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Review Article

Cerebral White Matter Changes and Geriatric Syndromes: Is There a Link?

Hsu-Ko Kuo[1,2,3,4] and Lewis A. Lipsitz[1,2,3]

[1]Hebrew Rehabilitation Center for Aged, Boston, Massachusetts.[2]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts.[3]Division of Aging, Harvard Medical School, Boston, Massachusetts.
[4]Department of Internal Medicine, National Taiwan University Hospital, Taipei.

Cerebral white matter lesions (WMLs), also called "leukoaraiosis," are common neuroradiological findings in elderly people. WMLs are often located at periventricular and subcortical areas and manifest as hyperintensities in magnetic resonance imaging. Recent studies suggest that cardiovascular risk factors are associated with the development of WMLs. These lesions are associated with different geriatric syndromes such as falls, executive cognitive impairment, depressive symptoms, and urinary incontinence. Damage to associative pathways in frontal and subcortical regions due to hypoperfusion may disrupt frontal executive, motor control, and other systems, resulting in these manifestations. WMLs are associated with substantial disability and should not be considered a benign and silent condition as once believed. Interventions addressing cardiovascular risk factors should be undertaken in early or mid-life in order to prevent late-life functional impairment associated with WMLs. After these lesions develop and impair executive cognitive functions, the patient's ability to comply with a complex risk reduction program may be significantly compromised.

THE improvement in imaging techniques of the brain during the past two decades has drawn attention to the occurrence of "silent" focal or diffuse lesions of the white matter among seemingly neurologically "normal" elderly patients. The white matter of the brain can be classified as subcortical, the area just under the cortex, and periventricular, the area adjoining the lateral ventricles. The term "leukoaraiosis" was introduced to describe the radiographic abnormalities of periventricular or subcortical white matter (1), without presumptions about etiology and neuropathology. Magnetic resonance imaging (MRI) of the brain in elderly people commonly shows incidental T2-weighted hyperintensities in the periventricular or subcortical areas, often reported as "white matter lesions" (WMLs). The extent of the WML may range from narrow rims or patchy subcortical areas to involvement of the entire white matter. The typical appearance of WMLs on MRI is illustrated in Figure 1.

Prevalence of WMLs

Recent epidemiological studies have reported a high prevalence of WMLs in the brains of elderly people. The Rotterdam Study is a population-based prospective follow-up study of the total population aged 55 years and older in the suburbs of Rotterdam, the Netherlands. This study has investigated determinants of chronic and disabling cardiovascular, neurological, locomotor, and ophthalmologic diseases in the older population. In a random sample from the Rotterdam Study population that consisted of 111 participants aged 65 to 84 years, the prevalence rate of WMLs was 27% (2). The prevalence and severity of WMLs increased with age. In addition, a history of stroke or myocardial infarction was significantly and independently associated with the presence of WMLs.

Another European population-based study, the Helsinki Aging Brain Study, examined randomly selected neurologically nondiseased participants aged from 55 to 95 years (mean, 71.5 years) and found a WML prevalence rate of 39% (3). Increased age, silent brain infarction, and central cerebral atrophy were also significantly associated with WMLs. The Cardiovascular Health Study, a large population-based cohort study, performed MRIs on elderly participants who were not institutionalized, wheelchair-bound, or under treatment for cancer from four United States communities, and found that WMLs were present in 87% of all participants and 83% of those without prior stroke (4). Increased age, hypertension, smoking, coronary heart disease, and myocardial infarction at baseline were also significantly associated with WMLs (5). Another community-based study conducted in the United States, the Atherosclerosis Risk in Communities Study, enrolled participants who were aged 55–72 years (mean, 62 years) and found an overall prevalence rate for WMLs of 86% (6). WMLs were also significantly associated with age, smoking, lower education, and hypertension.

