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The microvascular frontal-subcortical syndrome of aging

Kenneth G. Pugh,[a,b,c,d,1], Lewis A. Lipsitz[a,b,c,2,*]

[a]*Beth Israel Deaconess Medical Center, Department of Medicine, Division of Gerontology, Boston, MA, USA*
[b]*Hebrew Rehabilitation Center for Aged, Boston, MA, USA*
[c]*Division on Aging, Harvard Medical School, Boston, MA, USA*
[d]*U.S. Navy, Naval School of Health Sciences, Bethesda, MD, USA*

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Abstract

Many features of aging suggest dysfunction in both frontal and subcortical regions. Connections between the two areas form a series of pathways that critically influence various aspects of cognition, motor control, affect, and as recently discovered, normal urinary function. Age-related changes in the structure and integrity of these circuits may be associated with cognitive impairment, mood disorders, loss of balance, falls, and urinary dysfunction. In addition, cardiovascular risk factors in elderly people are associated with the development of cerebral microangiopathic changes in both the periventricular white matter and basal ganglia. These lesions are common, usually unsuspected, and were previously believed to be clinically innocuous. However, increasing evidence supports a role for these lesions as a cause for both dysfunction in frontal-subcortical systems, and many clinical features of aging that account for substantial disability. Because this form of cerebrovascular disease is potentially preventable, interventions that address risk factors for the development of cerebral microangiopathy may go a long way in preventing disability for the next generation of elderly persons.

Keywords: Subcortical; Aging; Cerebrovascular disease; White matter; Leukoaraiosis

1. Introduction

The process of human aging often results in changes within motor and cognitive systems that are sufficiently characteristic; they might arguably be described as "phenotypic." For example, motor and cognitive slowing leads to age-related differences in reaction times, gait speed, and "fluid" intelligence [9,48,106]. It is not surprising that these are key features of geriatric syndromes that include falls, cognitive impairment, and depression. We believe considerable evidence to date suggests that pathophysiologic processes of the human frontal lobes and their subcortical connections may in part account for the "phenotypic" changes and syndromes that occur with aging. The frontal-subcortical model is helpful in understanding why geriatric syndromes often coexist within an individual patient.

Cognitive neuroscientists were among the first to speculate on a relationship between the frontal lobes and clinical features of aging. One popular theory of cognitive aging attempts to understand age-related cognitive decline in terms of frontal lobe impairment [130]. Compared with young adults, elderly persons often show relative deficits in abstract reasoning, problem solving, psychomotor speed, and memory retrieval, with little evidence for change in linguistic abilities or general knowledge [78]. Many studies demonstrate age-related declines in working memory, memory retrieval, loss of inhibitory control, and alterations in complex attention [2,51,68,87]. A feature common to these cognitive processes is their apparent localization within an extensive network of prefrontal neural pathways, which connect to both subcortical and posterior parietal regions [61,71].

We argue that frontal-subcortical dysfunction may result from a combination of age-dependent neuronal changes that are often exacerbated by microangiopathic vascular dam-

* Corresponding author. Tel.: +1-617-363-8318; fax: +1-617-363-8929.

E-mail address: lipsitz@mail.hrca.harvard.edu (L.A. Lipsitz).

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[2]Dr. Lipsitz holds the Irving and Edith S. Usen and Family Chair in Geriatric Medicine at the Hebrew Rehabilitation Center for Aged, Boston, MA.

