Major or Mild Vascular Neurocognitive Disorder

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21.1 Background

21.1.1 Definition

According to the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [1], those cases that meet the criteria for major or mild neurocognitive disorder (NCD) (formerly dementia), but with suggestion of a link to cerebrovascular pathology, are referred to as "probable" or "possible" major or mild vascular NCD. The "probable" designation is given when at least one of the following criteria is met:

- Clinical criteria are supported by neuroimaging evidence of parenchymal injury attributed to cerebrovascular disease.
- There is a temporal relationship between the neurocognitive syndrome and one or more documented cerebrovascular events.
- Both clinical and genetic evidence of cerebrovascular disease is evident; this is relevant to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

The "possible" designation is used for a suggestion of vascular contribution to NCD without meeting any of the above criteria [1].

The *International Classification of Diseases*, 10th revision (ICD-10), published by the World Health Organization [2] uses "vascular dementia" as the main terminology for this illness, with subtypes including:

- Vascular dementia of acute onset
- Multi-infarct dementia
- Subcortical vascular dementia
- Mixed cortical and subcortical vascular dementia

The terminology of this illness has evolved over time. Early terminology included multi-infarct dementia, which referred to dementia in the context of a diagnosed stroke (single or multiple) [3]. The Hachinski Ischemic Index Score was developed in the mid-1970s to differentiate between Alzheimer disease and multi-infarct dementia; it is composed of 13 features, each assigned 1 or 2 points. This tool has reasonable sensitivity (89%) and specificity (89.3%) to distinguish multi-infarct dementia from Alzheimer disease using a cutoff of 4 or below for Alzheimer dementia and 7 or above for multi-infarct dementia. Using the same cutoff scores, this tool is not as specific when it comes to distinguishing Alzheimer disease from mixed dementia (specificity of 29.4%) or multi-infarct dementia from mixed dementia (specificity of 17.2%) [4]. The scale was modified subsequently reducing the items to five composite or seven single-item scales that fare as well or better than the original index score [5]. Eventually, the term vascular dementia was used to refer to cognitive disorders stemming from a variety of cerebrovascular lesions, including overt strokes involving major vascular distribution, small but strategic strokes, and/or significant subcortical white matter hyperintensities [6]. This was summarized in the diagnostic criteria published by the National Institute of Neurological Disorders and Stroke and Association Internationale Pour La Recherché et L'Enseignement en Neurosciences (NINDS-AIREN) that identifies vascular dementia based on establishing the presence of dementia whereby two or more cognitive domains (including memory) are significantly impaired compared to previous baseline on objective examination, establishing the presence of cerebrovascular disease, and establishing a relationship between the two. This results in the following designations:

- Definite vascular dementia (requires probable vascular dementia confirmed by neuropathology with absence of tangles and plaques beyond normal or other pathology)
- Probable vascular dementia (evidence of NCD, cerebrovascular disease, and relationship between the two)
- Possible vascular dementia (evidence of NCD and cerebrovascular disease but the relationship between the two is not clear)
- Alzheimer disease with cerebrovascular disease (evidence for both Alzheimer disease and cerebrovascular disease)

Other published criteria for vascular NCD are the State of California Alzheimer Disease Diagnostic and Treatment Centers (ADDTC) criteria for probable and possible ischemic vascular dementia [7]. These criteria include cognitive impairment, though not specific to memory impairment of specific domains, and a focus on acute and chronic ischemic cerebrovascular disease (not hemorrhagic). These criteria do not specify associated neurological findings on physical exam, but, instead, require brain imaging finding of relevant cerebrovascular disease for probable ischemic vascular dementia to be diagnosed.

The inter-rater reliability for different criteria, including the DSM-IV (previous version of DSM-5) [8], the Hachinski Ischemic Index Score (original and modified), NINDS-AIREN, and ADDTC, was assessed using 25 standardized case vignettes rated by seven ADDTC centers using an established checklist from the criteria. This study demonstrated significant variability in frequency of the diagnosis of vascular dementia (highest for modified Hachinski Ischemic Index Score or DSM-IV, intermediate for original Hachinski Ischemic Index Score and ADDTC, and lowest for NINDS-AIREN). Inter-ratter reliability was the lowest for ADDTC and highest for the original Hachinski Ischemic Index Score [9]. This study identified the need for prospective clinico-pathological studies to establish better validity for diagnostic criteria.

As the field of NCD moved to detecting earlier stages of dementia such as mild cognitive impairment (MCI), a risk state/prodrome for Alzheimer disease, so did the field of cognitive disorder due to cerebrovascular disease. This led to the proposal of using more inclusive terms, like vascular cognitive impairment, as a preferred terminology, which is more inclusive to the full range of cognitive difficulties stemming from a wide range of cerebrovascular lesions [10]. The term "dementia" was somewhat problematic from

the beginning, as it was associated with neurodegenerative illnesses such as Alzheimer disease, while "pure" vascular NCD can range in the level of impairment from single cognitive domain impairment with otherwise relatively preserved function (vascular MCI) to impairment in multiple cognitive domains with impaired daily function reaching the threshold of "dementia" or major NCD. In 2011, a consensus scientific paper was published by the American Heart Association and American Stroke Association that covered the contribution of cerebrovascular disease to cognitive impairment and dementia [11]. In this paper it was proposed that vascular cognitive impairment refers to the range of cognitive changes from MCI to full spectrum dementia (i.e., major NCD) of vascular origin. The diagnosis would then range from vascular MCI to vascular dementia. Vascular MCI is diagnosed when there is an objective decline from baseline of at least one cognitive domain with normal or only mildly affected instrumental activities of daily living independent from motor or sensory deficit. Vascular dementia is diagnosed when there is an objective decline from baseline of two or more cognitive domains (amnesia is necessary to make the diagnosis) resulting in significant impairment in daily functioning, independent from deficits caused by motor or sensory deficits. Like DSM-5, a designation of "probable" versus "possible" vascular MCI or vascular dementia depends on the certainty of the association between vascular pathology and the cognitive impairment. Table 21.1 summarizes the clinical criteria for vascular NCD in the DSM-5 [1], ICD-10 [2], and criteria proposed in the American Heart Association/American Stroke Association (AHA/ASA) consensus scientific paper [11]. Other criteria can be accessed from the references listed (see Table 21.1 [1, 2, 6, 11]).

Teaching Point

Published clinical criteria for vascular NCD require first establishing the presence of a NCD, specify if it is major (significant impact on function) or mild (minimum impact on function), and establish the link between vascular factors and the NCD (this can be "definite" as determined at autopsy or "probable" or "possible" depending on the strength of the association). Coding for behavioral symptoms is added similar to other NCDs.

21.1.2 Epidemiology

It is difficult to estimate the prevalence and incidence of NCDs due to cerebrovascular disease because of the overlap with Alzheimer disease and the differences in the threshold for detection of cerebrovascular lesions depending on the clinical and neuroimaging tools used. There is a range of disorders that span from "pure" Alzheimer disease, mixed Alzheimer and vascular NCD, and "pure" vascular NCD [12]. In clinical samples, vascular NCD is the second most common case of "dementia" [13]. Age-adjusted rate of 14.6/1000 per person-year for vascular NCD compares to 19.2/1000 per person-year for Alzheimer disease [14].

About two thirds of stroke survivors suffer some degree of cognitive impairment [15], and one third will have frank dementia (or major NCD) [16–18]. Also, there is a significant overlap between vascular and neurodegenerative neuropathology in autopsy studies [19–24]. Despite significant contribution of vascular disease to cognitive impairment, stroke scales do not assess cognitive function, with the exception of the Toronto Stroke Scale, which is not commonly used in clinical trials.

This has resulted in difficulty in getting better understanding of the true epidemiology of vascular NCDs. To counter some of these challenges, a joint workshop of the NINDS and Canadian Stroke Network was assembled from experts in the field of vascular cognitive impairment. A paper was published by Hachinski et al. in 2006 which summarized this important effort to harmonize the standards for screening and diagnosis of vascular cognitive impairment, which may help generate better epidemiological data [25].

Teaching Point

There is significant overlap between Alzheimer disease and vascular NCD; on one extreme there is pure Alzheimer's disease and the other extreme there is pure vascular NCD, while mixed cases are in between, where both pathologies are present. Epidemiological data are affected by this overlap making it difficult to establish accurate prevalence data for vascular NCD. Better definition and diagnostic tools may improve this.

21.1.3 Etiology

It is assumed that the underlying etiology of vascular NCD is related to vascular lesion(s) directly resulting in cognitive impairment by disrupting cognitive brain networks. On the other hand, this relationship is complex because of the overlap and coexistence of vascular and neurodegenerative processes in NCDs. In this section we will outline some of the factors that have been associated with a higher risk for cerebrovascular changes and associated cognitive impairment, underlying neuropathological features, and the possible underlying mechanisms involved.

Risk Factors

Several risk factors have been investigated in terms of association with cognitive impairment. In general, these associations are difficult to study given the variety of confounds that affect the interpretation of positive and negative results. Some of these factors are non-modifiable:

- *Demographics:* There is an exponential increase in risk of vascular NCD with age that follows the stroke risk. Some ethnic groups are at a higher risk of developing major vascular NCD ((also referred to as vascular dementia) after stroke than others (e.g., black compared to white

Table 21.1 Summary of main clinical criteria for vascular neurocognitive disorders [1, 2, 6, 11]

