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Subcortical Ischemic Vascular Dementia (SIVD)

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Abstract

Subcortical ischemic vascular dementia (SIVD) has been proposed as a subtype of vascular cognitive impairment (VCI). The syndrome is defined clinically by cognitive impairment and evidence of subcortical vascular brain injury, including lacunar infarcts and deep white matter changes. SIVD has been traditionally recognized as lacunar state, strategic infarct dementia, and Binswanger syndrome, but these clinical syndromes represent the tip of the iceberg. Proton density magnetic resonance (MRI) often discloses “silent” hyperintensities in 20–40% of community dwelling elderly. Efforts to relate MRI-measured lacunes and white matter changes to cognitive impairment have not been straightforward. The hidden possibility that concomitant Alzheimer disease pathology contributes significantly to cognitive impairment increases with age. Nonetheless, new knowledge is being gained from longitudinal MRI and systematic neuropathological studies. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a rare genetic disorder, provides an opportunity to study pure SIVD in the absence of AD. Dysexecutive syndrome characterized by slowing of mental processing speed, decreased working memory, and impairment of abstract reasoning are associated with lacunes and deep white matter changes. But data related to sensitivity and specificity which would support dysexecutive syndrome as diagnostic criteria are limited. Hypertension, by far the leading risk factor for sporadic SIVD, is eminently treatable. High priority must be given to reducing vascular risk profiles.

Keywords

vascular dementia; subcortical; ischemia; lacunes; white matter changes

Introduction

This review focuses on subcortical ischemic vascular dementia (SIVD), a proposed subtype of vascular cognitive impairment (VCI). To the neurologist, this label conjures up hypertension, diabetes mellitus, small artery disease, lacunar infarcts, white matter changes, subcortical dementia, and dysexecutive syndrome. This chapter is divided into three main sections: 1) a brief review of the historical syndromes, the conceptual neurobehavioral framework of frontal-subcortical loops, and currently proposed diagnostic criteria, 2) lessons emerging from recent neuroimaging, neuropsychology, and neuropathology studies, and 3) the importance of recognition and treatment of vascular risk factors, particularly hypertension.

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I. Conceptualization: History, Frontal-Subcortical Loops, Diagnostic Criteria

The wide range of cerebrovascular disease (CVD) and its associated clinical phenotypes has inspired numerous classification schemes. CVD is divided into large vs. small artery disease. Stroke is divided into ischemic vs. hemorrhagic subtypes. Multi-infarct dementia was split into cortical vs. subcortical dementia. Here we focus on a proposed subtype known as subcortical vascular dementia (SVD) or subcortical ischemic vascular dementia (SIVD), which is characterized by lacunar infarcts and deep white matter changes. Since lacunar infarcts represent 20-30% of symptomatic strokes, SIVD is considered as important subtype of VCI.

A. History

Three historical syndromes would fall under the current rubric of SIVD: 1) lacunar state, 2) thalamic or strategic-infarct dementia, and 3) subcortical arteriosclerotic encephalopathy (Binswanger's syndrome).

Lacunar state—The syndrome of lacunar state was first described by Marie (1) and Ferrand (2) in 50 residents of a chronic care facility. Clinical features included sudden hemiparesis, dementia, dysarthria, pseudobulbar palsy and affect, crying, small-stepped gait and urinary incontinence. Aphasia and hemianopsia were rarely seen. The distribution of lacunes in subcortical gray matter and diffuse softening of the white matter, particularly of the frontal lobe were noted (3,4,5). Behavioral features including lack of volition and akinetic-mutism, were typically attributed to prefrontal lobe lesions.

Strategic infarct dementia (e.g., thalamic dementia)—Bilateral infarction in the distribution of the paramedian thalamic artery is associated with a dementia syndrome. At times, a single paramedian branch arising from basilar artery often supplies both anteromedial thalamic regions. This region includes the dorsomedial nuclei (closely connected with the prefrontal lobes) and the mammillothalamic tracts (integral components of the limbic-diencephalic memory system) (6). The dementia syndrome associated with such strategic infarcts is characterized by marked apathy, impaired attention and mental control, and anterograde and retrograde amnesia (7,8), a picture characteristic of executive dysfunction.