Participants with psychiatric disorders such as depression or dementia have been reported to have a higher prevalence rate of WMLs than the general population (7). The European studies excluded participants with major psychiatric disorders while the American studies did not. This may explain why the prevalence rate of WMLs is higher in the American studies versus the European studies. Thus, WMLs are extremely common in elderly people and they increase in

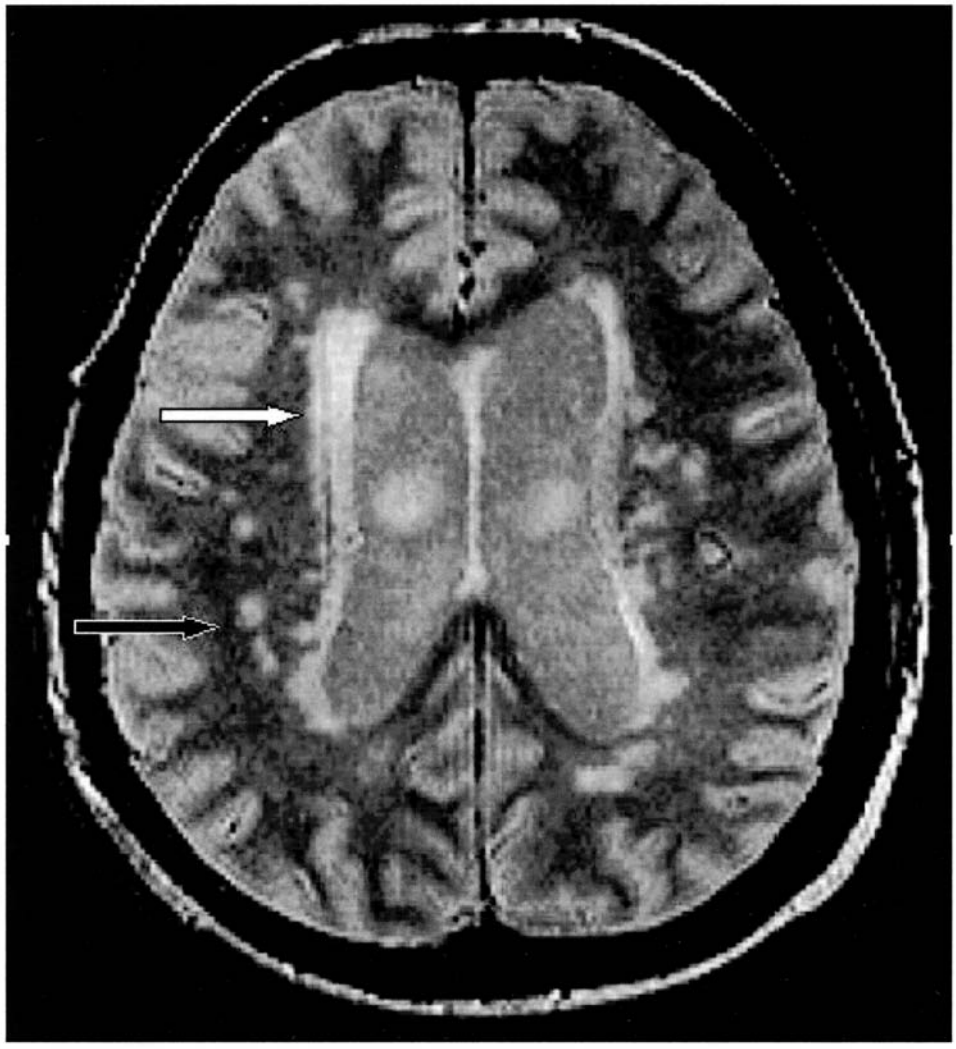

Figure 1. Typical appearance of cerebral white matter lesions shown in T2-weighted magnetic resonance imaging (MRI). Example of an MRI scan in an 81-year-old man with both periventricular (white arrow) and deep subcortical (black arrow) white matter lesions.

prevalence with age, cardiovascular risk factors, dementia, and depression.

Pathophysiology of WMLs

The presence of WMLs indicates damage to brain parenchyma but is not specific to any one particular pathophysiologic process. Several etiologies, including ischemic, inflammatory, toxic, metabolic, infectious, and degenerative conditions, can lead to the presence of hyperintense lesions on T2-weighted MRI scans (8,9). However, in most elderly patients, WMLs are strongly correlated with cardiovascular disease and are most likely the result of cerebral ischemia (10). WMLs are seen more frequently in patients with a history of stroke and in individuals with cognitive deterioration of presumed vascular origin (11,12). Also, persons with severe WMLs are at increased risk of developing stroke (13). The ischemic etiology of WMLs in elderly patients is further supported by the characteristic location of WMLs. Periventricular and subcortical white matter are located in arterial border zones (watershed areas) that are particularly susceptible to ischemic injury as a result of systemic or local decreases in cerebral blood flow. Furthermore, an elevation in cerebrospinal fluid glutamate concentration, which is considered to be the result of cerebral ischemia, has been reported in participants with leukoaraiosis (14,15), leading additional support to an ischemic origin of WMLs (16).