Source	Designation	Criteria
DSM-5 [1]	Probable or possible: Major NCD due to VD Mild NCD due to VD Code: With/without behavioral disturbance Specify: Mild, moderate, or severe	Meet criteria for major or mild NCD At least one of the following for probable: Neuroimaging evidence of VD Temporal relationship between VD and NCD Both clinical and genetic evidence of VD (e.g., CADASIL)
ICD-10 [2]	Vascular dementia of acute onset	Usually develops rapidly after a succession of strokes from cerebrovascular thrombosis, embolism, or hemorrhage. In rare cases, a single large infarction may be the cause
	Multi-infarct dementia	Gradual in onset, following a number of transient ischemic episodes, which produce an accumulation of infarcts in the cerebral parenchyma. Predominantly cortical dementia
	Subcortical vascular dementia	Includes cases with a history of hypertension and foci of ischemic destruction in the deep white matter of the cerebral hemispheres. The cerebral cortex is usually preserved, and this contrasts with the clinical picture, which may closely resemble that of dementia of Alzheimer disease
	Mixed cortical/subcortical, other VaD, and unspecified	Other forms of vascular cognitive disorders
AHA/ASA scientific consensus paper [11]	VCI	Inclusive of the full spectrum of cognitive changes attributed to CVD. It cannot be used for those with active drug/alcohol abuse/dependency (3 months substance-free required). It cannot be used for those with delirium
	Probable VaD	Criteria for dementia are met: Objective decline from baseline of two or more cognitive domains Testing should include executive, attention, memory, language, and visuospatial functions, but amnesia is not necessary for the diagnosis Significant functional impairment independent of motor/sensory deficit There is clear temporal relationship between CVD and onset of CI or clear relationship in the severity and pattern of CI and the presence of diffuse, subcortical CVD
	Possible VaD	Criteria of dementia are met as per above and imaging findings of CVD but: There is insufficient information to confirm the relationship between dementia and CVD Difficulty testing due to severe aphasia (can be diagnosed with other evidence) There is evidence to suggest neurodegenerative process in addition to CVD
	Probable or possible VaMCI	Evidence of objective deficit in at least one cognitive domain (listed above) with IADLs normal or only mildly impaired independent of motor/sensory deficit Evidence of CVD Probable and possible designation is based on establishing the relationship between CVD and CI similar to VaD
	Unstable VaMCI	Those designated as VaMCI that revert to normal
NINDS-AIREN [6]	Probable, possible, or definite VaD	Probable VaD requires all of the following: Evidence of dementia (impairment of two or more cognitive domains including memory from baseline affecting function) not due to other causes Clinical and imaging evidence of CVD Evidence of a relationship between the above two as inferred by: Temporal relationship (within 3 month) Clinical features (abrupt cognitive deterioration, fluctuating or stepwise course) Clinical features consistent with probable VaD include: Early gait changes not explained on other basis Unsteadiness, unexplained falls Urinary symptoms not explained on other basis Pseudobulbar palsy Personality changes, abulia, depression, emotional incontinence, and other subcortical features like psychomotor retardation and executive dysfunction Definite VaD: requires probable VaD confirmed by neuropathology with absence of tangles and plaques beyond normal or other pathology Possible VaD: when criteria for probable VaD are not met despite meeting criteria for dementia and suggestion of CVD or when there are course features suggestive of other etiology AD with CVD is reserved for those with possible AD plus clinical or imaging evidence of relevant CVD

AD Alzheimer disease, *AHA/ASA* American Heart Association/American Stroke Association, *CADASIL* cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, *CI* cognitive impairment, *CVD* cerebrovascular disease, *DSM Diagnostic and Statistical Manual of Mental Disorders*, *NCD* neurocognitive disorder, *VaD* vascular dementia, *VaMCI* vascular mild cognitive impairment, *VD* vascular disease

and Hispanic Americans). Differences in risk between females and males have not been confirmed.
- *Genetics:* CADASIL that is causative of vascular NCD is discussed below. Other genetic markers are more along the line of susceptibility genes. One such gene is apolipoprotein E4, a risk gene for Alzheimer disease but which seems to increase risk for vascular NCD as well. The relationship is complex due to the overlap in diagnosis and comorbidity between the two illnesses.
- *Education:* Education is difficult to separate from sociodemographic factors and difficult to modify as it mainly refers to early education. Cognitive rehabilitation has limited evidence in vascular NCD at this time.
- *Diet:* Several nutrients have been considered including antioxidants (vitamin E, vitamin C, beta-carotene), vitamin D, as well as vitamin B_6 and B_{12}, which are both part of the homocysteine pathway; high homocysteine results in cerebrovascular disease. The Mediterranean diet is reasonable as an early prevention strategy. All these factors have suggestive rather than confirmed evidence.
- *Physical activity:* This may enhance cognitive and cerebrovascular well-being.
- *Alcohol intake:* Moderate intake is advised that might be protective.
- *Smoking:* This increases risk for cerebrovascular disease and therefore increases risk for vascular NCD.
- *Obesity:* This has an increased risk for vascular NCD.

Details around modifiability and recommendations regarding risk factors are available in the treatment section of this chapter.

Teaching Point

Risk factors for vascular NCD include non-modifiable (demographics, ethnicity, genetics) and potentially modifiable factors (lifestyle, physiological and concomitant vascular diseases). The section on treatment will detail recommendations regarding modification of risk factors.

Neuropathology Lesions

There are several neuropathological lesions identified in vascular NCD. Below we briefly summarize the most clearly substantiated causative lesions. In the subsequent section we will discuss some of the known and proposed mechanisms underlying these neuropathological lesions. This section is based on a review of a few key publications that the reader is referred to for more details [11, 25, 26].

A. Cerebral infarcts. These are the most common lesions associated with vascular neurocognitive impairment. These usually refer to discrete lesions of brain tissue loss that can be "macroscopic" or "microscopic." The designation of "macro" or "micro" infarct is somewhat arbitrary. Some authors suggested a cutoff of 4 millimeters (lesion diameter) [27], while others used 2 millimeters [28]. The National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) vascular cognitive impairment harmonization standards suggest reserving microinfarcts to lesions that are not visible to the naked eye, but detected on histological examination [25].
- *Macroscopic infarcts:* In general, the larger the volume and number of these lesions and the more "strategic" the location they affect, the more likely that they will contribute to cognitive impairment. But, again, the correlation between these variables and cognitive impairment is weak and inconsistent. Some strategic locations that have been reported include the thalamus, basal ganglia, and angular gyrus, but several other cortical and subcortical areas have been suggested as well. Multi-infarct dementia is usually caused by atherosclerosis and thrombosis affecting cranial blood vessels, but can also be due to emboli from atrial fibrillation and other distant sources [29].
- *Microscopic infarcts:* These tend to be even more prevalent than macroscopic infarcts, and it was suggested that they are more likely to cause vascular NCD [30].

B. Non-necrotic white matter hyperintensities. This refers to white matter lesions that do not involve microinfarcts but rather other changes in the integrity of white matter. These lesions can be focal, patchy, or confluent and are common in the periventricular area (periventricular hyperintensities). They are usually attributed to partial ischemia [31, 32], but they do have pathological features such as myelin membrane changes (pallor), astrocytosis (change in morphology, ballooning), decline in oligodendrocytes, and clasmatodendrosis (loss of astrocyte processes) [33] in addition to spongiosis [34] that suggests other mechanisms [26].

C. Microhemorrhages. This refers to hemorrhages that typically happen spontaneously in cortical or cortical-subcortical (lobar) areas. They are caused by several factors, but apart from direct trauma and excess anticoagulation, they all involve a structural defect in arterioles and capillaries. Structural abnormalities in vessel walls can be the result of inborn error in vascular genesis, aging, hypertension, and atherosclerosis but can also be due to abnormal protein accumulation such as cerebral amyloid angiopathy, which involves infiltration of cerebral arterioles and capillaries with amyloid-beta peptide, which result in structural deficits in vessel walls and several lesions such as microaneurysms, perivascular leakage, and fibrinoid necrosis [35–37]. This pathology can happen sporadically in the population (10–30%) but more commonly coexists in brains with Alzheimer disease pathology [38], although it has also been independently associated with cognitive changes in old age [39].

The basic mechanism underlying cerebrovascular changes is complex. Full discussion of these mechanisms is beyond the scope of this chapter. Below is a brief discussion of some of the key mechanisms being investigated in the field of vascular NCD:
- Arteriosclerosis/lipohyalinosis: This refers to stiffening of arteries that commonly happens with age and involves loss of elastin and an increase in collagen fibers in the arterial wall [40]. This can be examined noninvasively by

measuring carotid-femoral pulse wave velocity [41] and, in addition to aging, is associated with hypertension [42] and structural and genetic factors [43]. Arterial stiffening has been associated with cognitive decline with and without major NCD in old age [44–48]. Thickness of the arteries negatively correlates with cognitive performance level [49].

- Atherosclerosis: Artery intima-media thickening due to atheroma formation is common with increased age and can be measured by Doppler studies in arteries like the carotid artery. This process can affect any artery, but carotid and cerebral arteries are particularly relevant in vascular neurocognitive impairment. There is an association between atherosclerosis and cognitive impairment in old age, the mechanism of which is multifactorial but likely involves thrombosis of large arteries and secondary hypoxia, emboli from ruptured atheroma, oxidative stress, inflammatory response, dysregulation of blood pressure control, and change in blood-brain barrier regulation. All of these factors are likely in play in other pathological changes related to vascular neurocognitive impairment.
- Neurovascular unit regulation: This mechanism assures consistency in cerebral blood flow despite variation in systemic blood pressure [50], and there is evidence of dysfunction in this mechanism in vascular and Alzheimer-related NCDs and disruption in the integrity of the blood-brain barrier [51–55]. Neurovascular unit dysfunction can be the result of structural changes affecting large and small cerebral vessels due to vascular risk factors and aging.
- Partial ischemia: As a consequence of several structural changes outlined above in large and small vessels, partial ischemia can result in local hypoxia in vulnerable areas such as the periventricular white matter and results in a cascade of neuroinflammatory and oxidative stress responses [34].
- Role of inflammation: Another possible aspect of vascular NCD pathophysiology is the role of inflammation [56]. Inflammatory mediators potentially contribute to further neuronal dysfunction and eventually result in cellular death.
- Genetic factors: Genetic factors have also been linked to vascular NCD. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a condition of heritable small-vessel disease caused by mutations in NOTCH3 gene, which is normally expressed in vascular smooth muscle cells and pericytes (including those of the cerebral vasculature). The gene encodes a cell-surface receptor which has a role in arterial development. It appears to be involved in directing smooth muscle cell proliferation and differentiation. About 95% of patients with the CADASIL condition have missense mutations of NOTCH3 gene (which is linked to cysteine metabolism), but the pathogenic mechanism is still unknown [57].
- Hyperhomocysteinemia: Homocysteine is a nonessential amino acid that contains sulfur. Vitamin B_{12}, B_6, and folic acid are cofactors involved in the formation and turnover of homocysteine, which is why hyperhomocysteinemia reflects deficiencies in these nutrients. Homocysteine is a product of methionine metabolism and can be remethylated to methionine with B_{12} as a cofactor or transsulfurated to cystathionine and then to cysteine, which then leads to the production of glutathione, an important antioxidant. The conversion to glutathione through the intermediates cystathionine and cysteine uses B_6 as a cofactor and is clearly delineated in the liver but remains to be confirmed in the brain. There is evidence of neurotoxicity and vasculotoxicity with high level of homocysteine [58]; the association of homocysteine to cognitive disorders is not specific to vascular cognitive impairment but rather affects the brain through a mechanism related to oxidative stress and glutamate-mediated toxicity [59].
- Choline acetyltransferase activity: There has been a link to choline acetyltransferase activity, which is reduced in patients with vascular NCD [60]. Recent studies have shown that loss of cholinergic function is greater if vascular NCD coexists with Alzheimer disease [61].