Binswanger's syndrome—Otto Binswanger (9) described 8 cases with slowly progressive mental deterioration and pronounced white matter changes and secondary dilatation of the ventricles. Alzheimer (10) subsequently reported the microscopic features, including severe gliosis of the white matter and hyalination, intimal fibrosis, and onion-skinning of the long medullary arteries. Chronic hypoperfusion of the periventricular and deep white matter border zones is postulated as the mechanisms of injury (11).

The clinical features of Binswanger's syndrome include insidiously progressive dementia, persistent hypertension or systemic vascular disease, lengthy clinical course with long plateaus and accumulation of focal neurologic signs, including asymmetric weakness, pyramidal signs, pseudobulbar palsy and gait disturbance. The neurobehavioral features of Binswanger's syndrome include apathy, lack of drive, mild depression, and alterations of mood. The reader is referred elsewhere for reviews (12,13). The periods of slowly progressive dementia may be mistaken for AD. The presence of gait disturbance, urinary incontinence, and ventriculomegaly may be mistaken for normal pressure hydrocephalus, although cerebral atrophy and widening of the cortical sulci distinguish Binswanger syndrome.

Evidence: Limited data are available regarding the prevalence of these three syndromes. In a longitudinal community survey of Japanese American men (Honolulu Asia Aging Study), 23% of VaD was attributed to large-vessel, 50% to small-vessel, and 16% to mixed-vessel disease

(14). In the subsample with small vessel distribution infarcts (n=34), lacunar state was diagnosed in 85% and Binswanger syndrome in 15%. In a hospital-based study, among the subset of patients with lacunar-type MID patients (n=39), 51% showed single and 49% showed multiple infarcts on CT scan (15). Among the MID patients (n=58), 12% had extensive white matter changes. According to these limited data, lacunar state (or multiple lacunes) is the most commonly recognized phenotype of dementia phenotype associated with SVD.

Unifying hypotheses:

A) Disruption of Frontal-Subcortical loops

B) Disruption of Long Association Fibers

All three classical SIVD syndromes described above are associated with predominantly “frontal” type behavioral features. A unifying hypothesis based on disruption of frontal subcortical circuits has been proposed (16). Five parallel frontal-basal ganglia-thalamic circuits were delineated in anatomical studies of non-human primates (17). Three of these circuits are relevant to non-motor behavior: 1) a dorso-medial prefrontal circuit related to executive function, B) a medial prefrontal circuit related to initiation and drive, and C) an orbital prefrontal circuit related to social behavior. These three circuits share a common anatomical motif: prefrontal areas project somatotopically to the subcortical gray matter (i.e., head of the caudate, globus pallidus, and dorso-medial or anterior thalamic nucleus), and then back to prefrontal cortex (Figure 1). A unifying hypothesis is that SIVD results from disruption of these frontal-subcortical circuits by lacunar infarcts or deep white matter changes.

An alternate, non-mutually exclusive hypothesis is that deep white matter lesions disrupt white matter tracts important for cognition and emotion. These include association, commissural, striatal, and subcortical fibers which interconnect distributed neural circuits. Widespread lesions of the white matter have major effects on initiation and frontal executive function, because of preferential disruption of long association fibers (e.g., cingulum, superior longitudinal fasciculus, fronto-occipital fasciculus) (18,19).

There are two major scenarios by which small-artery disease leads to ischemic brain injury. The end-stages of the two pathways correspond with the classical syndromes of lacunar state and Binswanger syndrome.

In Scenario A, the lumen of a single artery becomes occluded, leading to a discrete lacunar infarct. The subcortical gray matter and white matter are most vulnerable. In a meticulous study, Dozono et al., (5) tabulated the distribution of 2567 lacunar infarcts: frontal white matter (35%), putamen (16%), thalamus (8%), caudate (8%), and pons (9%)(17) (Figure 2). Note that 75% of these infarcts fall in locations that could disrupt frontal-subcortical loops.

In Scenario B, the borderzone between two or more arteries becomes ischemic, because of stenosis and hypoperfusion affecting multiple arteries simultaneously. The periventricular and deep white matter are most vulnerable (20,21, as these zones are perfused by long, narrow medullary arteries (Figure 3). The added presence of high-grade carotid artery stenosis or systemic hypotension could exacerbate ischemia. Note that deep white matter changes can disrupt frontal-subcortical loops, as well as long association fibers (e.g., cingulum, superior longitudinal fasciculus, fronto-occipital fasciculus).