The notion that ischemia plays an important role in the pathogenesis of WMLs is also suggested by histological studies. Van Swieten and colleagues (17) examined 19 brain specimens and found a strong correlation between lesions of increased signal intensity in the white matter on T2 MRI and the presence of demyelination and astrocytic gliosis, which are typical changes of cerebral ischemia (18). Fazekas and others (19) found that punctate, early confluent, and confluent white matter hyperintensities corresponded to increasing severity of ischemic tissue damage, ranging from mild perivascular alteration to large areas with variable loss

of fibers, multiple small cavitations, and marked arteriolosclerosis. Taken together, all of these studies support the notion that WMLs in elderly people are due to cerebral hypoperfusion in watershed areas of the brain (10).

Risk Factors for WMLs

Age

Evidence from population-based cohort studies suggests that age is closely associated with cerebral WMLs (2,5,6). A ''dose–response relationship'' between age and severity of WMLs has been widely demonstrated. It is not clear whether age is an independent risk factor or whether the accumulation of cardiovascular risk factors with advancing age is the primary determinant.

Diabetes

Several population-based cross-sectional studies failed to demonstrate a significant association between diabetes and WMLs (2,4,6). However, a recent prospective study did demonstrate a relationship between diabetes and WMLs (20). Taylor and colleagues enrolled 117 community-dwelling elderly participants without neuropsychiatric disease and found that the mean volume of cerebral hyperintensities increased from a baseline of 4.91 cc to 6.42 cc, a mean increase of 26.7%, after 2 years of follow-up ($p < .0001$). The presence of diabetes was associated with greater change and was hence a predictor for progression of WMLs.

Hypertension

WMLs have been found by many investigators to be associated with hypertension. The Cardiovascular Health Study demonstrated cross-sectionally that both a diagnosis of hypertension at baseline and blood pressure measurements at physical examination were independently associated with the severity of WMLs (5). The Atherosclerosis Risk in Communities Study also concluded that hypertension is cross-sectionally associated with increased odds of WMLs. Moreover, treated but uncontrolled hypertensive participants had greater odds of WMLs than those with treated controlled hypertension (21). The causal inference between hypertension and WMLs was further established in several longitudinal follow-up studies. The Epidemiology of Vascular Ageing Study (22), a longitudinal study with 845 participants and 4 years of follow-up, concluded that hypertension is a major risk factor for severe WMLs. Treated hypertensive participants whose blood pressures were controlled had a reduced risk of developing severe WMLs. The Rotterdam Scan Study (23) followed 1077 participants aged 60 to 90 years from two prospective population-based cohorts and found that a 20-year duration of hypertension increased the risk of WMLs about 20-fold, especially among middle-aged individuals. Successful control of hypertension appears to reduce the risk of developing WMLs.

Atherosclerosis

Atherosclerosis has been shown to be associated with WMLs in a cross-sectional study (24) and a longitudinal follow-up study (25). Bots and colleagues, using a cross-sectional design, concluded that atherosclerosis, indicated by increased common carotid intima to media wall thickness (IMT), carotid plaques, and a lower ankle-to-arm systolic blood pressure ratio (ABI), is related to WMLs. The Zoetermeer Study, a substudy of the Rotterdam Scan Study with a mean follow-up of 19.6 years, found that the presence of aortic atherosclerosis during midlife was significantly associated with the presence of periventricular WMLs almost 20 years later (adjusted relative risk 2.4; 95% CI [confidence interval]1.2 to 5.0). Any therapeutic intervention should therefore take place at the early stages of atherosclerosis in order to prevent late life WMLs and related morbidity.

Hemodynamic Dysregulation

Impaired cerebral blood flow.—Fazekas and others (26) used the xenon-133 injection method to measure cerebral blood flow (CBF) and found that CBF was lower in participants with WMLs compared with those without. Using positron emission tomography (PET) and the oxygen-15 steady state technique, Meguro and colleagues (27) found that those with severe WMLs showed decreased CBF and a normal cerebral metabolic rate for oxygen, due to a compensatory increase in oxygen extraction fraction. In addition to global reduction in CBF, decreased regional CBF within WMLs has also been demonstrated by several studies. Oishi and colleagues (16), in a case-control study, used the stable xenon computed tomography (CT) method and found that CBF was significantly lower in the WML area in the WML group than in the same area in the control group. Marstrand and others (28), using magnetic resonance perfusion imaging, examined cerebral hemodynamics within the same participant. When comparing WMLs to normal white matter, a significantly lower CBF was present within WMLs ($p = .004$), making these areas more susceptible to ischemic injuries. Because these are cross-sectional studies, it is not clear whether decreased CBF is the cause of WMLs or the result of subcortical and periventricular tissue loss.