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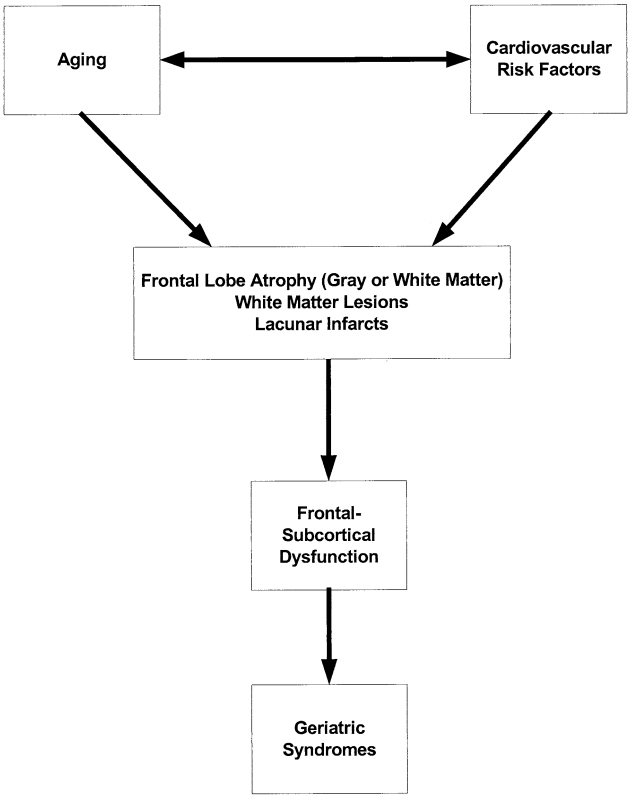

Fig. 1.

age, which develops as elderly persons progressively accumulate cardiovascular risk factors. The link between microangiopathic vascular damage and several geriatric syndromes will be explored. We hope this model provides a foundation for further multidisciplinary research into the pathophysiologic mechanisms, prevention, and potential treatment for several conditions associated with aging (Fig. 1).

2. The microvascular frontal-subcortical syndrome of aging

Evidence for small-vessel subcortical ischemic cerebrovascular disease is extremely common among otherwise neurologically normal elderly patients. The usual findings include radiographic changes in the subcortical white matter and deep gray nuclei. For consistency and clarity, we collectively refer to the combination of these lesions as subcortical ischemic microangiopathy (SCIM). Small-vessel vascular lesions that comprise SCIM are perhaps the most significant cause for frontal-subcortical dysfunction among the elderly. Subclinical damage from SCIM is usually underappreciated despite the potential to disrupt the integrity of frontal-subcortical circuits. Conceptually, it is reasonable to view this damage in terms of a "Microvascular Frontal-Subcortical Syndrome of Aging." To appreciate the basis for this argument, a brief understanding of frontal-subcortical anatomy is required.

Table 1
Clinical features of aging related to frontal-subcortical structures

Clinical feature	Anatomic region
Executive dysfunction	Dorsolateral prefrontal cortex, caudate nucleus, and thalamus
Apathy/anhedonia	Anterior cingulate
Parkinsonism/motor slowing	Basal ganglia
Urinary urgency/incontinence	Right inferior frontal cortex, basal ganglia

2.1. Anatomy of frontal-subcortical circuits

Using modern neuroanatomical techniques, a series of parallel pathways that interconnect various regions of the frontal lobes to subcortical structures have been characterized [73]. It has been accepted that at least five distinct circuits exist; including motor, supplementary motor, orbitofrontal, dorsolateral, and anterior cingulate circuits [17]. though recent evidence suggests a more complicated arrangement, with perhaps as many as seven separate circuits [61]. Each circuit shares similar anatomic features; they originate in the frontal lobes, pass through a set of input structures, (including the caudate, putamen, or ventral striatum) then project to the globus pallidum and substantia nigra, to ultimately relay information back to the frontal cortex via the thalamus. The five circuits appear to remain relatively segregated as they pass through large frontal cortical regions and project to progressively smaller, topographically mapped subcortical structures.

Three of the five circuits appear to have circuit-specific behavioral correlates; executive dysfunction with the dorsolateral prefrontal circuit, disinhibition or mood lability with the orbitofrontal circuit, and apathy/abulia with the anterior cingulate circuit [19,61]. A critical feature of these circuits is that lesions at any point may influence the integrity of the entire circuit. Consequently, different lesions can result in similar clinical findings. A typical example includes patients with movement disorders due to pathology in the basal ganglia, many of whom display a "frontal lobe syndrome," characterized by psychomotor slowing, apathy, and executive dysfunction [26,28].