Evidence: There is ample evidence from case studies that supports the plausibility of the frontal-subcortical loop hypothesis, but few systematic studies that put this hypothesis to test. Case studies demonstrate that single, strategically placed lesions may result in dementia. Key locations include the head of the caudate (22), genu of the internal capsule (23), and thalamus (6,6,24). Recently, Carrera and Bogousslavsky (25) described the behavioral patterns associated with infarction in each of the four main thalamic arterial territories: tuberothalamic, paramedian, inferolateral, and posterior choroidal. Infarction of the anterior thalamic nucleus results from occlusion of the tuberothalamic artery and is associated with apathy, amnesia, perseverations, and “palipsychism” (superimposition of unrelated information). Infarction of the dorsomedial nucleus of the thalamus follows occlusion of the paramedian artery and is associated with personality changes fluctuating between apathy, disinhibition, and at times manic psychosis.

Tulberg et al. (26) observed that the severity WMH (regardless of lobar distribution) correlates inversely with glucose metabolism in the dorsolateral frontal lobe. This finding is consistent with the notion that the long association fibers reaching the pre-frontal cortex are vulnerable to the centripetal spread of WMH, which begins in the periventricular end-arteriole zone and advances toward the cortical ribbon. Direct test of this hypothesis is now possible using diffusion tensor imaging and tractography.

Gold et al. (27) related lacunar and microvascular pathology to cognitive status in 72 elderly individuals without significant neurofibrillary tangles or macro-vascular lesions. In a multivariate model, cortical microinfarcts, and thalamic/basal ganglia lacunes explained 22% of variance; amyloid deposits and microvascular pathology 12%; while deep white matter lacunes were not significant contributors. These data confirm the importance of lacunes in subcortical gray matter, but indicate that other lesions such as cortical microinfarcts and amyloid may contribute to cognitive impairment in SIVD.

Diagnostic Criteria

Sensitivity for detecting vascular brain injury widened significantly with the advent of modern imaging: CT in 1970's and MRI in the 1980's. Previously, the threshold occurred at the level of symptomatic stroke; nowadays, neuroimaging often reveals evidence of “silent” vascular brain injury without a history of corresponding clinical event. Recently, criteria have been proposed for SVD (Table 1) which includes criteria for brain imaging with either CT or MRI (Table 2) (28).

Evidence

Evidence-based studies which address sensitivity and specificity of clinical criteria against a reference standard are limited. In contrast to AD, there is no agreed upon gold standard for the diagnosis of vascular dementia. In reference to idiosyncratic pathological definitions of VCI, positive likelihood values in the range of 2-5 have been reported for Hachinski, DSM-IV, ICD-10, NINDS-AIREN, and ADDTC criteria (reviewed by Chui [29]). This range of positive likelihood ratios may produce small, but sometimes important, changes in pre- to post-test probability (30).

In an autopsy sample of AD, SIVD and normal controls (31), reported that the clinical diagnosis of SIVD by modified ADDTC criteria showed a sensitivity of 57%, a specificity of 85%, and positive likelihood ratio of 3.7. In this same autopsy sample, Reed et al. (32) noted that the presence of a “low executive function profile” showed a sensitivity of 67%, a specificity of 86%, and a positive likelihood ratio of 4.7) for the diagnosis of pure SVD. There are no published studies attempting to validate the criteria for SVD.

An impasse has seemingly been reached in the traditional approach to clinical diagnosis. One hopes that clinical and pathological correlations with rapidly accumulating neuroimaging data will suggest new approaches to characterizing the contribution of vascular brain injury to cognitive impairment.

II. Brain-Behavior Correlations: Imaging-clinical-pathological data

The versatility and power of magnetic resonance imaging (MRI) is exciting. High field MRI at 3 or more Tesla offers unprecedented anatomical resolution, fMRI and perfusion MRI give excellent temporal resolution, and diffusion tensor imaging provides information about architectural integrity. This review focuses on new findings using structural MRI (i.e., T-1, proton density, and T-2 weighted sequences).