Blood pressure dysregulation.—Alterations in blood pressure regulation in elderly people might also contribute to the pathogenesis of WMLs. Matsubayashi and colleagues (29) studied 334 community-dwelling elderly adults aged 75 years and older and found that both postural hypotension and postural hypertension were closely related to WMLs. Those who had more advanced WMLs demonstrated exaggerated postural changes in blood pressure. Puisieux and colleagues (30) retrospectively reviewed CT scans and 24-hour ambulatory blood pressure monitorings of 79 elderly patients and found that higher leukoaraiosis scores were associated with increased blood pressure variability. In Binswangers patients with WMLs, Tohgi and colleagues (31) reported greater 24-hour within-participant systolic blood pressure standard deviations, and a larger difference between the maximum and minimum systolic blood pressures compared with normal controls. These studies suggest that blood pressure dysregulation may contribute to the pathogenesis of WMLs in elderly people.

Impaired cerebral vasomotor reactivity and autoregulation.—The maintenance of optimal cerebral perfusion for

brain metabolic activity depends not only on adequate resting blood flow, but also on an active autoregulatory process that can rapidly adjust vascular resistance in response to changes in metabolic demand or perfusion pressure. A variety of measures of cerebral vasoreactivity have been used to assess the integrity of CBF regulation. Isaka and colleagues (32), using a noninvasive xenon 133 clearance technique in resting participants and after the intravenous injection of acetazolamide, found that there was a decrease in vasodilatory capacity in the cerebral cortex of participants with WMLs. Bakker and colleagues (33), using transcranial Doppler to measure vasomotor reactivity to carbon dioxide, randomly selected 80 participants from the Rotterdam Scan Study and confirmed a strong association between impaired vasomotor reactivity and WMLs. These studies suggested that impaired cerebral autoregulatory processes may play an important role in the pathogenesis of WMLs. However, longitudinal studies are needed to exclude the possibility that WMLs themselves are responsible for alterations in cerebral autoregulation.

Genetic Factors

A recent study of elderly twins indicated that susceptibility to WMLs was largely determined by genetic factors (34). The identification of hereditary factors is important because the presence of WML is associated with several unfavorable outcomes such as stroke and cognitive impairment. This review will introduce some commonly studied genes in WMLs.

Notch3 gene.—Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, or CADASIL, is an autosomal dominant inherited disease characterized by an onset around 30–40 years of age, recurrent migraine headaches, ischemic strokes or transient ischemic attacks, mood disturbances, and finally cognitive decline and dementia (35). CADASIL is caused by missense point mutations in the Notch3 gene, which encodes a transmembrane receptor protein with an important signaling function during development (36). Cranial MRI of CADASIL patients often shows characteristic periventricular hyperintensities or deep white matter nodular hyperintensities, which are essentially identical to those seen in late life. Periventricular hyperintensities are so common—present in 96% of CADASIL patients—that their absence virtually excludes the diagnosis of CADASIL (37). The similarity of CADASIL to the symptoms and MRI findings of many elderly people suggests that there may be a genetic basis for WMLs in late life.

Apolipoprotein E (apoE) gene.—The apoE gene has been extensively studied because of its relationship to Alzheimer's disease and atherosclerosis. Given the fact that WMLs are associated with dementia and atherosclerosis, the relationship between the apoE genotype and WMLs has also been the focus of several studies. However, this relation is still controversial. A population-based study, the Austrian Stroke Prevention Study (38), enrolled community-dwelling individuals (aged 50–75 years) without neuropsychiatric disease and found several predictors for cerebral WMLs including age (OR 1.1 per year, 95% CI 1.05–1.18), hypertension (OR [odds ratio] 3.4, 95% CI 1.83–6.44), and the apoE ε2/ε3 genotype (OR 3.0, 95% CI 1.35–6.69). The apoE ε4 allele, however, was not associated with WMLs in this study. The finding that the apoE ε4 allele is not associated with WMLs is consistent with an earlier study performed with normal elders (39). A similar controversy exists regarding the association between the apoE genotype and WMLs in demented patients because some studies show a positive association, specifically between the apoE ε4 allele and the WML (40,41), but some do not (42–44). More research is needed in this area.