Several clinical features observed in elderly patients suggest that frontal-subcortical circuits play a crucial role in the development of phenotypic characteristics associated with aging (summarized in Table 1). In addition to influencing cognition [17,130], motor control [15,103], and affect [52, 57,93,95], recent studies emphasize that normal urinary function is dependent upon the integrity of frontal-subcortical structures [3,7,8,20,79].

3. Evidence for age-related frontal-subcortical dysfunction

Frontal-subcortical structures are highly vulnerable to the process of aging, yet drawing firm conclusions about

Table 2
Previously reported age-related changes in frontal-subcortical structures

Cerebral region	Anatomic/physiologic abnormalities
Frontal lobes	⇓ Prefrontal gray matter
	⇓ Frontal perfusion
	⇓ Frontal white matter volume
Subcortical nuclei	⇓ Striatal volume
	⇓ Striatal dopamine binding
Periventricular white matter	Dilation of Virchow-Robin spaces
	⇓ Myelin/loss of oligodenrocytes

(⇓ = decreased)

what is "normal" and what represents neurodegenerative or cerebrovascular disease remains difficult. Because of the cross-sectional design of most studies on aging, investigators are frequently unable to determine whether aging per se, or simply intergenerational variation in factors such as nutrition, education, or prevalent disease are responsible for observed differences in brain morphology. Nonetheless, we briefly examine some of the better data available to date from neuroimaging, metabolic, and cerebral hemodynamic studies (summarized in Table 2) that support the view that frontal-subcortical structures are preferentially vulnerable to "normal" aging.

3.1. Volumetric studies of cerebral aging

The belief that aging is inevitably associated with substantial loss of cerebral neurons is under challenge [76]. Despite this encouraging discovery, at least some age-related structural changes are inexplicable. Neuroimaging studies in both monkeys and humans have revealed an age-related loss of striatal volume [66,89]. In addition, an age-related decline of dopamine binding sites within the striatum appears to correlate with both cognitive and fine motor performance [128]. Aging has also been associated with loss of either the gray or the white matter of the frontal lobes. A recent magnetic resonance imaging (MRI) study of 148 cognitively normal volunteers, ages 18–77 years, revealed an age-related volume loss of 4.9% per decade in the prefrontal gray matter, predominately in the dorsolateral and lateral orbitofrontal cortex [88]. Only minimal volume loss in subcortical white matter was observed in this group of carefully screened subjects. In contrast, other studies report a selective loss of the prefrontal white matter as a more typical finding [45,105].

3.2. Functional studies of aging and frontal-subcortical circuits

Functional imaging provides additional evidence for frontal-striatal dysfunction with normal aging. A review of positron-emission tomography (PET) studies in both aging and dementia concluded that normal aging is associated with a relatively specific reduction of prefrontal metabolism [74]; a finding that has been replicated by recent studies [6,25]. Unfortunately, reduction of cerebral blood flow and metabolism within the prefrontal cortex may start relatively early in life; perhaps even in middle age [110].

Age-related changes in frontal lobe metabolism may be associated with frontal-executive cognitive abilities. In a group of twenty cognitively normal, elderly persons, proton magnetic resonance spectroscopy (1H-MRS) was used to examine the relationship between N-acetylaspartase levels (NAA) in the frontal-subcortical white matter; a marker of neuronal density and viability, and neuropsychological performance [124]. Attention and executive control functions, but not memory or verbal abilities, showed a strong correlation with frontal white matter NAA concentrations. This led the authors to speculate that interindividual differences in the metabolism of frontal-subcortical white matter tracts may underlie some of the variation in higher order cognitive functioning seen among otherwise healthy elderly persons.

3.3. Aging, hemodynamics, and the frontal lobes

Orthostatic and postprandial hypotension are frequent findings in elderly patients [49,62]. Orthostatic hypotension is particularly common in those with underlying hypertension [62]. A limited, but emerging set of data suggests that abnormalities of blood pressure regulation may lead to perfusion abnormalities in the frontal lobes and contribute to frontal-subcortical cognitive deficits. With near-infrared spectroscopy, it was shown that healthy elderly persons frequently develop decreased cortical oxygenation levels in the frontal lobes when assuming an upright posture, even in the absence of clinical symptoms of orthostasis [69]. Both orthostatic hypotension and postprandial hypotension are associated with cognitive abnormalities and white matter lesions that disrupt frontal-subcortical circuitry [55,67,84].