There are several challenges when it comes to confirming the contribution for cerebrovascular lesions to cognitive impairment:

- These lesions are common in older adults with and without cognitive disorders occurring in a third to one half of this population [62–64] and even higher if microscopic infarcts are included [20].
- They tend to vary in volume and location, and there are no specific neuropathological criteria to help confirm a diagnosis of vascular NCD.
- They are common in neurodegenerative illnesses like Alzheimer disease, likely interact with underlying Alzheimer pathology [63, 65], and have an additive negative effect [66–68].

Teaching Point

Several pathological lesions have been identified in vascular NCD including cerebral infarcts (macroscopic and microscopic), white matter lesions, and microhemorrhages. These lesions stem from different pathological processes including arterial stiffening, atherosclerosis, partial ischemia, neurovascular unit impairment, and blood-brain barrier abnormalities. Causes of these processes come from multiple sources including aging, genetics, physiological factors, metabolic factors, oxidative stress injury, and inflammatory factors.

21.1.4 Clinical Description

Vascular NCD symptoms vary, depending on brain regions and networks affected. Symptoms often overlap with those of other NCDs, especially Alzheimer disease, and can vary depending on the subtype of vascular NCD [69]. Clinical cri-

teria described previously include features that increase the likelihood of vascular NCD (possible or probable) as the clinical designation used after certain criteria are met. Although a cognitive concern by the patient or family/caregiver is usually the main reason for assessment, it is important for clinicians to identify those at risk for vascular NCD. This may help in prevention of further cognitive, functional, and behavioral changes by controlling vascular risk factors and lifestyle modification.

The presence of significant vascular risk factors and history of clinical stroke or stroke-like event, like transient ischemic attacks temporarily affecting aspects of neurological function, should raise suspicion of vascular NCD. Sudden onset, stepwise worsening, although not always present, would also raise suspicion of vascular contribution to the cognitive presentation. Quality of cognitive and behavioral symptoms can be helpful as well. Below we will outline key components of the diagnostic evaluation for vascular NCD and key features that the clinician should look for.

21.1.5 Diagnostic Evaluation

The clinical diagnosis is made based on diagnostic criteria in DSM-5 for major or mild NCD plus specific criteria for vascular NCD. The ICD-10 criteria are used in many jurisdictions especially for coding purposes, and therefore it is advisable of the clinician to be familiar with them.

The NINDS-AIREN criteria or the proposed AHA/ASA criteria described above are likely to be used in specialized memory clinics and in research settings, but clinicians should be familiar with these criteria given their higher specificity. This set of criteria is based mainly on three core features [6, 11, 70]:

1. Acute onset of NCD
2. Neuroimaging of cerebrovascular lesions
3. Evidence of a relation between stroke and cognitive loss

Diagnostic evaluation aims to verify and rule in and out criteria to support or dispute the diagnosis of vascular NCD and consider alternative diagnoses. Core elements of the workup for vascular NCD typically include several domains, which will be described below.

Clinical History

Like other NCDs, it is not usually sufficient to obtain history solely from the patient alone due to cognitive impairment and limited insight in some cases. Therefore, history from a reliable informant who interacts with the patient frequently is essential.

Elements from the clinical history that need to be elicited and verified that suggest vascular neurocognitive impairment include:

- Cognitive change from baseline with or without major impact on function (to establish the presence of major or mild NCD).
- The presence of vascular risk factors especially if there is indication of poor control (e.g., uncontrolled high blood pressure, untreated atrial fibrillation).
- History of possible or confirmed cerebrovascular events (stroke or stroke-like event). This could be recent or remote, single or multiple.
- Temporal relationship between the cerebrovascular event and cognitive change. This requires careful inquiry around the recovery from strokes and residual symptoms.
- The course of change in cognitive function might be suggestive of vascular origin especially when it follows a stepwise course with episodes of acute decline and periods of plateau as related to the cerebrovascular events. On the other hand, it is important to note that subcortical white matter hyperintensity-related vascular NCD can have a course that is difficult to distinguish from that of Alzheimer disease. A clinical cohort study of 970 patients comparing baseline and course characteristics among pathologically confirmed pure vascular NCD (n = 141), pure Alzheimer NCD (n = 663), and mixed vascular and Alzheimer NCD (n = 166) reported better baseline cognitive function and slower rate of decline in the pure vascular group followed by the mixed group and the fastest for the pure Alzheimer group [71].
- The pattern of cognitive impairment tends to be more patchy and involves more prominent executive dysfunction (discussed in cognitive and functional assessment section below).
- There are often prominent features of mood, anxiety, and apathy. This is usually the result of disruption of frontal-limbic networks especially due to subcortical vascular lesions but can be a feature of other NCDs (see ► section Neuropsychiatric Symptoms of Vascular Neurocognitive Disorder for discussion).
- There are frequently features of gait impairment including unsteadiness, fear of falling, and actual falls. This is usually the result of disruption of frontal-subcortical gait regulation networks, although the mechanism might involve other elements (see ► section Gait Issues in Vascular Neurocognitive Disorder for discussion).

The above elements are suggestive of vascular neurocognitive impairment, although they are not very specific as they can be present in other forms of NCDs like in Alzheimer disease.

Neuropsychiatric Symptoms of Vascular Neurocognitive Disorder

Neuropsychiatric symptoms of NCDs are covered in more details in another chapter of this text. (See ► Chap. 22). Here we highlight some of the clinical findings relevant to neuropsychiatric illness in the context of vascular NCDs. Depressive disorders [72] and apathy [73] have been reported as being particularly common in vascular NCD. In a study comparing neuropsychiatric symptoms in vascular versus Alzheimer-related NCDs, anxiety and depression were found to be higher in vascular NCD [74]. Euphoria, in contrast, has been shown to be the least common symptom [73], whereas other studies demonstrated that sleep disturbances and depressive disor-

ders are very common [75]. Sleep disturbance seems to be particularly common in cortical vascular NCD [76]. Apathy is known to be common in subcortical ischemic vascular disease because of the occurrence of white matter lesions and/or lacunar infarcts in the basal ganglia and thalami, which lead to interruption of the cortico-subcortical circuit. Patients with multi-infarct dementia tend to have wider range of neuropsychiatric symptoms including hallucinations, agitation, aggression, irritability, and/or euphoria [73].

These symptoms cause significant distress to patients and their families and caregivers, so appropriate identification and management of these problems is in the core of managing patients with vascular NCD. The NINDS-Canadian Stroke Council vascular cognitive impairment harmonization standards [25] recommended the use of the Neuropsychiatric Inventory Questionnaire version (NPI-Q) as a screening tool [77]. Several tools have been used to detect depression related to cerebrovascular disorders, e.g., the Center for Epidemiological Studies Depression Scale (CES-D) [78]. The Geriatric Depression Scale (GDS); the Zung Self-Rating Depression Scale (SDS), both self-rated; and the Comprehensive Psychopathological Rating Scale-Depression (CPRS) were shown to have good sensitivity and predictive value in poststroke depression [79].

Gait Issues in Vascular Neurocognitive Disorder

Patients with vascular NCD (pure or mixed with Alzheimer disease) have more gait impairment compared to those with pure Alzheimer disease. Changes in gait due to motor impairment as a result of strokes (e.g., in multi-infarct dementia) are usually obvious. On the other hand, there are a set of changes in gait resulting from disruption of frontal-subcortical networks that require further clarification. Clinically, gait changes can be confused with Parkinson disease features. Reports of slowing down, shuffling gait, smaller strides, falls, or fear of falling are elements that can be elicited from clinical history. It has been long known that subcortical white matter changes can cause "parkinsonism" [80] especially in illnesses like Binswanger disease, whereby extensive periventricular white matter abnormality is found and seen on brain imaging as hyperintensities. This illness has been linked to chronic hypertension and is associated with cognitive, functional, behavioral, and gait changes simulating Parkinson disease [81]. More studies have confirmed this association and described it as "parkinsonism" [82, 83] or apraxia of gait [84]. Using perfusion scanning such as single photon emission computed tomography (SPECT), a study showed that impairment in higher processing of gait in 12 older patients with significant cerebrovascular changes (multi-infarct, single infarct, and leukoaraiosis) with gait apraxia was associated with lower activation in medial frontal gyrus (including supplementary motor area) and anterior lobes of the cerebellum bilaterally, supporting the role of higher cortical centers in processing gait control information [85].

Functional Changes in Vascular Neurocognitive Disorder

Functional inquiry is part of the clinical history and is usually obtained from the patient and from a reliable informant. This is covered in more detail in other chapters of this text. (See ▶ Chap. 18). Using questionnaires to assess basic and instrumental activities of daily living is very helpful especially when obtained from the patient and an informant to counter some of the confounds related to the patient's cognitive and insight deficits. There are several useful validated tools to use in the clinic that were found to be helpful in supporting the diagnosis of major NCDs (dementia) including the Index for Activities of Daily Living, the Modified Blessed Dementia Scale, the Instrumental Activities of Daily Living, and the Functional Assessment Questionnaire [86]. The Functional Assessment Questionnaire was studied specifically in vascular NCD and found to be useful [87].