Angiotensin-converting enzyme (ACE) gene.—The ACE insertion/deletion (I/D) polymorphism is an important candidate gene in ischemic cerebrovascular disease. A recent meta-analysis by Staessen and colleagues (45) reported that the D allele of the ACE gene was associated with a high risk of atherosclerotic complications such as coronary heart disease, myocardial infarction, and stroke. Hassan and colleagues (46) enrolled 84 consecutive patients presenting with classic lacunar syndromes and found that the ACE DD genotype occurred more often in patients with leukoaraiosis than those without. A similar association was established in different patient populations, including patients with essential hypertension (47) or memory impairment (48).

Relationship Between Cerebral White Matter Changes and Selected Geriatric Syndromes

It is clear that the small and often occult cerebrovascular lesions that we label as ''leukoaraiosis'' or ''white matter lesions'' are not clinically ''silent'' as once believed. This is particularly true given that these lesions appear frequently associated with common functional problems that are seen with aging. The potential links to each of these functional problems are summarized in Figure 2.

Gait, Balance, and Falls

Gait abnormalities are common causes of falls and slow gait predicts future functional decline (49) and dementia (50). From 8% to 19% of noninstitutionalized older adults admit to walking difficulty or require the assistance of another person or special equipment to walk (51). The incidence of walking difficulty is as high as 40% in noninstitutionalized adults aged 85 and older; and among older nursing home residents, it reaches 60% or higher (51,52). Gait and balance disturbances may be due to identifiable causes such as medication use, bodily pain, sensory impairment, degenerative joint disease, acquired musculoskeletal deformities, stroke, and postural hypotension. However, a large proportion of gait and balance abnormalities remain incompletely understood. In several cross-sectional studies, WMLs have been reported to be associated with gait and balance disturbances. Briley and colleagues (53) enrolled 130 participants with head CT scans and found leukoaraiosis was linked to gait disturbance. In the absence of leukoaraiosis, 60% of patients had normal gait, 27% had mild gait disturbance, and 12% had moderate-to-severe gait disturbance. Whereas with leukoaraiosis, only 20% had normal gait, 31% had mild gait disturbance, and

24% had moderate-to-severe gait disturbance ($p < .001$). Using quantitative MRI, Guttmann and colleagues (54) grouped older individuals into those with normal and impaired mobility based on performance on the Short Physical Performance Battery (55). They concluded that white matter abnormalities were independently associated with impaired mobility in older persons. The balance-impaired group had an average volume of white matter signal abnormalities that was nearly double that of controls. In the Cardiovascular Health Study, WMLs were associated with lower extremity weakness, balance disturbance, diminished walking speed, and impaired fine motor performance (5). Inability to balance, measured by a single-leg balance ability test (56), has been shown to be associated with WMLs (57).

The association between gait and balance abnormalities and WMLs is further strengthened by several prospective follow-up studies. Baloh and colleagues (58) followed 59 normal elderly participants aged 75 years and older for a minimum of 8 years (range, 8–10 years). They found that WML were highly correlated with changes in gait and balance. Whitman and colleagues (59) studied 81 participants with normal gait and balance on study entry who underwent 2 brain MRI studies over a mean of 4 years. They found that participants who experienced greater than 4-point declines in Tinetti Gait and Balance scores had a significant increase in volume of cerebral WMLs.

Direct evidence for an association between WMLs and falls is scarce, but can be inferred from the multitude of studies showing associations between WML and gait/balance disturbances (5,53,54). Also, as reviewed above, WML have been shown to be related to orthostatic hypotension, impaired CBF autoregulation and decreased CBF, all of which may result in inadequate cerebral perfusion, falls, and syncope. A cross-sectional study published in Japanese (60) found that the propensity for falling was associated with the volume of frontal periventricular hyperintensity in neurologically normal elders. In the Cardiovascular Health Study, cerebral WMLs were shown to be related to frequent falls within 1 year (5). Briley and colleagues followed a cohort of 218 veterans for a median of 14 months (61). They found that leukoaraiosis predicted fall-related fractures and hospitalization, with a hazard ratio of 6.8 ($p = .013$).