4. Subcortical ischemic microangiopathy: the most common cause of frontal-subcortical dysfunction in aging?

Vascular disease may be the most common pathway to frontal-subcortical dysfunction in aging. The sheer volume of the frontal lobes, nearly 30% of total cerebral volume, suggests that vascular lesions are likely to affect the integrity of frontal-subcortical circuits. Much of this tissue lies at the boundaries of large vessel perfusion territories and represents the "watershed" regions of cerebral circulation.

4.1 Defining subcortical ischemic microangiopathy (SCIM)

Magnetic resonance imaging (MRI) is well suited to the detection of subcortical microangiopathic changes because

of its excellent resolution and clear distinction between the gray and white matter. A common finding in elderly people is the appearance of incidental T2-weighted hyperintensities in the subcortical white matter (both periventricular and centrum semiovale). Many patients with extensive white matter changes also have lesions in the basal ganglia and thalamus that often correspond to "silent" lacunar infarction. However, not all white matter or gray nuclei hyperintensities represent silent cerebral infarction; some lesions are actually dilated Virchow-Robin spaces (so-called état criblé). The distinction between silent infarction and état criblé may be possible based on radiographic characteristics of size and shape [120].

The term "leukoaraiosis" was introduced to describe these radiographic abnormalities of periventricular and deep white matter [46]. Unfortunately, "leukoaraiosis" is often loosely used to describe a variety of pathologic entities with both different risk factors and clinical manifestations [70]. For simplicity, we refer to both white matter changes and silent lacunar infarctions as subcortical ischemic microangiopathy (SCIM).

4.2. Pathophysiology of SCIM

The presence of white matter lesions indicates damage to myelin but is not specific to any one particular pathophysiologic process. Several etiologies including toxic, metabolic, infectious, and degenerative conditions can lead to the presence of hyperintense lesions on T2 weighted MRI scans [33,126]. However, in most elderly patients, white matter lesions are strongly correlated with cardiovascular disease and are likely the result of cerebral ischemia [82].

Both focal and diffuse forms of white matter disease can exist either alone, or in combination. Generally, focal white matter lesions represent completed lacunar infarcts, usually as the result of obstruction of small subcortical arterioles secondary to hypertensive and arteriosclerotic changes. Other common sites of lacunar infarction include the thalamus, basal ganglia, internal capsule, and brain stem [34]. Diffuse white matter changes usually occur in the periventricular regions. They are likely caused by brief periods of hypoperfusion with resultant diminished oxygen delivery that is insufficient to cause necrosis [83,82]. Oligodendroglial cells are known to be quite sensitive to ischemia [85] resulting in so-called "incomplete infarction" [83]. Several pathologic studies reveal that most age-related white matter lesions are due to diffuse areas of demyelination [31,121]. This represents the histologic correlate of periventricular T-2 weighted MRI hyperintensities commonly observed in elderly patients at risk for cerebrovascular disease.

4.3 Epidemiologic studies of SCIM

Results from two large community based studies suggest that unsuspected cerebral infarction involving the deep small vessels is common. In the Cardiovascular Health Study (CHS), the prevalence of silent lacunar infarction found on MRI was 28% among 3660 persons ages 65 and older [86]. Again in a MRI study, investigators from the Atherosclerosis Risk in Communities Study (ARIC), reported similar findings with a 15% prevalence of silent lacunar infarction among a community based sample of 1890 people ages 55 to72 years [12]. One autopsy study of community-dwelling elderly Japanese residents reported similar prevalence estimates using pathologic criteria to identify silent lacunar infartion [111]. More recently, a study from Rotterdam involving 1077 subjects, ages 60–90 years, found that lesions within the deep subcortical and periventricular white matter were common, with a tendency for age-related increases in both prevalence and severity [23]. In this community based sample, only 5% of the participants were entirely free from white matter lesions at either site. A greater burden of frontal and periventricular white matter lesions was observed for women than men, despite adjustment for hypertension, diabetes, and low ankle-brachial index, leading the authors to suggest this may underlie a higher incidence of dementia observed among women during later life [23].