Cognitive Profile

The cognitive profile of patients with vascular NCD includes a wide range of cognitive deficits, but typically shows impairment in executive functioning (including elements of slowed processing speed), difficulty with working memory (e.g., holding and manipulating information online), difficulty in shifting attention, and deficits in multitasking. Therefore, when testing cognitive function in this context, we need to use tools that are broad enough, but also need to be sensitive to deficits in executive functioning. The NINDS-Canadian Stroke Council vascular cognitive impairment harmonization standards recommend comprehensive cognitive profiling to cover executive (frontal-subcortical) function and to use operational definitions for cognitive decline (e.g., 1–1.5 standard deviation below norm for vascular MCI and two or more standard deviations for "vascular dementia") [25]. This group's neuropsychology section recommended three levels of testing, 60-minute, 30-minute, and 5-minute protocols taking into account several factors including psychometric properties, feasibility for the clinical setting, domain specificity, repeatability (to avoid practice effect), cross-cultural generalizability, ceiling and flooring effect of the tests, and previous use in this population. The 60-minute protocol is comprehensive, usually applied in subspecialty and research clinics, and includes coverage of executive/activation, visuospatial, language/lexical retrieval, memory/learning, neuropsychiatric/depressive symptoms, and premorbid status. Tests selected are standardized and validated and testing will result in giving patient performance statistical reference compared to age and education normative data. The 30-minute protocol is an abbreviation of the 60-minute protocol including semantic and phonemic fluency, digit symbol-coding, and the revised Hopkins Verbal Learning Test in addition to CES-D and NPI-Q. Supplemental tests include trail making test, parts A and B, and the Mini Mental State Examination (MMSE). For the 5-minute protocol, the decision was to not use the MMSE due to its limited testing of executive function and limited sensitivity of the 3-item delayed recall for memory impairment. Instead,

a subset of the Montreal Cognitive Assessment (MoCA) test [88] was proposed including 5-word immediate and delayed recall, letter "F" 1-minute phonemic fluency test, and 6-item orientation task. Most clinics would do the full MoCA test or supplement with other tests like the MMSE. (See ► Chap. 4).

The quality of memory impairment in vascular NCD is usually different from that in Alzheimer disease. While difficulty in episodic memory *encoding* is the core early deficit (related to early hippocampal complex involvement) [89] in Alzheimer disease resulting in anterograde episodic memory impairment [90], deficits in memory *retrieval* are usually more prominent in vascular NCD resulting in consistently better recognition memory compared to Alzheimer disease [76].

Mental Status and Physical Examination

Mental status examination includes the following elements:

- General appearance of the patient: elements of executive functioning and ability to care for him or herself, signs of cardiovascular impairment.
- Attitude: cooperativeness.
- Language/speech: from direct examination, the examiner should attend to aspects of speech and language, including, but not limited to, comprehension, fluency, grammar, paraphasic errors (substituting one word for another that could be conceptually or phonetically related), repetition, reading, and writing.
- Movements: gait changes observed as the patient walks to the exam room, any evidence of abnormal movements, as psychomotor slowness is common in vascular NCD.
- Mood: as reported by patient such as irritability, depression, and anxiety.
- Affect: emotional status as observed during the interview; apathy (with flattening of affect) can be seen in these cases quite commonly.
- Cognitive function: from the interview and from testing (as previously described).
- Thoughts: assessment of thought content for any delusional material like paranoia or mood-congruent delusions related to depression. Thought process is also important and can show slowness but usually no disorganization such as is seen in primary psychotic disorder.
- Perception: any hallucinations in any modality. These symptoms are usually suggestive of other processes like delirium or Lewy body disease but can also occur in vascular NCD.
- Suicidal and homicidal ideations: particularly in the context of depression or psychosis.
- Insight: usually relatively preserved regarding cognitive deficits as compared to other illnesses like Alzheimer disease or frontotemporal lobar degeneration, but issues like neglect can result in impaired insight into having deficits (anosognosia).
- Judgment: impairment in judgment is not uncommon given the impairment in executive function, and this affects safety and management of vascular risk factors.
- General physical examination is important because of the need to assess general health, to look for other causes of neurocognitive changes, and to identify and assess vascular risk factors such as high blood pressure and evidence of complications from chronic and poorly controlled diabetes mellitus and high lipids.
- Careful attention to gross and subtle neurological findings is essential; e.g., focal neurological signs due to underlying stroke and features related to frontal-subcortical disconnection syndromes can be seen.

Laboratory Examination

The investigation of any NCD requires ruling out reversible factors. Laboratory tests should be performed including a complete blood count, chemistry, thyroid function, vitamin B_{12} level, and urinalysis, in addition to other tests when there is suspicion of specific medical processes like infection (e.g., serology for syphilis and human immunodeficiency virus), autoimmune disease (e.g., systemic lupus erythematosus), and neoplasm (e.g., paraneoplastic syndrome). When it comes to vascular NCD, brain imaging holds the most value in the diagnostic process as it identifies cerebrovascular lesions that likely contribute to the clinical presentation. Neuroimaging modalities are discussed in a separate chapter in this volume. (See ► Chap. 3). In the following section we will highlight the role of clinical neuroimaging tools in identifying cerebrovascular lesions.

Structural Brain Imaging

Given the wide range of cerebrovascular pathology that can be identified by structural brain imaging, it is important to interpret imaging findings in the clinical context and take into account their nature, severity, and location.

Computed tomography (CT) and magnetic resonance imaging (MRI) findings that are suggestive of vascular neurocognitive impairment include:

- Multiple and/or large infarcts involving the dominant hemisphere or bilaterally
- Single or few infarcts involving strategic areas involved in cognitive processing
- Multiple lacunar strokes
- Periventricular white matter lesions (also known as leukoaraiosis) extending into the deep white matter

Patients with vascular MCI (which can be a prodromal stage for subcortical vascular neurocognitive impairment) have MRI features that differ from patients with amnestic MCI (which can be a prodromal stage for Alzheimer disease). The former tends to show more extensive white matter abnormality, lacunar infarcts, and leukoaraiosis, with minimal hippocampal and cortical atrophies [91].

When considering the significance of cerebrovascular lesions identified by structural imaging in relation to neurocognitive impairment, one needs to take into account the size, count, location, and distribution of the lesions. Despite neuroimaging-neuropathological validation studies, it is still not possible to ascertain the pathological nature of lesions seen on routine structural imaging. The following are neuroimaging findings that suggest different subtypes of vascular NCD.

A. Multiple infarcts. Multiple infarcts found on brain imaging that are likely to disrupt cognitive networks can support vascular contribution to neurocognitive impairment and are consistent with the definition of multi-infarct dementia coined by Hachinski et al. in the 1970s [3].

B. Lacunar infarcts. The number and location of lacunae required to make the diagnosis of vascular NCD is nonspecific, but it is generally accepted that multiple lacunae and the ones that involve strategic cognitive structures are more likely to contribute to vascular NCD. The appearance of a lacuna on brain imaging can be due to lacunar infarct, lacunar hemorrhages, or dilated perivascular space, the latter being a benign finding [91]. Lacunar infarcts generally refer to the occlusion of small penetrating vessels and are of two main pathological types: (i) lipohyalinosis (which mainly results from chronic hypertension) and (ii) microatheromatosis (which usually results in a single clinically significant lacuna) [92]. Subtyping of lacunae to these two entities was supported by a large study in which lacunae associated with leukoaraiosis, which was thought to share the same pathology as lipohyalinosis subtype of lacunae, had stronger association with hypertension and was found to have higher mortality and worse overall outcome (higher re-stroke and lower functional recovery) [93]. Lacunae are seen on T1-weighted MRI but are best visualized on proton density/T2-weighted MRI or fluid-attenuated inversion recovery (FLAIR) MRI scan. It appears as a small hypointense area surrounded by a rim of hyperintensity [94]. What is termed "silent" lacunae (without overt neurological findings on exam) measuring 3 or more millimeters in diameter are 10–20 times higher in prevalence than overt strokes in older adults, occurring in about 25% in those 60 years and older [95]. These lesions contribute to a higher risk of developing a major NCD (dementia) [96].

C. White matter hyperintensities (leukoaraiosis). The other type of cerebrovascular lesion that can be seen on structural brain imaging is white matter hyperintensity (or leukoaraiosis) [97], which can be focal or multiple and can become confluent to involve much or all of the white matter [98]. Studies have shown that white matter hyperintensities are common in old age [95]. It is difficult to estimate the exact amount of these lesions to be considered clinically significant [99]. Some rating scales have been developed to estimate the extent of white matter hyperintensities and to correlate them with cognitive function [100]. These scales are not normally used in clinical practice as they require further validation to assess their diagnostic merits, but they are useful in research setting. Some of these scales depend on visual inspection of brain images (usually T2-weighted MRI) and rating of the white matter lesions in terms of size, number, location, and distribution. Visual rating scales include scales like Manolio, Fazekas, and Schmidt [100]. A study that examined the validity and inter-rater reliability of these scales demonstrated reasonable validity and reliability but gave Fazekas and Schmidt scales the edge over the Manolio scale, which is more global and less detailed [100]. Other methods have been developed that include automated and semiautomated segmentation of brain tissue to gray and white matter and delineation of white matter hyperintensities with a relatively high level of accuracy, but these methods tend to be applied in research settings [101].

White matter hyperintensities are seen in patients with Alzheimer disease, Lewy body disease, and frontotemporal lobar degeneration [26]. Hippocampal atrophy is associated with vascular cognitive impairment [102]. This adds to the challenge to the specificity of these lesions in diagnosing vascular NCD. The exact nature of white matter hyperintensities is still not clear but includes necrotic and non-necrotic lesions, as previously described in the neuropathology lesions section (see ▶ section Neuropathology Lesions).

D. Microhemorrhages. Fresh blood from large vessel rupture can be seen on CT scan, but asymptomatic microhemorrhages are not visible [103]. The best diagnostic tests to detect microhemorrhages are iron-sensitive MRI sequences, including gradient-echo T2 and susceptibility weighted image (SWI) [104]. What is being imaged are actually hemosiderin deposits around the affected vessels. SWI is the standard test in visualizing these lesions because it is the most sensitive tool detecting as small as 1 mm size lesions [105]. Causes for microhemorrhages include cerebral amyloid angiopathy and hypertension-induced changes [106]. ◘ Table 21.2 summarizes brain imaging correlates of vascular cognitive impairment lesions.

Teaching Point

Pathological lesions can be detected in vivo via brain imaging. There have been several imaging-pathological validation studies. Structural imaging (CT and MRI) both can detect clinical stroke (macroinfarct), but MRI (especially T2 FLAIR sequence) can detect smaller infarcts and infarcts adjacent to bone or cerebrospinal fluid. For microhemorrhages, imaging hemosiderin is important and two MRI sequences have been used: gradient-echo T2 and susceptibility weighted image (SWI), the latter having higher resolution.

Genetic Testing

Genetics plays a role in vascular neurocognitive disorders. Genetic testing is usually considered when there is suspicion of CADASIL, which is characterized by vascular smooth muscle defects and is caused by a mutation in the NOTCH 3 gene (previously discussed) [107]. Another cause of vascular lesions in the brain that can present with cognitive disorder after set of strokes and stroke-like events is a rare syndrome called mitochondrial myopathy encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). This syndrome is usually caused by a mutation in mitochondrial DNA and can be diagnosed through clinical course, metabolic changes, and muscle biopsy in addition to genotype analysis [108].