When studies are designed to address specific hypotheses, a combination of imaging, clinical, and pathological data promises to revolutionize our understanding of brain-behavior relationships. Cross-sectional studies provide correlative data, but are non-informative about causality. Longitudinal study designs allow more inferences relevant to determining cause and effect. Autopsy studies are still necessary to assess microscopic changes, including microinfarcts, hippocampal sclerosis, or the presence and severity of Alzheimer disease.

The brain-behavior question relevant to SIVD focuses on the relationship between vascular brain injury (i.e., lacunar infarcts and deep white matter changes) and cognitive impairment. In clinical practice, however, answers to this question are not straightforward. The likelihood that multiple pathologies contribute to cognitive impairment increases exponentially with age. The risk for Alzheimer disease doubles every five years; the risk for stroke every ten. For older persons with a history of slowly progressive cognitive impairment and evidence of vascular brain injury on neuroimaging, the possibility of concomitant vascular and AD pathology is very real.

Pure SVD occurs in young stroke patients and in the rare genetic disorder, known as cerebral autosomal dominant arteriopathy subcortical infarcts and leukoencephalopathy (CADASIL). In older persons who are at greatest risk for cognitive impairment, Alzheimer disease often obscures or confounds the relationship with vascular brain injury. Since our ability to characterize the presence and severity of AD in vivo is still limited, our knowledge about the interaction between vascular brain injury and AD pathology (e.g., whether additive or synergistic) is also unclear.

A. MRI – Neuropsychological Correlations

Loss of brain volume and accumulation of brain hyperintensities can be assessed by qualitative rating scales or volumetric analyses of structure MRI. In 2006, a workshop to harmonize data acquisition related to VCI recommended several rating scales for measuring white matter changes and classifying lacunes (33), including those developed by the Cardiovascular Health Study (Figure 4) (34). Volumetric measures of cortical gray matter, white matter, abnormal white matter can be obtained by computerized k-means cluster analyses and voxel-based morphometry (35; Figure 5). Various semi-automated techniques are available to determine hippocampal volumes and number of lacunes

Several large-scale epidemiological studies include prospective longitudinal MRI and neuropsychological measures and sometimes neuropathology, but rarely all three sources of information together. Semi-quantitative rating scales are used in several longitudinal epidemiological studies (e.g., Rotterdam, Cardiovascular Health Study [CHS], Atherosclerosis Risk in Communities [ARIC]), while volumetric analyses are employed in the Framingham Study and Austrian Health Prevention Study. The Subcortical Ischemic Vascular Dementia

(SIVD) program project is a longitudinal prospective study of SIVD, AD, and normal controls that acquires quantitative MRI, psychometric measures with linear response properties, and neuropathology.

Rotterdam Scan Study—In 1995 to 1996, 1077 subjects were randomly selected from two large epidemiologic studies (Rotterdam and Zoetemeer Studies) to undergo longitudinal cranial MRI (Rotterdam Scan Study). Periventricular WMH, generalized brain atrophy, and brain infarcts on MRI were associated with steeper decline in information processing speed and executive function during 5.2 years-mean follow-up (36).

Atherosclerosis Risk in Communities (ARIC)—At Visit 3 (1993-1995) of this prospective, biracial, population-based study, a subset of participants underwent brain MRI. White matter hyperintensities, ventricular size, and sulcal size were rated on a 10-point scale. Cognitive status was assessed using a Delayed Word Recall Test (DWRT), Digit Symbol Substitution test (DSS) and Word Fluency Test (WFT). High grade ratings on each of the MRI variables, including high grade WMH, were independently associated with diminished cognitive functioning (37).

Cardiovascular Health Study (CHS) (1989), Cardiovascular Health Cognitive Study (CHCS) (1998)—In 1998-1999, the Cardiovascular Health Cognitive Study (CHCS) was implemented for 3,608 participants who had undergone MRI in 1991-1994. The CHS uses the 3MS (54) to assess cognitive status, a 0-9 point White Matter Grade (WMG) rating scale (34), and a stroke risk score (38). Increasing severity of WMH was correlated with lower scores on 3MS and digit symbol substitution test at baseline (39). Among a subset of 1919 subjects with 2 MRI scans separated by 5 years, 28% showed worsening of WMG and associated greater decline on 3MS and Digit-Symbol Substitution test (both $p < 0.001$) (Figure 6).