4.4. Newly identified risk factors for SCIM

In addition to conventional cardiovascular risk factors such as age, hypertension, and diabetes, potential risk factors for the development of white matter lesions (WMLs) might include: increased plasma homocysteine [30], decreased serum tryptophan [132] and low serum antioxidant levels [109], hyperinsulinemia [133], and hyperfibrinogenemia [109].

The role of genetics in the development of age-related white matter lesions is an area worthy of future research. Inherited forms of non-hypertensive cerebral microangiopathy, including Cerebral Autosomal Dominant and Subcortical Ischemic Leukoencephalopathy (CADASIL), have provided a useful model for understanding the influence of genetics on subcortical microangiopathy. This syndrome presents at a relatively young age with many features of premature frontal-subcortical dysfunction, including early dementia, gait disturbance, and urinary dysfunction and has been linked to a specific genetic defect on the Notch 3 gene of chromosome 19 [127]. In the Austrian Stroke Prevention Study, genetic factors accounted for as much as 73% of interindividual differences in total volume of white matter hyperintensities [108]. Racial variation may also be important. In the ARIC study, African-Americans were more likely to have severe microangiopathic changes on MRI scans compared to whites, though the high prevalence of hypertension found in African-American's might account for this finding [60]. Epidemiologic studies reveal that African-Americans are particularly susceptible to small vessel stroke [41]. It is tempting to speculate whether genetic and ethnic differences in susceptibility to occult microvascular

damage could account for variation in the vulnerability to late life geriatric syndromes.

4.5. How does SCIM cause frontal-subcortical dysfunction?

Because frontal white matter is heavily connected to subcortical regions, diffuse white matter disease may preferentially affect attention, frontal lobe function, and affect, while leaving language relatively unaffected [33]. Long cortico-cortico connections between frontal cortex and the posterior parietal cortex are also important for both executive functions and working memory [71]. A study examining electroencephalographic (EEG) coherence, a purported measure of shared electrical activity between cerebral regions, demonstrated that EEG coherence was lower in patients with periventricular white matter lesions (PVWMLs) compared to those free from PVWMLs. These lesions may disrupt connectivity along white matter fiber tracts traversing the periventricular region [59].

Frontal-subcortical dysfunction may also be caused by diaschisis; the phenomena by which remote lesions in one part of the brain cause metabolic effects at a distant site [4,72]. This is exemplified by patients with vascular dementia due to basal ganglia and thalamic infarcts that demonstrate severe frontal cortical hypometabolism on PET scan but have no frontal lobe structural abnormalities [90,119]. White matter tracts connecting frontal-subcortical regions are critical to the functional connectivity of the five circuits. Reciprocity may exist between different points along frontal-subcortical circuits. Just as basal ganglia and thalamic lesions can cause frontal cortical hypoperfusion; subcortical white matter lesions have been reported to cause hypoperfusion deep within the basal ganglia [47].

5. Clinical implications of SCIM for the geriatric patient

It is clear that the small and often occult cerebrovascular lesions that we define as SCIM are not clinically "silent" as once believed. This is particularly true given that these lesions appear frequently associated with the common functional problems that characterize the phenotype of aging. The link to each of these functional problems is discussed below.

5.1 Vascular dementia & cognitive impairment

Population based epidemiologic studies implicate vascular dementia as the second most common cause of dementia in western nations, and the most common cause in Asian countries [37]. Curiously, vascular dementia appears to be relatively uncommon in referral-based memory disorders clinics [77], though one community-based study suggested that vascular dementia is more common than Alzheimer's disease in the "oldest" old [114]. Operational definitions of dementia are based on a paradigm similar to Alzheimer's disease, requiring an amnestic syndrome as the predominant cognitive abnormality along with impairment in activities of daily living. However, an amnestic syndrome is not a major feature of vascular dementia until the degree of cerebral pathology is very advanced.