Table 21.2 Summary of cerebrovascular lesions implicated in vascular neurocognitive impairment and their brain imaging correlates

Lesion	Imaging finding	Comment
Multi-infarct (macro)	Several strokes involving cortical areas	This is visualized on T1 and T2 MRI
Lacunar infarcts (macro)	Multiple and/or strategic lacunae in subcortical structures (gray and white matter). Strategic location: Frontal and parietal cognitive areas including angular gyrus Basal ganglia Thalamus Hippocampus	Can be seen on both T1 and T2 MRI T2 fluid-attenuated inversion recovery (FLAIR) is useful for lacunae adjacent to ventricles as it attenuates cerebrospinal fluid signal to make the lacunae more visible
White matter hyperintensities	Focal, multiple, or confluent opacities in periventricular, subcortical, or deep white matter areas	Can be necrotic due to microinfarcts or non-necrotic due to other pathologies (myelin changes, glial cell change, spongiosis). Amount and location can be rated for significance. Best visualized on T2 FLAIR
Microhemorrhages	Multiple small amount of blood or hemosiderin deposits in cortical or lobar locations (cortical-subcortical)	Due to hypertensive vessel changes or cerebral amyloid angiopathy, best visualized on susceptibility weighted image (SWI) or as a second choice gradient-echo MRI; both visualize hemosiderin deposits

21.1.6 Differential Diagnosis

Like other NCDs, one needs to consider cognitive impairment as a result of:

- Other major or mild NCDs: Alzheimer disease, frontotemporal lobar degeneration, and Parkinson-related NCD all have clinical overlap with vascular NCD.
- Medication- and substance-induced cognitive changes (e.g., alcohol, anticholinergic drugs).
- Cognitive changes due to general medical conditions, including metabolic disease (e.g., hypothyroidism, B_{12} deficiency), cardiac disease (e.g., heart failure with low cardiac output), respiratory disorders (e.g., uncorrected sleep apnea, chronic obstructive pulmonary disease), and infections (e.g., urinary, pulmonary, tertiary syphilis, Lyme disease, human immunodeficiency virus dementia complex). Abrupt onset of cognitive and behavioral changes from baseline in a patient with marked inattention and fluctuating course over the day are suggestive features of delirium.
- Normal pressure hydrocephalus can present similarly to periventricular white matter disease, with impaired gait, cognitive changes, and urinary incontinence. This triad will prompt brain imaging and a finding of out of proportion enlargement of the ventricles, however, with no significant white matter changes.
- Depression can be associated with stroke. It is very important to diagnose depression early as it is treatable, and treatment may improve cognitive function.
- Cerebral vasculitis may cause a progressive major NCD. Its course is usually faster than vascular NCD. It usually manifests with focal neurological signs and white matter changes.
- Multiple sclerosis can present with very similar picture to subcortical white matter vascular NCD. There are different subtypes of multiple sclerosis including relapsing-remitting course—with/without residual deficit—and primary and secondary progressive course, with/without superimposed acute episodes [109]. Clinical history and findings of neurological deficits may help in differentiating multiple sclerosis from vascular NCD, but in some cases further investigations are needed, including brain imaging and immune markers from cerebrospinal fluid. On brain imaging there are certain criteria that suggest multiple sclerosis. Those cases should meet three out of the following criteria [110]:
  1. One gadolinium-enhanced lesion or nine hyperintensity lesions on T2 if there is no gadolinium-enhancing lesion
  2. At least one infratentorial lesion
  3. At least one juxtacortical lesion
  4. At least three periventricular lesions

Teaching Point

Like other NCDs, vascular NCD needs to be differentiated from other causes of cognitive impairment (e.g., other major or mild NCDs, NCD due to another medical condition or substance use, delirium, and other psychiatric illnesses).

21.1.7 Treatment

The mainstay for the treatment of vascular NCD is prevention of further vascular lesions by controlling modifiable vascular risk factors. Other treatments target improvement of symptoms in areas of cognition, behavior, and function. This section will summarize recommendations from the AHA/ASA scientific statement [11]. The recommendations vary in

strength based on current evidence from clear recommendation, reasonable recommendation, to no recommendation. They classified the evidence as *Class I* where there is established benefit outweighing the risk, *Class IIa* where there is indication of benefit exceeding the risk but more studies are needed, *Class IIb* where benefit might outweigh or equals the risk and more studies are needed to clarify, and *Class III* where there is either no benefit or clear harm. Certainty was rated as Level A, B, or C based on the quality of the studies.

Lifestyle Modification

The AHA/ASA scientific statement considers reasonable to recommend smoking cessation (*Class IIa; Level A*), moderation in alcohol intake, weight control, and physical activities (*Class IIb; Level B*). Consideration of the use of antioxidants and vitamin B is not beneficial (*Class III; Level A*).

Physiological Risk Factor Modification

The AHA/ASA scientific statement definitively recommends treatment of hypertension (*Class I; Level A*) and considers it reasonable to recommend treatment of hyperglycemia (*Class IIb; Level C*) and hypercholesterolemia (*Class IIb; Level B*). There is a stated uncertainty around treatment of inflammation (*Class IIb; Level C).*

Treatment of Concomitant Clinical Vascular Disease

This includes coronary artery disease, stroke, chronic kidney disease (resulting in uremia and hypertension, both of which increase risk of cognitive decline), atrial fibrillation, peripheral arterial disease, and low cardiac output. Optimizing the treatment of these factors is recommended.

Modifying Symptoms with Pharmacological Interventions

Modest cognitive improvement has been shown with donepezil, galantamine, and memantine, although a positive impact on function is less clear, except in some cases of mixed Alzheimer and vascular NCD. The AHA/ASA stated that donepezil can be useful for cognitive enhancement in patients with vascular dementia (i.e., vascular major NCD) (*Class IIa; Level A*). Galantamine can be beneficial for patients with mixed Alzheimer and vascular NCD (*Class IIa; Level A*). The benefit of rivastigmine and memantine is not well established (*Class IIb; Level A*).

Some agents used in Europe and elsewhere but not in North America include pentoxifylline and, to a more limited extent, ergoloid mesylates (Hydergine). These agents may be useful for increasing cerebral blood flow. In the European Pentoxifylline Multi-Infarct Dementia Study, a double-blinded, placebo-controlled, multicenter study treatment with pentoxifylline was found to be beneficial for patients with multi-infarct NCD. Significant improvement was observed with pentoxifylline in the scales used for assessing cognitive function [111].

The potential for calcium channel blockers as neuroprotective agents due to controlling excessive calcium influx-related excitotoxicity has been studied. A small study using nimodipine showed a nonsignificant trend of benefit in subcortical white matter disease but not in multi-infarct dementia [112]. More recently, a Chinese group studied the combination of nimodipine with acupuncture in poststroke patients for cognitive improvement and found that the combination was significantly better than each treatment alone in improving MoCA scores and that acupuncture alone fared better than nimodipine alone [113].

It is important to note that with the high level of depression in the context of vascular neurocognitive impairment, the use of antidepressant is common. The use of antipsychotic medications for aggressive agitation is confounded by risk of mortality and morbidity including increased risk of stroke. The use of psychotropic medications in treating neuropsychiatric symptoms of NCDs is discussed in ► Chap. 22 in this textbook.

Non-pharmacological Interventions

There is a paucity of literature on the role of non-pharmacological interventions in vascular NCD. Most of the studies targeted Alzheimer disease with and without a vascular component. Evidence for cognitive rehabilitation remains inconclusive and needs to be studied further. The rule of acupuncture in enhancing cognition in animal models of vascular cognitive disorder is not yet confirmed in humans. Non-pharmacological interventions for psychological and behavioral symptoms arising in the context of vascular NCD are discussed in ► Chap. 22.

Primary Prevention

The AHA/ASA scientific statement addressed question related to preventing NCDs (including Alzheimer and vascular type) through lifestyle and risk factor treatment. The recommendations include lowering blood pressure in patients with stroke (*Class I; Level B*) and lowering blood pressure in middle-aged and younger-old-aged as being useful in preventing late-life dementia (*Class IIa; Level B*), but not for lowering blood pressure in older adults above age 80 (*Class IIb; Level B*). The usefulness of treating hyperglycemia and hyperlipidemia for prevention of dementia (major NCD) was uncertain (*Class IIb; Level C*). There was no evidence to support the benefit of antiplatelet therapy in the prevention of major NCDs, and therefore it is not recommended (*Class IIb; Level B*).

When it comes to lifestyle modification, a Mediterranean-type diet has been associated with less cognitive decline in several studies and is reasonable to recommend (*Class IIb; Level B*); vitamin supplements had no clear benefit on cognition even if they lowered homocysteine levels (*Class IIb; Level B*). It is reasonable to recommend physical activity as potentially useful in prevention of major NCD (*Class IIb; Level B*). ◘ Table 21.3 lists the risk factors, evidence-based recommendations regarding these factors, and potential for modifiability.

Table 21.3 List of risk factors for vascular neurocognitive disorders, recommendations from AHA/ASA scientific statement and modifiability

Risk factor	Recommendation	Comment
Demographics, ethnicity	Be aware of the risk, no recommendations	Unmodifiable
Education	Be aware of the risk, no recommendations	Unmodifiable, confounded by socioeconomic status
Lifestyle		
Diet		
Mediterranean diet	Reasonable to recommend for primary prevention (Class IIb; Level B)	Mainly from epidemiological data (fish, green leaves, nuts, olive oil, etc.)
Vitamins (including B_6, B_{12}, D, E, other antioxidants)	No evidence of benefit for primary or secondary prevention (both Class IIb; Level B)	Modifiable and relatively safe (except for cost) but no evidence of benefit
Smoking	Recommend smoking cessation for secondary prevention (Class IIa; Level A), likely the same for primary prevention, although not specifically done	Modifiable, challenging, and need significant support to implement
Alcohol intake	Reasonable to recommend moderation in intake for secondary prevention (Class IIb; Level B)	Modifiable, challenging, and need significant support to implement
Weight control	Reasonable to recommend for secondary prevention (Class IIb; Level B) likely the same for primary prevention, although not specifically done	Modifiable, challenging, and need significant support to implement
Physical activity	Reasonable to recommend for primary and secondary prevention (Class IIb; Level B)	Modifiable, challenging, and need significant support to implement
Physiological markers		
Hypertension	Definite recommendation to treat for secondary prevention (Class I; Level A), secondary prevention after stoke (Class I; Level B), reasonable as primary prevention in middle age and younger seniors (Class IIa; Level B) but not in age > 80 seniors (Class IIb; Level B)	Modifiable, definite adherence can be a challenge
Hyperglycemia	Reasonable to treat hyperglycemia for secondary prevention (Class IIb; Level C), uncertain benefit for primary prevention (Class IIb; Level C)	Modifiable, secondary prevention is reasonable, adherence can be a challenge
Hyperlipidemia	Reasonable to treat hyperglycemia for secondary prevention (Class IIb; Level B), uncertain benefit for primary prevention (Class IIb; Level C)	Modifiable, secondary prevention is reasonable, not clear if specific to cholesterol or include triglycerides, adherence can be a challenge
Anti-inflammatory	Uncertain	
Antiplatelets	Not recommended for primary prevention (Class IIb; Level B), but can be a treatment of concomitant clinical vascular disease	
Concomitant clinical vascular disease	Recommend optimizing treatment, no specific evidence recommendation	Includes coronary artery disease, stroke, chronic kidney disease, atrial fibrillation, peripheral vascular disease, and low cardiac output

Teaching Point

Treatment of vascular NCD follows the same principles of other NCDs: supporting the patient and family/caregivers, maintaining safety, and addressing any unmet needs of the patient. Prevention of further vascular lesions is a core component of treating this illness, and the evidence-based recommendations regarding modifying risk factors are discussed previously. Specific symptomatic treatment of vascular NCD is limited where some studies addressed cognition and some addressed behavioral symptoms.

