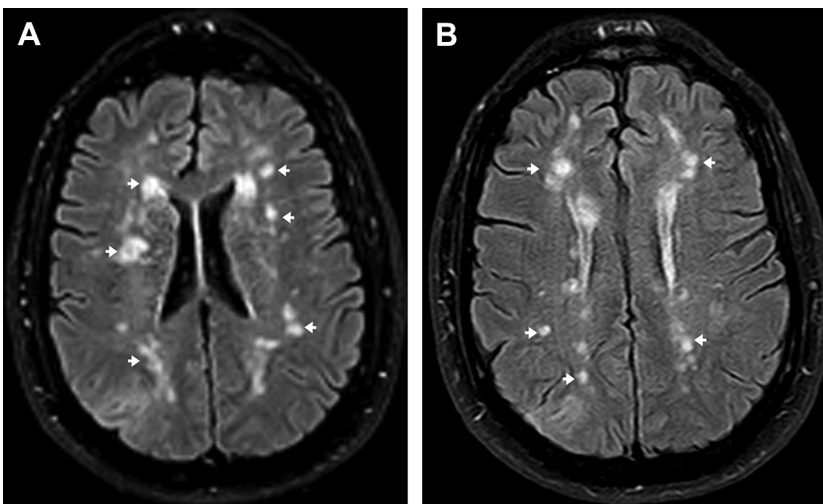

Fig. 11. Deep WMLs in 63-year-old male patient with mood disorders. Axial FLAIR (*A, B*) MR images show multifocal, rounded hyperintensities in the deep white matter bilaterally (*arrows*).
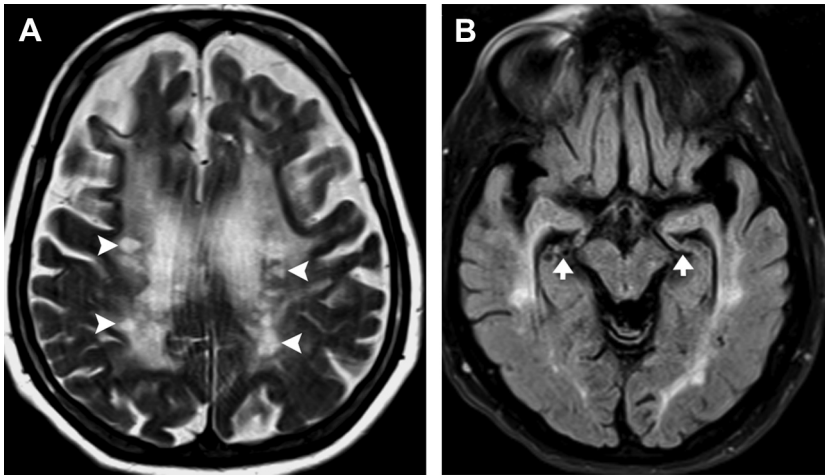
Fig. 12. SVD with lacunes. Axial T2 (*A*) and FLAIR (*B*) MR images show diffuse confluent hyperintensity in the white matter with multiple tiny lacunes (*arrowheads* in *A*). There is atrophy of the hippocampus bilaterally (*arrows* in *B*).
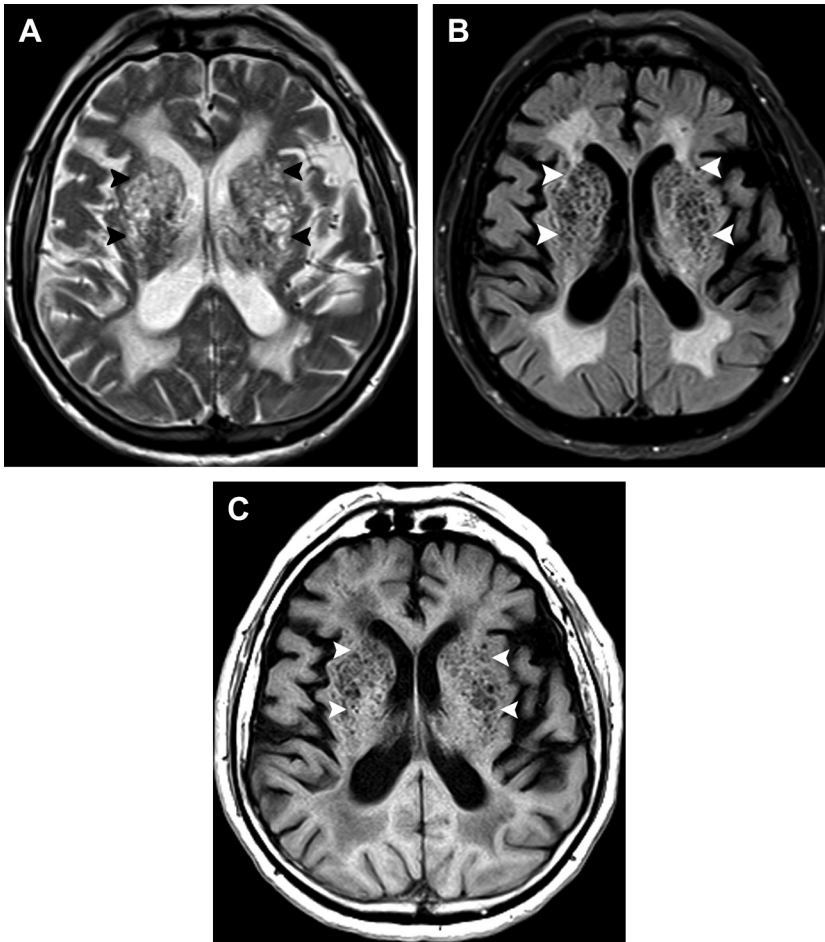
Fig. 13. État criblé and SVD in 71-year-old man with dementia. Axial T2 (*A*), FLAIR (*B*), and T1 (*C*) MR images reveal multiple enlarged PVS in the basal ganglia, which are isointense to the CSF space on all 3 sequences (*arrowheads*). There is generalized prominence of convexity sulci, ventricular system, and diffuse periventricular white matter hyperintensity caused by ischemic SVD.