Further complicating the diagnosis of vascular dementia is the fact that cerebrovascular pathology frequently coexists with Alzheimer's disease and may present in a similar insidious fashion. Moreover, it has recently been shown that basal ganglia and thalamic lacunar infarcts, again often silent, may profoundly modulate the clinical expression of Alzheimer's disease [115]. Even in those without co-existing Alzheimer's pathology, several different pathophysiologic mechanisms including, large vessel or embolic cortical stroke, hemorrhage, strategic infarcts, Binswanger's disease, multiple lacunes, or any combination can prompt a diagnosis of vascular dementia [80]. There is no reason to suspect that only one neuropsychological profile could capture these differences in underlying pathologies.

Vascular dementia based on small vessel disease, including combinations of lacunes and white matter lesions is the most common subtype of vascular dementia [94]. Many of the features typical in mild forms of small vessel dementia are reminiscent of the cognitive profile seen with aging. Most studies suggest that patients with subcortical vascular dementia are more impaired on frontal-executive tasks as compared to memory, specifically free recall, as recognition or cued memory is often well-preserved [63]. Unfortunately, most brief cognitive screening instruments emphasize domains mostly associated with posterior cortical functions, and lack any significant measure of executive function [96,101].

As vascular dementia probably represents a late stage of cerebrovascular disease, early identification of mild degrees of cognitive impairment due to vascular disease becomes critical. In fact, considering the number of exposed persons, milder forms of cognitive impairment from vascular causes are potentially an enormous public health concern. Most of the major risk factors for cerebrovascular disease including hypertension and diabetes [29,54] are themselves associated with cognitive decline. Though the mechanisms are not entirely understood, the development of subcortical vascular changes is felt to play a significant role [129]. The transition from risk factor to cognitive decline may occur early as even subclinical markers of vascular disease have recently been associated with lower performance on a broad range of neuropsychological measures [107].

In the CHS, individuals with silent lacunar infarcts performed worse on the digit symbol test, a measure of psychomotor speed and attention [86]. In the Rotterdam Scan Study [22], the investigators attempted to further examine the effect of location of white matter lesions on cognitive function. Among 1077 non-demented elderly men and women, those with the most severe periventricular WMLs

Table 3
Geriatric syndromes related to subcortical ischemic microangiopathy

Clinical condition	Features
Cognition	Executive dysfunction, psychomotor slowing, poor retrieval
Gait	Disequilibrium, postural instability, slow gait speed, falls
Mood	Depression, apathy, disinhibition
Urinary function	Detrusor hyperactivity, urgency, incontinence

scored nearly 1SD below the mean on tests of psychomotor speed, while tests of global cognitive function and memory were less affected. Subcortical WMLs did not appear to significantly contribute to cognitive impairment when analyzed conditionally on the presence of periventricular WMLs. This is consistent with the influence that periventricular WMLs may exert on long cortico-cortico and frontal-subcortical connections involved in tasks of working memory, speed of cognitive processing, and executive function. Episodic memory, dependent on medial temporal lobe structures would not be expected to show substantial changes.

Though the cognitive deficits associated with SCIM are usually not severe enough to warrant a diagnosis of dementia, they may nonetheless be devastating and lead to decreased quality of life. Because frontal-executive skills involve planning, sequencing, organization, and mental flexibility, it is not surprising that executive dysfunction might predict a person's ability to live independently. In fact, several recent studies have found impairments in frontal-executive skills to be more closely related to decline in instrumental activities of daily living than memory deficits [13,97–99]. These findings imply that cardiovascular and other risk factors for SCIM might be a significant, preventable, and potentially reversible cause for loss of independence among elderly persons. Several non-cognitive consequences of SCIM may further contribute to conditions that frequently affect the quality of life of older persons (Table 3).

5.2. Mood disorders

Late-life affective disorders may be related to microvascular changes in elderly patients [38,92]. Neuroimaging studies commonly demonstrate lesions in both the subcortical white matter [21] and deep nuclei [118] in late-life depression. These findings linking cerebral microvascular disease to late-onset depression has lead to the development of a "Vascular Depression Hypothesis" [1]. Subcortical vascular changes in depressed elderly patients are associated with executive cognitive impairment [58], poor response to both antidepressants [113] and electroconvulsive therapy [117], and greater risk for dementia and death [81, 125].