21.2 Case Studies

The following case-based studies are reflective of the symptomatology of the clinical variants of major or mild vascular NCD and the intricate neuropathology and comorbidity that may present in such cases. For further review, other illustrative case examples are presented in ► Chap. 3.

21.2.1 Case 1

Case 1 History

Mrs. A., a 75-year-old woman, was referred by her primary care physician for a cognitive assessment. She was previously seen by geriatric medicine team along with her son one and a half year ago for mild cognitive changes. Since then, her family noticed further subtle cognitive changes over the previous year, which they reported as being mild and slowly progressive. The patient had become more repetitive, and she was relying more on notes to remember things. Her planning and problem-solving skills had changed requiring more help from her family, although she was still relatively independent in most of her tasks, including taking care of her household and basic financial affairs, and she continued to drive safely. She recognized that she had some cognitive challenges but thought that they were "normal for age." Her son reported that she had also developed increased anxiety around events and showed signs of depression and irritability. She now called her children more for help when faced with new instrumental tasks like preparing her tax returns.

Mrs. A. had no previous psychiatric or substance use history. There was no family history of diagnosed major NCDs.

Medical history included:

- Hypertension for many years, on antihypertensive medications.
- Osteoarthritis of right hip, with previous joint cortisone injection.
- Vaginal sanguineous discharge.
- Gastroesophageal reflux disease.
- Hypothyroidism.
- There was no history of traumatic brain injury or stroke.

Surgical history included:

- Childhood appendectomy
- Left breast carcinoma resected with total mastectomy 8 years previously, without chemotherapy, radiotherapy, or tamoxifen treatment
- Partial thyroidectomy for a benign goiter over 10 years previously

Mrs. A. lived a relatively healthy lifestyle, used wine occasionally, and never smoked tobacco, although her late husband was a smoker. Mrs. A. was a former schoolteacher with a teacher's college degree.

Her current medications were set up in a dosette box by her family and included rabeprazole, levothyroxine, metoprolol, hydrochlorothiazide, perindopril (started recently), enteric-coated small-dose aspirin, estrogen vaginal cream, and over-the-counter probiotics, lutein, vitamin D, and magnesium powder for bowel function. She had allergies to penicillin and celecoxib.

Functionally, Mrs. A. was independent in all her basic activities of daily living. Her family visited every 1–2 days. Regarding instrumental activities, Mrs. A. was managing her finances independently up until 1 year previously. Her friend helped setting her up with online banking. She was able to do online banking independently. She made no financial errors. She was still driving. One year prior, she hit a low post in a parking lot.

On examination, her weight was 137 pounds, and height was 5 foot 3 inches. She had an adequate hearing and corrected vision. Neurological exam was largely non-focal except for slight bradykinesia (right more than on the left side) and a subtle resting tremor on the right side, which was uncovered with distraction when she performed motor task with her left hand. She was unable to perform the Luria Hand Test with either hand. She could arise independently from a chair without the use of her arms. Romberg test was negative. She could perform tandem stance bilaterally. Her Timed Up and Go test (getting up from sitting, walk for 3 meters, turn around, walk back, and sit again) was 9 seconds (normal 10 seconds or below) [114].

Her blood pressure supine with rest was 198/80 mm Hg; heart rate was 47–50 beats per minute. At 2 minutes of standing, her blood pressure was 170/84 mm Hg, with a heart rate of 51 beats per minute. She had pitting edema to mid shin. She had a loud S1-S2 with no added sounds. She had a small vaginal prolapse with small amount of sanguineous discharge. Cognitive scores showed that MMSE was 26/30 while MoCA was 16/30.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. At this stage, what would be the differential diagnosis?

? Question 2. What is the most appropriate next step to clarify the diagnosis?

? Question 3. What is the differential diagnosis now, and what are the changes from initial impression?

? Question 4. What would be the most appropriate management plan?

Case 1 Answers

Case 1 Answer 1 (Question 1—At this stage, what would be the differential diagnosis?)

This is a case of insidious onset, slowly progressive NCD in an older adult female. As such, Alzheimer disease needs to be on top of the differential diagnostic list. On the other hand, having subtle neurological signs, history of hypertension that was in suboptimal control, and history of cancer required further workup to rule out other central nervous system pathology such as cerebrovascular disease and brain metastasis. Other differential diagnosis items could be

general medical conditions like infections (e.g., urinary tract infection), hypothyroidism (if not adequately corrected), electrolyte imbalance, and medication and substance effect, but all were lower on the list given that the patient was alert with no indication of delirium.

Case 1 Answer 2 (Question 2—What is the most appropriate next step to clarify the diagnosis?)

In addition to a general screening with chemistry, renal, liver, and thyroid function tests and other more targeted tests based on the patient's medical history, review of medication intake adherence, and assessment for inappropriate consumption of substances (like excessive alcohol or over-the-counter medications), the next step is brain imaging to rule out cerebrovascular disease and/or brain metastasis. In Mrs. A.'s case, an order for a clinical MRI was appropriate including using contrast to rule out metastasis but also use of susceptibility weighted image (SWI) sequence, which will allow for the detection of microbleeding.

Case 1 (Continued)

Six months later, Mrs. A. was seen again by the geriatrician because of changes in her mood and behavior. Family members had noticed that Mrs. A. was needing more cueing, often called her son about medication clarification (although she used a dosette system), and did not know what to do sometimes. She had also developed more anxiety.

MRI of brain scan obtained after the first assessment was reviewed and, although it did not show any evidence of metastatic disease, it did show punctate lesions on SWI indicating microhemorrhages with mild white matter hyperintensity. Mrs. A. was referred to geriatric psychiatry for increasing difficulty with anxiety, irritability, and agitation. (See Fig. 21.1 for MRI images in this case.)

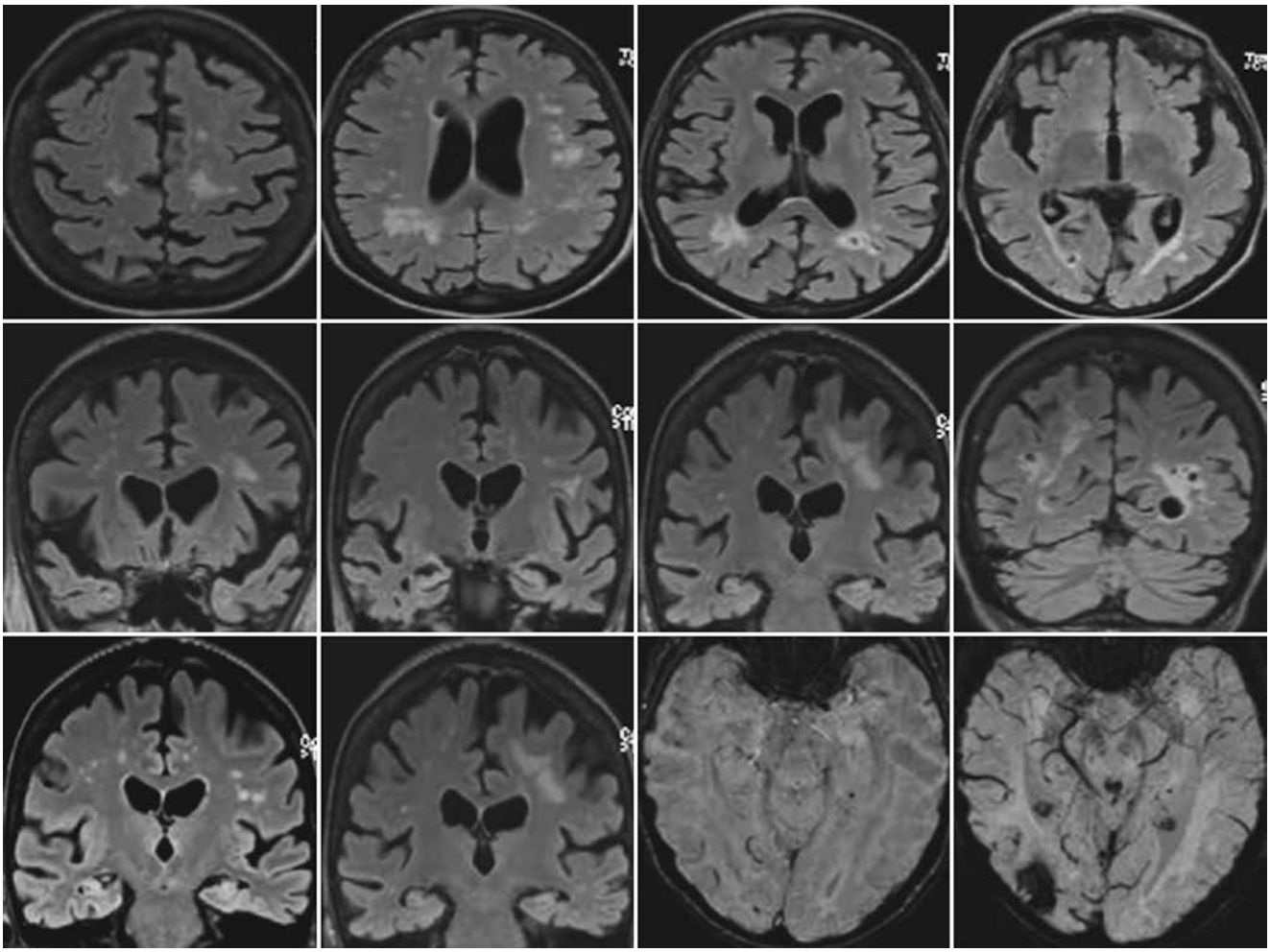

Fig. 21.1 MRI images from Case 1, upper panel: selected T2 FLAIR MRI images in transverse sections showing significant white matter hyperintensities in subcortical and deep white matter areas. Middle panel: selected T2 FLAIR MRI images in coronal sections also showing significant white matter hyperintensities in subcortical and deep white matter areas; some hippocampal volume loss is seen but difficult to confirm with visual examination alone. Lower panel: from left to right, two MRI T2 FLAIR images taken 1 year apart showing progression of white matter hyperintensities (the sections are approximately at the same level); the last two images show susceptibility weighted images (SWI) also 1 year apart showing new cortical bleeding in the latter image. The location of the bleeding suggests hypertensive microbleeding, although clinically the patient has been normotensive raising the possibility of amyloid angiopathy. Transverse and coronal images are displaced in radiological convention (left side of the image is right side of the patient)