from the silent infarctions results in disruption and degradation of white matter pathways connecting the cortical (particularly frontal) and subcortical structures.[39] It is also presumed that the vascular lesions somehow also increase the development of plaques and tangles.

MICROHEMORRHAGE AND DEMENTIA

Primary, large, intracerebral hemorrhage is a rare cause of dementia. A primary bleed can cause cognitive decline only if they are in a strategic location, such as basal ganglia and thalamus. With the advent of susceptibility-weighted imaging techniques, MR is capable of detecting millimeter-sized paramagnetic blood products including hemosiderin stored in macrophages from the leakage of small blood vessels in the basal ganglia or subcortical white matter. Microbleeds are defined as small, rounded, hypointense foci on T2* or susceptibility-weighted images not attributable to vessels, calcification, or other pathologic conditions like cavernomas. Microbleeds caused by sporadic SVD are often central in distribution involving the basal ganglia, whereas their distribution is mostly cortical-subcortical (lobar) in specific disorders, such as CAA.[40]

CAA

CAA has been defined as an amyloid deposition in the cerebral vessels sufficient to cause vascular dysfunction, mainly microhemorrhages.[41,42] CAA may be either hereditary or sporadic. Sporadic CAA is a common cerebrovascular pathology of the elderly and is caused by the deposition of β-amyloid in the media and adventitia of small- to medium-sized cerebral arteries.[41,42] Age is the strongest risk factor for sporadic occurrence of CAA. The prevalence of CAA on autopsy is around 2% at 50 years of age and increases to 74% to 100% in patients older than 90 years.[43] In *sporadic* CAA, the apolipoprotein E e2 and e4 alleles are risk factors: the latter leads to a higher propensity for β-amyloid 40 to be deposited in vessel walls.[41,42,44] Histopathologically, degenerative vascular changes are mainly seen affecting the capillaries, arterioles, and small- and medium-sized arteries of the cerebral cortex, overlying leptomeninges, and cerebellum. White and deep gray matter vessels are relatively spared. Changes in the vessel include amyloid deposition, fibrous thickening of the vessel wall, fibrinoid necrosis, and leakage of blood through the degenerated vessel wall.