Whether WMLs identified on CT or MRI are a direct cause of gait and balance abnormalities or simply a marker of the aging effects on gait and balance cannot be answered by these studies. WMLs may interrupt frontal lobe circuits responsible for normal gait and balance or they may interfere with long loop reflexes mediated by deep white matter sensory and motor tracts (62). In addition, the periventricular and subcortical distribution of WMLs could interrupt the descending motor fibers arising from medial cortical areas, which are important for lower extremity motor control (58).

Cognitive Impairment

There is considerable evidence from cross-sectional studies of an association between cerebral WMLs and cognitive impairment in both demented and nondemented elderly participants. The Cardiovascular Health Study found an inverse relationship between WML grades and Mini-Mental Sate Examination (MMSE) scores. In the Rotterdam Scan Study (63), participants with the most severe periventricular WMLs performed more than 0.5 *SD* (standard deviation) below average on measures of global cognitive function. Matsubayashi and coworkers (64) found a similar relation only if they neglected the small WML. Skoog and others (65) found that WMLs were strongly associated with lower score in global cognitive tests in both demented and nondemented patients. A potential problem with tests of global cognitive function such as the MMSE is their focus on cortical functions such as memory, rather than on subcortical dysfunction such as executive function (66). This may make the MMSE insensitive for the detection of early or mild WMLs. Some investigators advocate a threshold effect for WMLs: a substantial number of WMLs needs to be present to have a measurable effect on the MMSE score (67).

WMLs are believed to affect fibers connecting the frontal cortex and subcortical structures, which are responsible for executive functions, including volition, planning, purposive action, and multitask performance. Components of executive functions include attention and speed of mental processing and planning and strategic reasoning. In the Cardiovascular Health Study (5), grades of cerebral WMLs were inversely associated with performance on the Digit-Symbol Substitution Test, a measure of psychomotor speed and attention. In the Rotterdam Scan Study (63), participants with the most severe periventricular WMLs performed nearly 1 *SD* below average on tests of psychomotor speed.

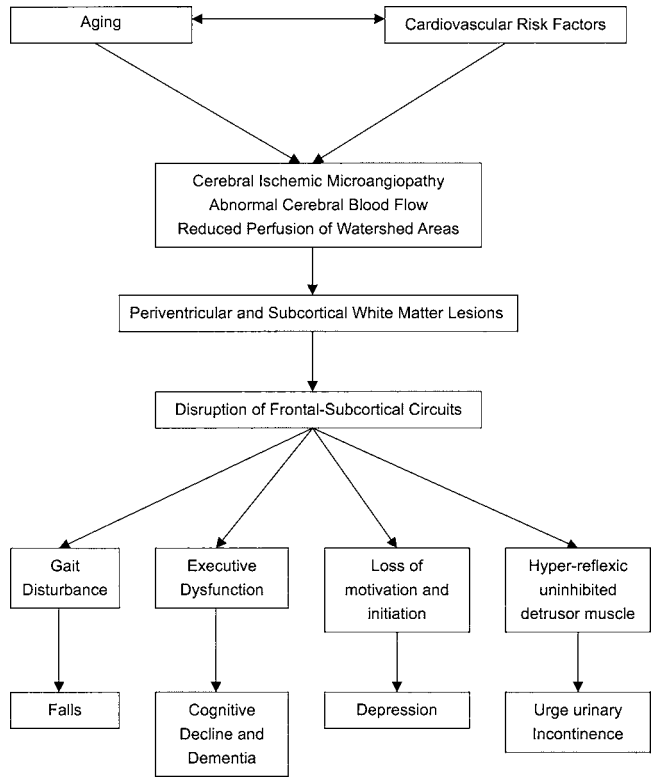

Figure 2. Pathophysiology of cerebral white matter lesions and their relationship to different geriatric syndromes.