A month later, she was seen in the geriatric psychiatry clinic. She had difficulty with her semantic memory, she had expressive aphasia and anxiety, and she expressed frustration. She was unable to drive any longer. Her MMSE at this visit (7 months after the initial assessment) was difficult to perform due to her anxiety and irritability, but with encouragement she eventually completed it and was scored at 17/30.

Case 1 Answer 3 (Question 3—What is the differential diagnosis now, and what are the changes from initial impression?)

At this stage, this case represents a rapidly progressive NCD. In general, illnesses like Alzheimer disease tend to be slowly progressive (approximately 3–4 points decline on MMSE annually). (See ▶ Chap. 18). In this case, MMSE score went down by 9 points in 7 months. Factors to consider in this case include a superimposed condition that could be a psychiatric, substance-related, or systemic medical illness. Details of the workup of a rapidly progressing NCD are beyond the scope of this chapter. The reader is referred to publications that provide guidance on how to work up a patient with this rapid course [115]. In this case, basic investigations including chemistry, metabolic screening (such as thyroid function and B_{12}), screening for infections, and screening for substance use including over-the-counter and herbal therapies were all negative. There was no indication of a seizure activity or delirium per se in this case. Due to the rapid decline, another MRI of the brain was ordered (8 months after her initial MRI). Findings now included new cortical bleeding that was most likely driven by high blood pressure, but with the possibility of amyloid angiopathy. In this case, vascular changes in the form of increasing white matter hyperintensity and spontaneous hemorrhages (exacerbated by hypertension) likely caused the rapid decline in her cognition. In this case, it is difficult to ascertain if there was any Alzheimer disease pathology at this point in time when significant vascular changes were prominent, but the course and the pattern of hippocampal atrophy now evidenced on her repeat MRI scan suggested a combined Alzheimer disease and vascular pathology.

Case 1 Answer 4 (Question 4—What would be the most appropriate management plan?)

General principles include supporting the patient, family, and caregivers and utilize non-pharmacological interventions to reduce anxiety and distress (e.g., reorientation, added functional support, safe activation, protection from harm, psychological support). Of great importance is psychoeducation and support to family and caregivers about the nature of the illness and prognosis and addressing issues with informed consent, substitute decision makers, placement, finances, and personal care decisions.

To modify the underlying illness, the clinicians should aim to control vascular risk factors but more urgently, as in this case, by controlling blood pressure, avoiding antiplatelet agents and other agents that may increase bleeding risk (e.g., aspirin, selective serotonin reuptake inhibitors), monitoring progression, and adding support as needed.

Case 1 Analysis In Mrs. A.'s case, the initial presentation was that of a typical neurodegenerative illness, such as Alzheimer disease, but because of vascular risk factors (hypertension with high blood pressure on examination), history of breast cancer, and subtle neurological findings, it was essential to rule out other brain processes, mainly cerebrovascular disease and brain metastasis. Initial brain imaging did show microbleeding suggesting an etiology of hypertensive and/or cerebral amyloid angiopathy. The patient's course became rapidly progressive with significant cognitive, functional, and behavioral deterioration within 6–8 months. A repeat MRI showed further bleeding likely from hypertension and/or amyloid angiopathy. The patient was diagnosed with rapidly progressive major NCD due to amyloid angiopathy. Susceptibility weighted image (SWI) would be helpful to show the bleeding. Finding evidence of atrophy involving hippocampal formation raised the possibility of Alzheimer disease pathology making this case a combined Alzheimer-related and vascular NCD with strong suggestion of a combination of hypertensive and cerebral amyloid angiopathy.

21.2.2 Case 2

Case 2 History

Mr. B., a 76-year-old man who lived with his wife of almost 50 years, was referred to you in the geriatric psychiatry clinic for clarification of his cognitive disorder and comment on prognosis. He was initially admitted to the hospital 6 months prior with an acute stroke. His stroke presented with word-finding difficulty, confusion, slurred speech, agitation, and aggressive behavior for a few days. The patient was known to have end-stage renal failure due to hypertension requiring hemodialysis. He had a 25-pound weight loss because of interruptions due to dialysis. When he was seen 1 month after his stroke by nephrology for his dialysis, he was becoming anxious, and his wife reported that he was becoming aggressive toward her and expressing thoughts that she was trying to kill him. Also, he made statements indicating wishing to die, but no suicidal behavior was noted otherwise. He had recently missed out on one of his dialysis appointments because of feeling confused about the dialysis dates; his confusion worsened and then improved after his next dialysis treatment. You learned that, as a result of his stroke, he was unable to drive any longer and his activity level had declined significantly. His medical and surgical history included:

- End-stage renal disease secondary to hypertension currently on hemodialysis
- Previous episodes of transient ischemic attacks, at least two over the previous 3 years
- Ischemic stroke 6 months prior, reportedly involving right occipital and temporal areas
- Neuropathic pain
- Restless leg syndrome
- Prostate cancer treated with transurethral resection of the prostate; no recurrence reported

He had no previous psychiatric history including no active substance use disorder. He did not use much alcohol but he had smoked many years ago. His father had multiple strokes and related memory impairment, but there was no history of other NCDs in the family. He was a former machinist, having worked for different companies, and had 10 years of formal education.

His current medications included small-dose enteric-coated aspirin, amitriptyline (25 mg for sleep), amlodipine, atorvastatin, furosemide, hydroxyzine, pantoprazole, tamsulosin, acetaminophen, diclofenac topical, docusate, lorazepam as needed for agitation (recently prescribed and used a few times with some sedating effect), levodopa-carbidopa (one tablet for restless legs at night), polyethylene glycol, and over-the-counter vitamins and natural health supplements. His medications on dialysis were dalteparin and Aranesp. He has no known drug allergies.

On a recent examination in the primary care physician office, Mr. B. had left homonymous hemianopsia with no other neurological symptoms. Vital signs included blood pressure 145/90 millimeter mercury and heart rate of 95 beats per minute. There were no respiratory abnormalities and heart sounds (S1, S2) were normal with no murmur. His MRI was reported as positive for white matter hyperintensity and a stroke in right occipital and temporoparietal lobe involving the angular gyrus, with some atrophy and white matter changes (see Fig. 21.2 for selected MRI images for this patient).

Mr. B. was scheduled to be seen by a geriatric psychiatry specialist based on a referral from his primary care physician for clarification of his cognitive disorder and prognosis, because the nephrology team and his wife were questioning the utility of continuing dialysis given that the patient had "advanced and progressive dementia." His current status was