Cerebral blood flow studies in late life depression have usually shown evidence for frontal hypoperfusion [116]. Similarly, evidence suggests that mania, and disinhibition syndromes, both of which are related to abnormalities of orbitofrontal circuits, may be associated with microangiopathic changes [112]. Location of the lesions may play a critical role. A recent study identified a specific association between orbitofrontal WMLs and late-onset depression [64].

5.3. Mobility and balance

Extrapyramidal findings are surprisingly prevalent among community-dwelling elderly persons; approximately 1/3rd of persons $>$ 85yrs demonstrate bradykinesia, and more than half show evidence of gait disturbance [5]. This may relate to medication use (drugs with anti-dopaminergic properties), or subclinical movement disorders, although white matter lesions and basal ganglia lacunes are likely to contribute. In the CHS, silent infarctions of the basal ganglia were associated with lower extremity weakness and diminished fine motor performance [86]. In another study of more than 700 community-dwelling participants from the CHS, white matter disease was associated with worse performance on tests of balance using both clinical and dynamic posturography measures [123].

Several case-control studies have demonstrated a higher proportion of ischemic white matter lesions in patients with balance abnormalities. Using quantitative MRI, investigators [44] grouped older individuals into those with normal and impaired mobility based on performance on the Short Test of Physical Performance Battery [43]. The balance-impaired group had an average volume of white matter signal abnormalities that was nearly double that of controls. An earlier case-control study of 29 persons $>$ 75 years with disequilibrium of unknown cause revealed significantly more severe subcortical white matter lesions among cases than age-matched controls [50].

Because of the close proximity of frontal-subcortical circuits that control both motor and cognitive functions, it is not surprising that small vascular lesions may simultaneously cause dysfunction in both systems. In a prospective study of 85 healthy individuals aged $>$ 65 years, who were followed up to three years, the strongest predictor separating those who developed mild cognitive decline from those who remained cognitively normal, was performance on both a finger tapping test and a slower 30ft. timed walk [14]. The same authors also reported that in healthy elderly men, periventricular white matter lesions were strongly associated with time to walk 30 feet and number of steps, suggesting early gait dysfunction [15]. SCIM is likely a significant factor in gait and balance abnormalities that are associated with loss of function and independence among elderly persons.

5.4. Urinary incontinence

Frontal-subcortical dysfunction may also play an underappreciated role in the pathophysiology of urinary symptoms commonly encountered by elderly people. Neuroimaging studies have revealed that micturition disturbances are more common in stroke patients with lesions that involve the frontal lobes [104]. In addition, urinary complaints are common in Binswanger's disease and may precede cognitive impairment by up to five years [56]. In elderly persons with urge incontinence and irritative voiding symptoms such as urgency and frequency, detrusor hyperreflexia is likely to be the underlying urodynamic abnormality [91]. Lesions in the medial frontal lobes and basal ganglia may reduce inhibitory input to the micturition reflex pathway and elicit detrusor hyperreflexia [20].

Lesions need not be large, as small silent vascular lesions can contribute to urinary symptoms. In a MRI study of 43 men $>$ 60 years who complained of irritative voiding symptoms, those who displayed detrusor hyperreflexia on urodynamic testing were more likely to have concurrent unsuspected lesions of the basal ganglia (83%) than in those without detrusor hyperreflexia (35%) [53]. Another case-control study [122] showed that elderly subjects with white matter lesions were also likely to have both gait disturbance and incontinence. Recently it was determined that urge, but not other types of incontinence, was associated with falls in a group of elderly women [11]. White matter lesions accompanied by frontal-subcortical motor and balance abnormalities might be a contributing factor [131].