A causal inference between cerebral WMLs and cognitive impairment can be made on the basis of several prospective longitudinal studies. Garde and colleagues (68) evaluated a healthy nondemented cohort born in 1914 and found that both periventricular and subcortical WMLs were significantly associated with intelligence decline (measured in Wechsler adult intelligence scale) from age 50 years to age 80 years (bivariate correlation coefficients 0.32, $p = .0087$, and 0.28, $p = .0227$, respectively). Investigators in the Rotterdam Scan Study examined the relation between severity of cerebral WMLs and cognitive decline over an approximately 10-year period in 563 elderly nondemented participants (69). They found that participants with severe periventricular WMLs experienced cognitive decline nearly three times as fast (0.28 MMSE points/year [95% CI, 0.20–0.36]) as the average (0.10 points/year [95% CI, 0.09–0.11]) for the total study population. There was no independent relationship between severity of subcortical WMLs and rate of cognitive decline. They concluded that severity of periventricular, but not subcortical, WML was related to the rate of cognitive decline.

Depression

Between 1% and 2% of elderly persons suffer from major depression (70). However, the prevalence of depressive symptoms that do not meet criteria for a clinical diagnosis of major depression is high in elderly people; the average prevalence is 13.5% (71). When a first depressive episode occurs in late life, a cerebrovascular cause may be more common than genetic or psychological causes (72,73). The concept that cerebrovascular disease may be a risk factor for depression has been suggested by studies showing an association between cardiovascular conditions such as hypertension and transient ischemic attacks, and depression (74). Neuroimaging studies in patients with late life depression commonly demonstrate lesions in both the subcortical white matter and deep nuclei. De Groot and colleagues (75) investigated the relation between WMLs and depression in the population of the Rotterdam Scan Study. They found that the presence as well as severity of WMLs, especially in subcortical white matter, is related to the presence of depressive symptoms. O'Brien and colleagues (76) found that deep white matter lesions were significantly more common in depressed participants and periventricular lesions were more common in Alzheimer's disease participants compared with controls. Another MRI study showed that participants with depression had smaller frontal lobe volume (7% less) and had a higher frequency of subcortical white matter hyperintensity (odds ratio 5.32, 95% CI 1.14–24.88) compared with controls (77).

WMLs are not only associated with depression, but their presence also indicates a poor outcome of depression. O'Brien and colleagues (78) followed 60 depressed participants for a mean of 31.9 months. They demonstrated that severe deep WMLs are associated with chronicity and relapse of depression. Subcortical changes in depressed elderly patients are also associated with poor response to therapy, such as antidepressants (79) and electroconvulsive therapy (80).

Dysfunction of frontostriatal neural systems and their limbic and hippocampal connections may contribute to depression (81). WMLs of older people with depression are most prominent in frontal subcortical areas, and thus basal ganglia and their frontal and limbic connections are affected. This may be the neuroanatomical basis for the relation between WMLs and depression.

Urinary Incontinence

Urinary complaints are common in elderly people with WMLs and silent vascular lesions on imaging. In a retrospective study by Kotsoris and others (82), urinary disturbances were found in 50% of patients with multiinfarct vascular dementia and preceded cognitive impairment by up to 5 years. A case-control study done in Finland (83) showed that elderly participants with leukoaraiosis were more likely to have urinary incontinence than age-matched participants without WMLs. Another study of 63 elderly participants with different grades of leukoaraiosis (84) showed that participants with grade 1–4 WMLs had detrusor hyperreflexia more commonly (82%) than those with grade 0 WMLs (9%) ($p < .05$). Therefore, leukoaraiosis appears to be associated with geriatric urinary dysfunction, particularly urge urinary incontinence. This association is plausible because lesions in frontal subcortical regions of the brain are involved in the inhibition of reflex detrusor contractions (85). Loss of neural connections from this area may result in a hyperreflexic uninhibited bladder and urge incontinence.

Opportunities for Prevention

Efforts aimed toward preventing damage from WMLs seem worthwhile based on their correlation to many clinically important outcomes. Recently, investigators from the Rotterdam Scan Study suggested that effective treatment of hypertension may prevent the development of WMLs (23). In a study of 74 elderly male monozygotic twins, the National Heart, Lung, and Blood Institute Twin Study (86), midlife cardiovascular risk factors such as glucose levels, high-density lipoprotein cholesterol, systolic blood pressure, and lifetime health practices were predictive of WMLs in old age. Although no randomized controlled trials of risk factor reduction have examined WMLs as an outcome, it is reasonable to aggressively manage cardiovascular risk factors in midlife to prevent WMLs as well as other cardiovascular events in later life.