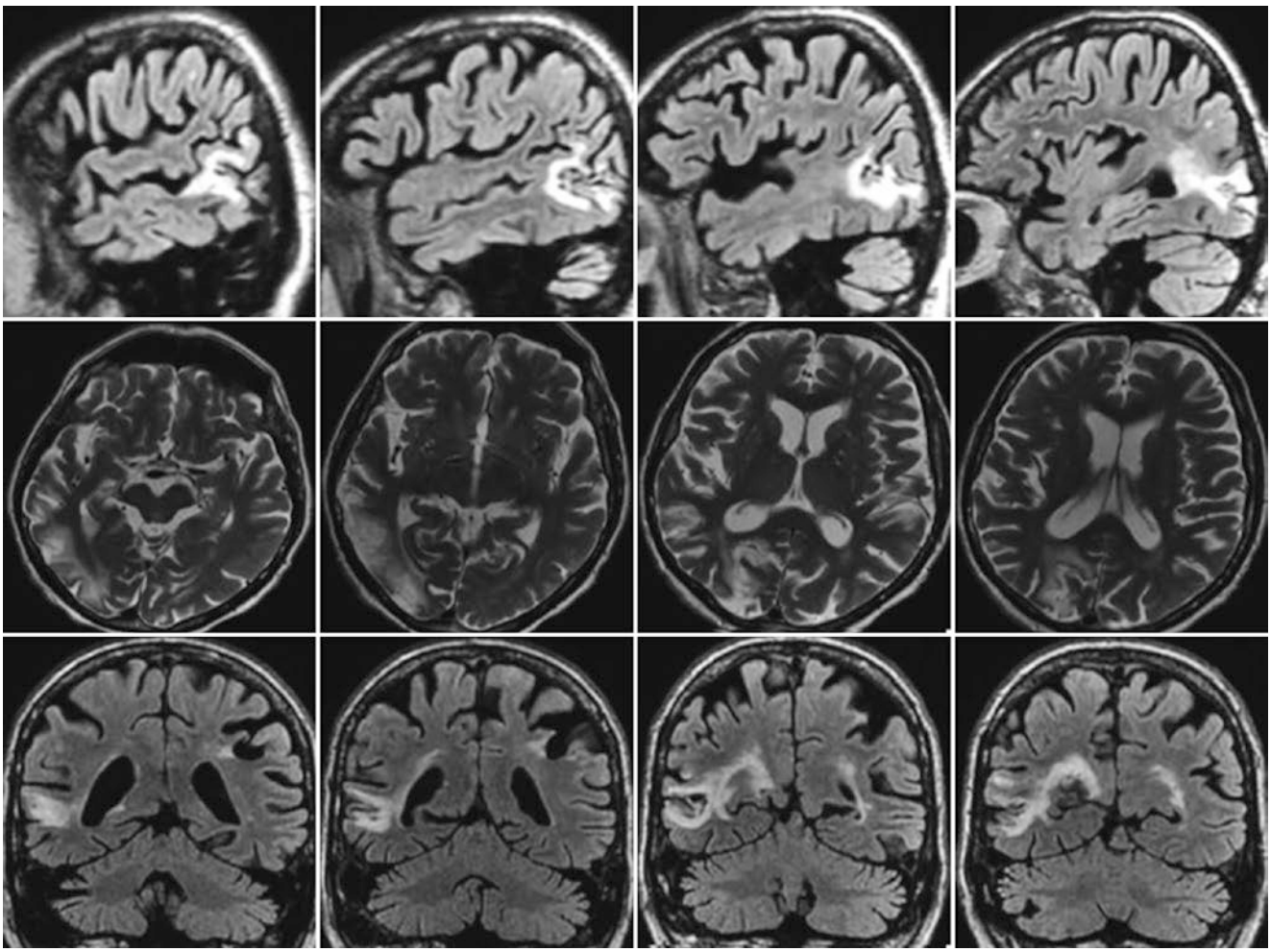

Fig. 21.2 MRI images from Case 2, upper panel: a set of T2 FLAIR images in sagittal sections showing the stroke involving posterior-inferior aspect of parietal lobe above the calcarine fissure, posterior aspect of superior and middle temporal lobe, and part of the occipital lobe; the angular gyrus is part of the inferior parietal lobule temporo-parietal junction and is affected in this case. Middle panel: same stroke demonstrated in T2 propeller images; notice the difficulty seeing the lesion adjacent to the ventricles due to cerebrospinal fluid white signal, which is removed in the FLAIR sequences in the top and lower panel. Lower panel: the same stroke demonstrated in T2 FLAIR coronal sections. The relationship to the calcarine sulcus is clearer in this section. Transverse and coronal images are displaced in radiological convention (left side of the image is the right side of the patient)

that he was more forgetful and wandered around the house without a clear purpose. His wife had noticed that he had been acting "very strange" since his stroke 6 months prior, repeating questions, and asking her to help him with things that were normally easy to perform for him. When you examined him in your office, his MoCA test now scored at 21/30. On executive functioning, he scored 1/5, and on spontaneous delayed recall, he scored 0/5, but he was able to recall all five words with a cue. All the other parameters such as naming, memory, attention, and language were normal. Geriatric Depression Scale (short version) was 6/15 indicative of some symptoms of depression, but Mr. B. did not think he was depressed. He had just noticed that he cried more easily.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What is the preferred diagnosis?

Question 2. What other diagnoses need to be considered?

Question 3. What would be the most appropriate management suggestion regarding the vascular NCD?

Question 4. What is the significance of stroke location in the major NCD in this case?

Case 2 Answers

Case 2 Answer 1 (Question 1—What is the preferred diagnosis?)

Mr. B.'s likely diagnosis is probable major vascular NCD. This diagnosis is supported by evidence of cognitive change from the baseline that impacted function (making the diagnosis of a major NCD), evidence of cerebrovascular disease involving strategic cognitive area (angular gyrus), and a temporal relationship between the cerebrovascular disease and cognitive changes (according to DSM-5 diagnostic criteria).

Case 2 Answer 2 (Question 2—What other diagnoses need to be considered?)

A. Major NCD due to Alzheimer disease and mixed with cerebrovascular disease: this is an important consideration because we do not have a clear understanding of this patient's baseline. It is not uncommon for Alzheimer disease to have an insidious and slowly progressive course, and it is not usually detected in very early stages unless the patient has thorough cognitive testing. Furthermore, comorbidity between Alzheimer disease and cerebrovascular disease is common. This has important implication on prognosis, as it is more likely to see a steady decline in cognition and function with the Alzheimer disease component, whereas vascular NCD can stay stable if vascular risk factors are controlled. This is relevant in this case because the assumption of the patient having a neurodegenerative dementia (major NCD due to Alzheimer disease) led the nephrology team to suggest discontinuing dialysis.

B. Delirium: this is a possibility especially at the time when the patient had missed dialysis (e.g., uremia, electrolyte, and acid-base balance disturbance), medications (e.g., anticholinergic drugs like amitriptyline), any infections that he was vulnerable to develop, and acute brain process after stroke (e.g., edema, neuroinflammation).

C. Depression-induced cognitive changes: at this point this is unlikely given his depressive symptoms were relatively mild.

Case 2 Answer 3 (Question 3—What would be the most appropriate management suggestion regarding the vascular NCD?)

It is important to clarify the patient's diagnosis and the level of cognitive impairment to the primary care and nephrology teams. At this stage, this patient is in a relatively mild-to-moderate stage of neurocognitive disorder (he scored 21/30 on MoCA test), and he is functionally independent in his basic activities of daily living. He would likely score 4 (out of seven stages) on the Global Deterioration Scale [116]. Furthermore, at this stage his diagnosis is probable major vascular NCD. As such, he should continue to be offered options to treat his illnesses including dialysis. This is part of educating other medical professionals on the nature of the illness and its prognosis and advocating for the patient to get optimum level of care. It would be essential to control his vascular risk factors and follow optimum stroke prevention strategy according to clinical guidelines. Also, reducing the burden of medications, like amitriptyline and other centrally acting drugs with anticholinergic and depressant mechanisms, is essential. Based on the evidence to date, it is not clear whether cholinesterase inhibitors are indicated. Some guidelines do not recommend these agents in pure vascular major NCD, but if there is concurrent with Alzheimer disease component, these agents may be beneficial. For this case, reassessment of cognitive scores in 6 months to 1 year will allow us to rule in or out an Alzheimer disease process. There are differences in the choice of agents when it comes to decreased renal clearance, so that galantamine would likely be safer. However, for patients on dialysis, the use of cholinesterase inhibitors that are renal clearance dependent like rivastigmine and donepezil can be considered.

Case 2 Answer 4 (Question 4—What is the significance of stroke location in the major NCD in this case?)

The angular gyrus is involved in this case. This is an area of heteromodal association cortex with role in executive functioning. Left-sided lesions would have affected language, calculation, finger identification, and left-right orientation (Gerstmann syndrome) [117]. Right-sided (non-dominant) angular gyrus lesions also affect executive functioning but would not affect language and calculation. Other strategic areas for stroke include thalamus, basal ganglia, and medial frontal areas. A small stroke in these areas can result in major vascular NCD.

Case 2 Analysis This case involves an infarct in right posterior circulation affecting posterior temporal, inferior parietal, and occipital cortex. One of the areas involved is the angular gyrus which is important for cognitive processing. The patient had a complex medical comorbidity including renal failure needing dialysis, which was likely a complication from hypertension, but which also resulted in difficulty with blood pressure control. His presentation with confusion after his stroke and after missing dialysis was almost certainly due to delirium induced by brain injury, uremia, and electrolyte imbalance. This was interpreted as advanced dementia by his spouse and medical practitioners caring for him, with the suggestion to move him to a palliative care level by stopping his dialysis. Geriatric psychiatry assessment pointed out that the picture is suggestive of vascular cognitive impairment due to a "strategically located" stroke and that patient's cognitive course can be stable if further cerebrovascular lesions are prevented. There was a possibility that this patient was experiencing a combined Alzheimer and vascular NCD; this assumption would be appropriate if his cognitive course continued to decline progressively, independent from vascular and general medical events. The hippocampal areas were not particularly atrophic, which argued against the possibility of Alzheimer pathology. His cognitive profile with intact cued recall on the MoCA test also supported a vascular process.

21.3 Key Points: Major or Mild Vascular Neurocognitive Disorder

- Vascular neurocognitive disorders are common and can cause cognitive disorder independently or in combination with other pathology like Alzheimer disease.
- Reaching the diagnosis of vascular neurocognitive disorder requires the presence of neurocognitive disorder (major or mild) and cerebrovascular disease that is deemed causative to the cognitive disorder based on established clinical criteria.
- There are several subtypes of vascular neurocognitive disorders including multi-infarct, strategic infarcts, subcortical white matter disease, microhemorrhages, or a combination of the above.
- There are several risk factors that increase the risk for this illness; some are modifiable like vascular risk factors, but these risk factors also increase the risk of Alzheimer disease.
- Diagnosis is established through clinical data, but brain imaging is essential in confirming cerebrovascular lesions relevant to the cognitive disorder.
- The course of this illness tends to be slower than that of Alzheimer disease and can be modified by preventing further cerebrovascular events.
- Apart from modifying risk factors, there are relatively few studies that examined therapies to modify this illness directly, although some of the therapies used in Alzheimer disease may have a role in vascular neurocognitive disorder especially when there is a comorbidity of Alzheimer disease pathology.

21.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which one of the following areas is *not* considered strategic when it comes to vascular neurocognitive disorder?

A. Thalamus
B. Amygdala
C. Hippocampus
D. Anterior cingulate
E. Angular gyrus

Answer: B

Although the amygdala is part of the limbic system and is in close proximity to the hippocampus, it has not specifically been identified as a strategic cognitive structure; instead it is involved in emotional tagging of information and emotional processing.

MCQ 2. Gait abnormality can be a feature of all of the following neurocognitive disorders, *except*:

A. Normal pressure hydrocephalus
B. Corticobasal degeneration
C. Lewy body disease
D. Subcortical vascular neurocognitive disorder
E. Angular gyrus stroke-related neurocognitive disorder

Answer: E

The angular gyrus is not significantly involved in gait control.

MCQ 3. Current recommendations for treatment of vascular neurocognitive disorder include:

A. The use of an antiplatelet agent
B. The use of a selective serotonin reuptake inhibitor to prevent depression
C. The use of memantine to improve function
D. Treating hypertension

Answer: D

Treating hypertension is a firm recommendation in the context of vascular neurocognitive disorder. The use of antiplatelet agents is not routinely recommended and can be harmful in the context of cerebral amyloid angiopathy and uncontrolled hypertension. Although selective serotonin reuptake inhibitors can be used to treat depression in the context of vascular neurocognitive disorders, they are not indicated as prevention of depression in this context. There has been some evidence to support the use of these antidepressants in the prevention of depression after acute stroke and evidence of improved mortality, cognitive, and functional outcomes [118–120]. The evidence for memantine is limited, and at this time it is not recommended for the symptomatic treatment of vascular neurocognitive disorders.

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