In summary, converging evidence from longitudinal epidemiologic studies indicate that progressive increase in white matter hyperintensities is associated with cognitive slowing and decline.

SIVD Program Project: MRI-Cognitive-Pathology—The SIVD program project is a prospective, longitudinal study to assess the interrelationships between quantitative MRI, neuropsychological testing, and ultimately neuropathology in subjects with SIVD, AD, and normal aging. The independent MRI variables were the volumes (expressed as a percent of intracranial volume) of white matter hyperintensity (WMH), lacunes (LAC), cortical gray matter (CGM) and hippocampii (HV) (35). The dependent measures were neuropsychological test results, as well as composite measures of global cognition (GLOB), memory (MEM), and executive (EXEC) function which had linear measurement properties. At the outset of the study, we hypothesized that lacunar infarcts and white matter hyperintensities would be markers of vascular brain injury and would predict decline in executive function, while hippocampal atrophy and gray matter atrophy would serve as a marker for Alzheimer disease and would predict decline in memory and global cognitive function (figure 7).

MRI – cognition—The relationship between MRI measures and neuropsychological test performance was examined using multi-stage, cross-sectional, regression models of the first 163 subjects enrolled in the study (40). The best predictors of global cognition proved to CGM which explained 14% of the variance in the Mattis Dementia Rating Score, followed by HV which explained an additional 11% of the variance. WMH independently, but weakly explained 3% of the variance in verbal fluency. Interestingly, lacune volume (most “silent lacunes” in this sample) was not a significant predictor of the cognitive measures.

Baseline MRI and cognitive decline—The relationship between baseline MRI measures and change in global cognition was next assessed among 120 subjects followed for 3.0 years (41). CGM predicted decline in global cognition (GLOB) irrespective of the presence or absence of lacunes. HV predicted decline only in subjects without lacunes (presumed AD), but not those with lacunes (presumed SIVD). WMH, but not lacune volume, was a weak predictor of cognitive decline.

Baseline and change in MRI vs. cognitive decline—Finally, the relationships between baseline and change in MRI measures and change in memory (MEM) and Executive (EXEC) function were examined among 103 subjects followed for 4.8 years (42). HV at baseline and HV change both predicted change in MEM. However, decline in EXE function was determined by multiple brain components, including CGM and change in CGM, HV, and LAC. The resulting model (shown graphically in figure 8) illustrates the expected change in MEM and EXEC in subjects with AD (HV and CGM) vs. AD+ SIVD (LAC). This shows the strong association between AD and decline and MEM and EXEC, and also the added effect of LAC in years 2 and 4 on EXEC, but not MEM function.

Path-cognitive correlations—We also examined the relative contribution of AD pathology, CVD pathology, and hippocampal sclerosis to cognitive status in 79 autopsy cases (31). In an ordinal logistic regression analysis that included interaction terms to assess the effects of each pathological variable when the other variables are interpolated to zero, each of the 3 pathology variables contributed independently to cognitive status: Braak & Braak Stage OR=2.84 [1.81 to 4.45], HS score OR=2.43 [1.01 to 5.85], and CVDPS odds ratio (OR)=1.02 [1.00 to 1.04]). However, advancing stages of AD pathology overwhelmed the effects of CVDPS and HS, to become the major determinant of dementia.

MRI-path correlations—MRI-path relationships were examined among 101 IVD subjects coming to autopsy (43). WMH and number of lacunes were both correlated with severity of cerebrovascular disease or vascular brain injury. Contrary to popular belief, however, CGM was determined not only by AD pathology, but also severity of vascular brain injury, and arteriosclerosis. Hippocampal atrophy was determined not only by AD pathology, but also by hippocampal sclerosis which is an alternate cause of amnesia but is rarely diagnosed premortem.