6. Areas for future research and present opportunities

We have presented substantial evidence for an association between age-related frontal-subcortical changes, ischemic microangiopathy, and several geriatric syndromes. Yet, despite this, it remains difficult to predict which individual patients will ultimately develop these syndromes. There are reports of patients with extensive white matter changes who seem to display no adverse effects [32]. It has been suggested that white matter lesions detected by computerized tomography, which is less sensitive than MRI, are more likely to be associated with clinical findings [75]. The relationship between subcortical vascular lesions and clinical syndromes is unlikely to be explained by a simple linear, or even dose related model, though some have suggested a critical threshold of lesion volume must be reached before resulting in clinical manifestations [10]. Recent reports point to location as a key factor [22,64]. Still, others suggest that neither lesion burden nor location is important, but rather the degree of cortical hypometabolism caused by the underlying subcortical lesion correlates most closely with clinical findings such as cognition [90,102]. While awaiting further clarification of the precise determinants, efforts aimed at preventing cerebral microangiopathic damage seem well worthwhile.

6.1. Prevention of SCIM should begin early

Since the time required to transition from cardiovascular risk factor to ischemic cerebral microangiopathy is relatively long, the best time to intervene may be in middle age.

Recently, investigators from Rotterdam reported an association between midlife atherosclerosis, detected by linear aortic calcifications on abdominal radiographs, and periventricular white matter lesions in late life [24]. Subjects with aortic abdominal calcification were more than twice as likely to display severe grades of periventricular hyperintensities 20 years later. A study of identical elderly male twins showed the most significant determinants of late life white matter lesions were: levels of glucose, high-density lipoprotein cholesterol, and systolic blood pressure in midlife [16]. Within pairs of male twins, differences in tests of cognitive and physical function, as well as self-report of depression, were significantly associated with an individual's total volume of white matter hyperintensitites.

Within the range of blood pressure generally considered normal, levels within the "higher" range of normal may increase the risk for both white and gray matter lesions. This was demonstrated in a study of 144 very healthy individuals aged 55–79 years in which 24-h ambulatory monitoring revealed that participants who displayed higher daytime and nocturnal blood pressures were at greater risk for having more severe grades of white and gray matter lesions [39]. It is noteworthy that the average blood pressure for the entire group was only 120/72 mm Hg and worrisome that among those with severe white and gray matter lesions, systolic blood pressure was typically less than 130 mm Hg. These studies suggest that midlife cardiovascular risk factors play an important role in determining cerebral function in late life, a point emphasized in a recent editorial by asking, "Can we save the brain from the ravages of midlife cardiovascular risk factors?" [40].

6.2. Identification of frontal-subcortical cognitive deficits in vascular patients

Because SCIM is most likely to cause cognitive changes in frontal-executive systems, new approaches to screening for cognitive impairment in primary care settings are needed [18,94]. Commonly used screening instruments such as the Folstein Mini-Mental Status Exam [36] lack significant measures of executive control functions [101]. Although some authors have developed brief frontal-executive inventories, these are not presently in widespread use [27,65, 100]. Because cognitive impairment associated with vascular risk factors preferentially involves executive control functions, affected patients may not have the cognitive skills needed to follow aggressive risk reduction strategies.

Today's treatments for cardiovascular risk modification

involve the management of multiple medications, dietary and lifestyle changes, self-monitoring of responses, and frequent follow-up. A patient with executive dysfunction from vascular disease might not be able to perform these complex tasks. In turn, this may set up a viscious cycle in which vascular disease leads to executive cognitive impairment that further makes it difficult to comply and adhere to changes required to manage vascular risk. Instead of being recognized as having a dysexecutive syndrome, these patients are often labeled as non-compliant, stubborn, or unmotivated. Some are probably apathetic because of frontal-subcortical dysfunction rather than lazy or unmotivated. Identifying patients with dysexecutive syndromes is of great clinical importance as they are likely to require a unique approach to care planning [35,42].

7. Conclusion

As we have shown, many phenotypic features of aging may be related to frontal- subcortical dysfunction. Features of the common geriatric syndromes that lead to disability may in fact be related to the influence these circuits have over cognitive, motor, affective, and urinary function. Aging itself seems to preferentially involve frontal-subcortical regions. In addition, subcortical ischemic microangiopathy is exceedingly common among older individuals and has its greatest impact on these same frontal-subcortical circuits. Since SCIM is potentially preventable, well-established therapies to prevent cardiovascular disease in midlife might have a great impact on future disability and quality of life for the next generation of elderly persons.

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