There are also hereditary forms of amyloidosis, the most widely studied is the APP gene on chromosome 21 having specific point mutations.[45] The age of onset of hereditary CAA is almost 3 decades earlier (30–60 years) to the sporadic aging-related CAA (60–80 years).[45,46] In all of these APP-related CAAs, meningocortical arteries are affected by β-amyloid deposits, leading to aneurysmal dilatation or thinning of the vessel wall and to fibrinoid necrosis. Vessels in the deep hemispheric structures and brainstem are relatively spared.

In both types of CAA, patients may present with focal neurologic signs, including spasticity, ataxia, facial paralysis, occasional seizures, and cognitive impairment often leading to dementia. It is mostly the subcortical type of dementia. Stroke, a common feature of sporadic CAA, is slightly less common in the hereditary type of CAA. Rapid decline of cognitive functions is thought to be caused by diffuse white matter changes. Neuroimaging, especially MR with susceptibility-weighted images, plays a vital role in the diagnosis of the CAA. On T2WI, white matter shows diffuse hyperintensities with lacunes caused by ischemia. One of the main findings is the presence of multiple microhemorrhages at the corticomedullary junctions on GRE or susceptibility weighted imaging (SWI) images (**Fig. 14**). There may be superficial siderosis caused by cortical bleeds. Patients may also show large acute or subacute lobar bleeds on CT or MR.

Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant arteriopathy with complete penetrance.[43] The estimated prevalence in Western countries is around 5 cases in 100,000.[47] Clinical symptoms may be seen as early as 10 years of age. Migraines, usually with auras, are the most common symptom. Other clinical features include transient ischemic attacks, recurrent strokes, depression, ataxia, cognitive decline, and dementia. CADASIL is caused by single missense mutations or exon deletions in the Notch3 gene on chromosome 19.[48] The gene encodes a type 1 transmembrane protein (Notch3), which is essential during development and for regulating cellular differentiation. A definitive diagnosis requires skin biopsy and genetic testing. Pathologically, the vessels show severe arteriopathy caused by deposition of the granular osmophilic material in the media of small vessels (diameter 100–400 μm).[49] A loss of vascular smooth muscle cells in the brain leads to wall thickening and fibrosis in small- and
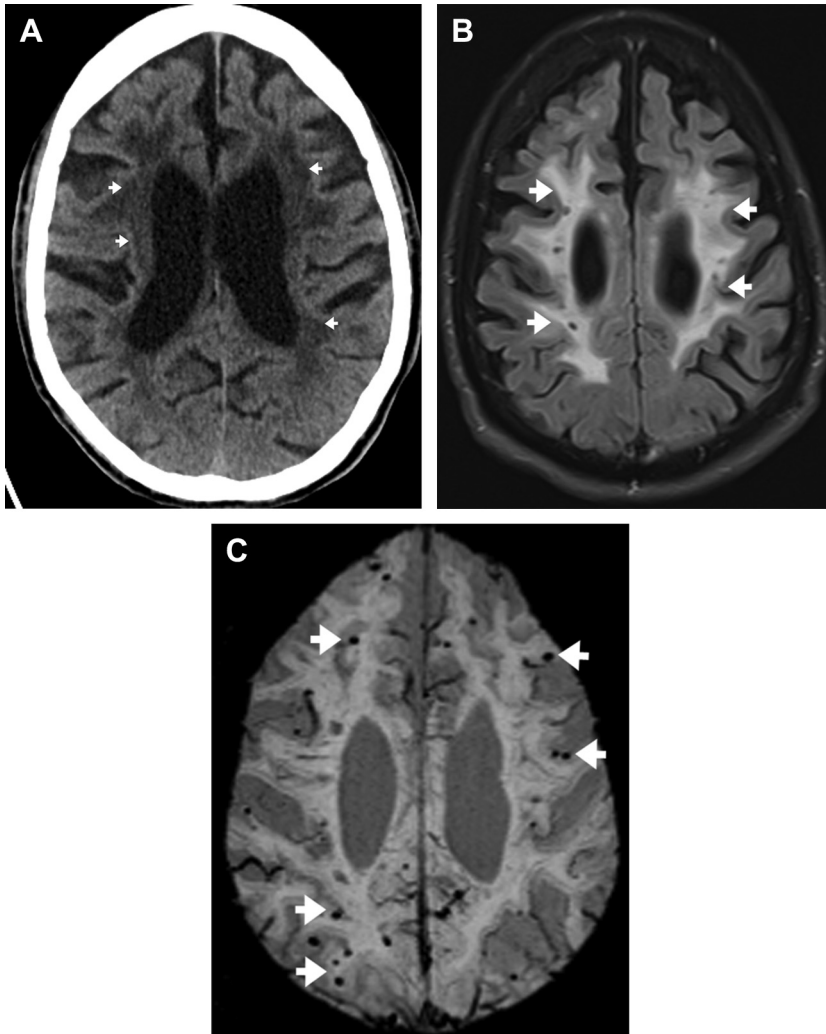
Fig. 14. Cerebral amyloid angiopathy. Axial CT (*A*) image shows generalized prominence of convexity sulci, dilatation of ventricular system, and diffuse hypodensity in the white matter (*arrows*). Axial FLAIR (*B*) MR image shows global cerebral atrophy with diffuse white matter hyperintensity (*arrows*) caused by ischemic SVD. Axial SWI (*C*) MR image shows multiple hypointensities in the cortical and subcortical region (*arrows*), suggestive of microhemorrhages.

medium-sized penetrating arteries. The wall thickening and fibrosis leads to a reduction in both cerebral blood flow and blood volume in the affected white matter with effects on the hemodynamic reserve by decreasing the vasodilatory response. The affected vessels progress to obliteration and/or thrombosis, leading to multiple subcortical infarcts predominantly involving the fronto-temporal white matter and lacunar infarcts, mainly in the basal ganglia.