Frontal–subcortical circuits are a series of pathways that interconnect various regions of the frontal lobes to subcortical structures. The circuits are responsible for executive functions and are often interrupted by development of WMLs. Ironically, executive functions, including multitasking, planning, and organizing, are essential for cardiovascular risk modification, which involves management of multiple medications, dietary and lifestyle changes, self-monitoring of responses, and frequent follow-up. Therefore, clinicians should learn to recognize signs of executive dysfunction including problems with: Stopping, Starting, Switching, Socialization, Planning, and Judgment. Examples of these abnormalities are shown in Table 1.

In elderly participants with cardiovascular risk factors, executive function should be tested. Commonly used cognitive screening instruments such as the MMSE lack sensitive measures of executive functions. Some tests such as

Table 1. Behavior Signs of Executive Dysfunction

Problems	Examples
Stopping	Disinhibited behaviors, such as blurting out socially inappropriate remarks; frontal release signs, such as the grasp and palmomental reflex
Starting	Lack of spontaneous retrieval of previously learned information; needing repeated reminder and monitoring for treatment plans; problems with initiation; lack of motivation; unable to maintain effortful behavior; mutism as most extreme example
Switching	Lack of mental flexibility; unable to change strategies for solving problems; difficulty in switching habitual behavior such as diet and lifestyle; self-management difficulty when there is a change in medical regimen such as dosage and schedule
Socialization	Poor interpretation of social cues; difficulties in socializing due to lack of motivation, personality changes, or uninhibited behaviors
Planning	Inability of volition, multitasking, and organizing; unable to manage polypharmacy and complex dosing regimen; unable to be compliant to suggestions from health care providers; ''stubborn'' or ''uncooperative'' patients not complaint with treatment advice
Judgment	Failure to anticipate consequences of behavior such as being unable to self-monitor blood sugar and becoming hypoglycemic; unable to identify signs of medication adverse effects

the executive Clock-Drawing Test (87–89), Trail-Making Test (90), or word list generation are easily administered and useful in identifying subtle executive dysfunction. If executive dysfunction is identified, instead of labeling patients as noncompliant and uncooperative, therapy should be simplified and prescribed in a clearly documented step-by-step fashion in order to achieve best possible outcomes.

Prospective studies suggest that WMLs and their associated outcomes are slowly progressive (91,92); 29% and 31.5% of patients with leukoaraiosis show evidence of deterioration after 3.2 and 6.4 years of follow-up, respectively (93,94). Beyond the preventive strategies mentioned above, WMLs may be a target for innovative therapies intended to improve functional recovery. Two recent animal studies have examined novel approaches to functional recovery in rats after experimental ischemia. Chen and colleagues (95) tested inosine, which promotes axon sprouting in vitro, and showed improvements in several behavior measures. Papadopoulos and others (96) used the monoclonal antibody, IN-1, which blocks the myelin-associated neurite inhibitory factor, NOGO, and showed functional recovery on a forelimb-reaching task in adult rats. In both cases, the experimental drugs seemed to promote recovery of behavioral function following experimental stroke.

Prevention of WMLs might be achieved through improving cerebral blood flow (26,27). Nitric oxide, a product of nitric oxide synthase activity, relaxes vascular smooth muscle and elevates cerebral blood flow. The endothelial isoform (eNOS) is constitutively expressed in cerebrovascular endothelium. Upregulation of eNOS gene expression and subsequent increase in cerebral blood flow has been demonstrated after adenoviral gene transfer in an animal model (97) and after statin treatment in humans (98). Whether cerebral blood flow elevation by these different interventions can prevent WMLs or improve symptoms is a topic for future research.

Conclusion

Leukoaraiosis, or cerebral white matter lesions, are common radiological findings in elderly people. More than half of all elderly people have some degree of cerebral white matter abnormalities. Common geriatric syndromes such as cognitive impairment, gait disturbance, depression, and urinary incontinence have been shown to be closely associated with WMLs. WMLs can no longer be considered an incidental, insignificant finding.

Leukoaraiosis has many risk factors including age, hypertension, diabetes, atherosclerosis, and the Notch3 gene mutation. We may be able to prevent late-life disability and functional impairment by treating modifiable cardiovascular disease risk factors that lead to periventricular and subcortical white matter damage.

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Address correspondence to Lewis A. Lipsitz, MD, Hebrew Rehabilitation Center for Aged, 1200 Centre Street, Boston, MA 02131. E-mail: lipsitz@mail.hrca.harvard.edu

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