An MR may show 2 main abnormalities in CADASIL: first, 0.5- to 2.0-cm linear or punctate sharply defined, lacunar infarcts in the periventricular deep white matter, subcortical white matter, external capsule, brainstem, basal ganglia, and thalamus and, second, large, confluent white matter changes predominately in the subcortical regions of the anterior temporal and frontal lobes with involvement of the subcortical U fibers. These changes are often symmetric (**Fig. 15**). Ribbonlike hyperintensities may also be seen in the external capsule, which are characteristic for CADASIL. Temporal white matter and paramedian superior frontal white matter regions and arcuate fiber involvement is the major finding differentiating CADASIL from Binswanger disease. An MR may also show areas of low signal intensity within the deep gray matter nuclei on T2 and GRE images thought to be caused by increased iron deposition, possibly resulting from disturbed axonal iron transport.
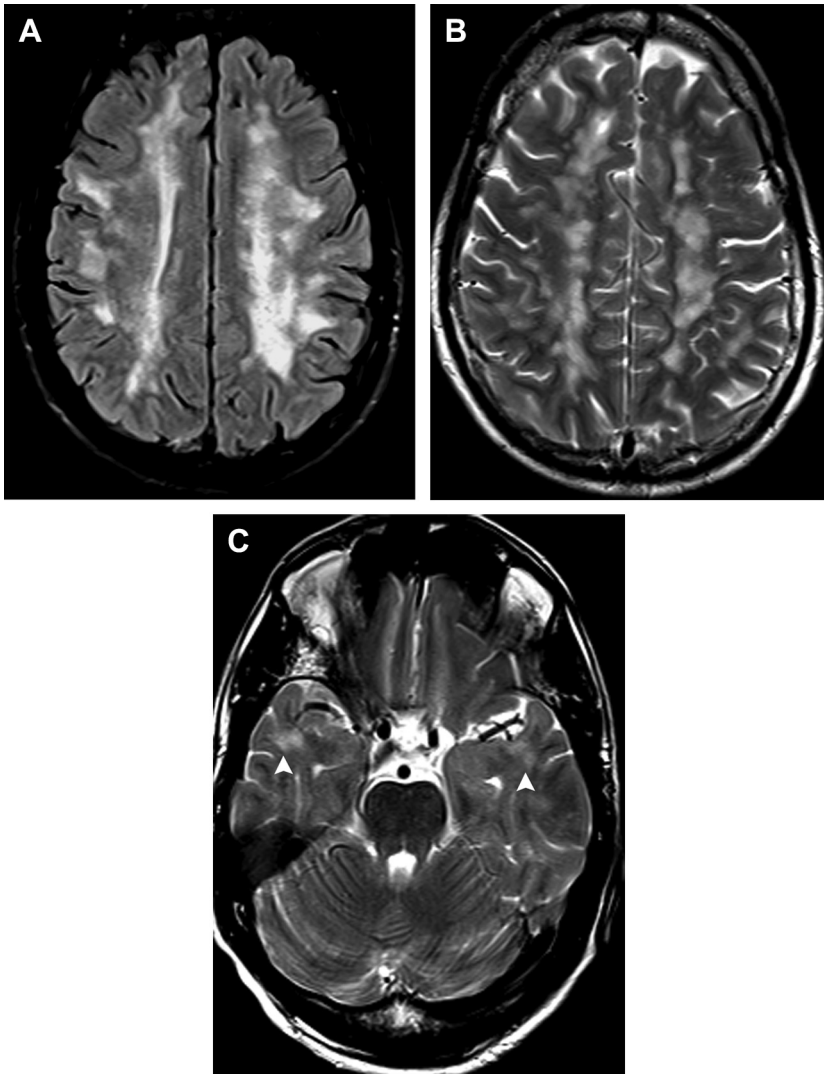
Fig. 15. CADASIL. A 43-year-old male patient with mild cognitive decline. Axial FLAIR (*A*), T2 (*B, C*) MR images reveal extensive white matter abnormalities with characteristic symmetric involvement of the anterior aspect of the temporal lobes (*arrowheads*).

SUMMARY

As people live longer, there is a corresponding increase in neurodegenerative disorders and dementia. More than 24.3 million people are currently estimated to have dementia, and 4.6 million new cases are diagnosed each year. It is predicted that worldwide, a new case of dementia is diagnosed every 7 seconds. When atrophy is seen on imaging in adult patients, it does not necessarily represent AD. Many cases of dementia or cognitive decline could be caused by reversible or preventable disease, such as VaD. This article familiarizes the physician with various types of vascular lesions leading to dementia and cognitive decline and their imaging appearances. Neuroimaging plays an important role in identifying vascular lesions of the brain very early, even before the clinical manifestation of the cognitive decline symptoms and, thus, can help to prevent or delay the symptoms related to the various vascular pathologic conditions.

REFERENCES

1. Rockwood K, Wenzel C, Hachinski V, et al. Prevalence and outcomes of vascular cognitive impairment. Neurology 2000;54:447–51.
2. Erkinjuntti T, Rockwood K. Vascular dementia. Semin Clin Neuropsychiatry 2003;8:37–45.

3. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. Lancet Neurology 2003;2:89–98.

4. Ganguli M. Epidemiology of dementia. In: Abou-Saleh MT, Katona C, Kumar A, editors. Principles and practice of geriatric psychiatry. 3rd edition. Hoboken (NJ): Wiley; 2011. Chapter 38.

5. Bowler JV. Vascular cognitive impairment. J Neurol Neurosurg Psychiatry 2005;76(Suppl V):v35–44.

6. Lobo A, Launer LJ, Fratiglioni L, et al. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;54:S4–9.

7. Hebert R, Brayne C. Epidemiology of vascular dementia. Neuroepidemiology 1995;14:240–57.

8. Kraepelin E. Das senile und präsenile Irresein. In: Psychiatrie: Ein Lehrbuch für Studierende und Ärzte. Leipzig (Germany): Johann Ambrosius Barth; 1910. p. 533–632.

9. Hachinski VC, Lassen NA, Marshall J. Multi infarct dementia. A cause of mental deterioration in the elderly. Lancet 1974;2:207–10.

10. DSM-IV criteria American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. Washington, DC: American Psychiatric Association; 1994.

11. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–60.

12. van Straaten EC, Scheltens P, Knol DL, et al. Operational definitions for the NINDS-AIREN criteria for vascular dementia: an interobserver study. Stroke 2003;34:1907–12.

13. Gorelick PB, Brody J, Cohen D, et al. Risk factors for dementia associated with multiple cerebral infarcts. A case-control analysis in predominantly African-American hospital-based patients. Arch Neurol 1993;50:714–20.

14. Pasquier F, Henon H, Leys D. Risk factors and mechanisms of post-stroke dementia. Rev Neurol (Paris) 1999;155:749–53.

15. Swartz RH, Sahlas DJ, Black SE. Strategic involvement of cholinergic pathways and executive dysfunction: does location of white matter signal hyperintensities matter? J Stroke Cerebrovasc Dis 2003;12:29–36.

16. Erkinjuntti T. Diagnosis and management of vascular cognitive impairment and dementia. J Neural Transm Suppl 2002;(63):91–109.

17. Guermazi A, Miaux Y, Rovira-Cañellas A, et al. Neuroradiological findings in vascular dementia. Neuroradiology 2007;49:1–22.

18. Pohjasvaara T, Mantyla R, Salonen O, et al. How complex interactions of ischemic brain infarcts, white matter lesions, and atrophy relate to post-stroke dementia. Arch Neurol 2000;57:1295–300.

19. Momjian-Mayor I, Baron JC. The pathophysiology of watershed infarction in internal carotid artery: review of cerebral perfusion studies. Stroke 2005; 36:567–77.

20. Bladin CF, Chambers BR. Frequency and pathogenesis of hemodynamic stroke. Stroke 1994;25: 2179–82.

21. Baron JC, Bousser MG, Rey A, et al. Reversal of focal "misery perfusion syndrome" by extra-intracranial arterial bypass in hemodynamic cerebral ischemia: a case study with 150 positron emission tomography. Stroke 1981;12:454–9.

22. Marks MP. Cerebral ischemia and infarction. In: Atlas SW, editor. Magnetic resonance imaging of the brain and spine, vol. 1, 4th edition. Philadelphia: Williams & Wilkins; 2009. p. 772–825.

23. Ferro JM. Hyperacute cognitive stroke syndromes. J Neurol 2001;248:841–9.

24. Desmond DW. Vascular dementia: a construct in evolution. Cerebrovasc Brain Metab Res 1996;8: 296–325.

25. Jellinger KA. The enigma of vascular cognitive disorder and vascular dementia. Acta Neuropathol 2007; 113:349–88.

26. Attems J, Jellinger KA. Hippocampal sclerosis in Alzheimer disease and other dementias. Neurology 2006;66:775.

27. Tomimoto H. Subcortical vascular dementia. Neuroscience Research 2011;71:193–9.

28. Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. Neurology 1995;45:1161–8.

29. Salonen O, Autti T, Raininko R, et al. MRI of the brain in neurologically healthy middle-aged and elderly individuals. Neuroradiology 1997;39:537–45.

30. Bennett DA, Gilley DW, Wilson RS, et al. Clinical diagnosis of Binswanger's disease. J Neurol Neurosurg Psychiatry 1990;53:961–5.

31. Roman GC. New insight into Binswanger disease. Arch Neurol 1999;56:1061–2.

32. Vernooij MW, Smits M. Structural neuroimaging in aging and Alzheimer's disease. Neuroimaging Clin N Am 2012;22(1):33–55.

33. Galluzzi S, Lanni C, Pantoni L, et al. White matter lesions in the elderly: pathophysiological hypothesis on the effect on brain plasticity and reserve. J Neurol Sci 2008;273(1–2):3–9.

34. Ay H, Oliveira-Filho J, Buonanno F, et al. Diffusion-weighted imaging identifies a subset of lacunar infarction associated with embolic source. Stroke 1999;30:2644–50.

35. Vital C, Julien J. Expanding lacunae causing triventricular hydrocephalus. J Neurosurg 2000;93:155–6.

36. Adachi M, Hosoya T, Haku T, et al. Dilated Virchow-Robin spaces: MRI pathological study. Neuroradiology 1998;40:27–31.

37. Vermeer SE, Prins ND, Den Heijer T, et al. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348(13):1215–22.

38. Boon A, Lodder J, Heuts-van Raak L, et al. Silent brain infarcts in 755 consecutive patients with a first-ever supratentorial ischemic stroke. Relationship with index-stroke subtype, vascular risk factors, and mortality. Stroke 1994;25:2384–90.

39. Fein G, Di Sclafani V, Tanabe J, et al. Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. Neurology 2000;55:1626–35.

40. Revesz T, Ghiso J, Lashley T, et al. Cerebral amyloid angiopathies: a pathologic, biochemical, and genetic view. J Neuropathol Exp Neurol 2003;62:885–98.

41. Weller RO, Preston SD. The spectrum of vascular disease in dementia. From ischaemia to amyloid angiopathy. Adv Exp Med Biol 2001;487:111–22.

42. Good CD, Ng VW, Clifton A, et al. Amyloid angiopathy causing widespread miliary haemorrhages within the brain evident on MRI. Neuroradiology 1998;40:308–11.

43. Dichgans M, Mayer M, Uttner DP, et al. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. Ann Neurol 1998;44:731–9.

44. Attems J. Sporadic cerebral amyloid angiopathy: pathology, clinical implications, and possible pathomechanisms. Acta Neuropathol (Berl) 2005;110:345–59.

45. Wattendorff AR, Frangione B, Luyendijk W, et al. Hereditary cerebral haemorrhage with amyloidosis, Dutch type (HCHWA-D): clinicopathological studies. J Neurol Neurosurg Psychiatry 1995;58:699–705.

46. Zhang-Nunes SX, Maat-Schieman ML, van Duinen SG, et al. The cerebral beta-amyloid angiopathies: hereditary and sporadic. Brain Pathol 2006;16:30–9.

47. Kalimo H, Ruchoux MM, Viitanen M, et al. CADASIL: a common form of hereditary arteriopathy causing brain infarcts and dementia. Brain Pathol 2002;12:350–9.

48. Joutel A, Favrole P, Labauge P, et al. Skin biopsy immunostaining with a NOTCH3 monoclonal antibody for CADASIL diagnosis. Lancet 2001;358:2049–51.

49. Mayer M, Straube A, Bruening R, et al. Muscle and skin biopsies are a sensitive diagnostic tool in the diagnosis of CADASIL. J Neurol 1999;246:526–32.