Summary—Some of our apriori predictions were born out. Baseline WMH, but not lacunes which were silent for the most part, contribute to impairment verbal fluency and predicts global cognitive decline. Baseline and change in HV are the primary determinants of baseline and change in MEM, particularly in subjects without lacunes. Other data, however, lead to important modifications of our apriori hypotheses (Figure 9). EXEC function is complexly related to baseline CGM and change in CGM, HV, and LAC. The two major predictors of cognitive status, namely CGM and HV are affected by multiple rather than single pathologies. Relatively speaking, AD pathology exerts a much greater impact than SIVD pathology on cognitive health.

B. CADASIL

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) provides examples of pure SIVD, without significant AD pathology. Resulting from mutations in the Notch3 gene on chromosome 19q12, CADASIL is associated with progressive degeneration of smooth muscle cells and the accumulation of granular osmiophilic deposits in the vascular basal lamina of small arteries (44). This disorder may be diagnosed by skin biopsy or by genetic testing (45). Patients experience migraine headaches, seizures, and progressive SIVD. MRI shows successive lacunar infarcts, microbleeds, and extensive WMH,

which involve not only the periventricular white matter but also the temporal pole, external capsule and corpus callosum (46,47) (Figure 10) Peters et al. (48) reported the results of neuropsychological testing among 65 subjects with CADASIL compared to 30 age-, sex-, and education-matched normal controls (Figure 11). The greatest impairments were noted on Stroop III and Trails B, as well as a compound executive score derived from symbol digit, digit span backwards, and digit cancellation. O'Sullivan et al. (49) used diffusion tensor imaging to support the hypothesis that damage to the cingulum bundle may underlie these impairments in executive processing.

III. Prevention & Treatment

A. Epidemiologic evidence

Many factors such as age, hypertension, diabetes mellitus, smoking, high cholesterol, and heart disease are risk factors for stroke, regardless of subtype (50) (Figure 12). In a recent meta-analysis of 16 studies, hypertension and diabetes appeared somewhat more common with lacunar vs. nonlacunar or cardioembolic stroke, but this may be confounded by the circular inclusion of risk factor profiles in the definition of stroke subtype (51). In ARIC, the population-attributable risk for hypertension was 35% regardless of ischemic stroke subtypes (52). The population-attributable risks associated with diabetes mellitus and smoking, however, were higher for lacunar stroke (26% and 22%) compared to non-lacunar stroke (11.3 and 11.4%) and the definition of stroke subtype was risk-factor free.

Several longitudinal community-based studies provide evidence that identification and control of risk factors in mid-life may reduce the risk of cognitive impairment in late-life. Hypertension is the single most important modifiable risk factor.

In the Framingham Heart Study, 1,695 stroke-free older participants aged 55-85 years had been followed every 2 years since 1950. A significant age-related decline was observed for all neuropsychological tests. In addition, lesser but independent declines in several tests (i.e., immediate and delayed logical memory and visual reproduction) correlated with the magnitude and duration of hypertension in mid-life (53).

In the Rotterdam Scan Study, current hypertension or established hypertension of 5 to 20 year duration were both associated with significantly increased white matter lesions (54). For participants with > 20 years of hypertension and aged 60-70 years at the time of follow-up, the relative risk of subcortical and periventricular white matter lesions were 24.3 (95% CI 5.1-114.8) and 15.8 (95% CI 3.4-73.5) respectively, compared to non-hypertensives. For subjects with successfully treated hypertension, the relative risks of subcortical and periventricular white matter lesions was only moderately increased (RR=3.3, 1.3 to 8.4 and 2.6, 1.0 to 6.8, respectively).

In the Honolulu Asia Aging Study (HAAS), 3,734 Japanese-American men (average age = 78 years) had been followed every 5 years since 1965. For every 10-mm Hg increase in systolic blood pressure (from < 110 to 160), there was a 7% increased risk for intermediate cognitive function and a 5% increase for poor cognitive function (55). In prospective follow-up, for each additional year of anti-hypertensive treatment there was a reduction in the risk of incident dementia (HR 0.94; 95% CI, 0.89 to 0.99) (56).

Epidemiology of Vascular Ageing (EVA) is a longitudinal study of vascular ageing and cognitive decline. In 1991-1993, 1,389 subjects age 59 to 72 were recruited from electoral rolls in Nantes, France and followed every 2 years. Risk of severe WMH was significantly reduced in subjects with normal blood pressure taking antihypertensive medications compared with

those with high blood pressure taking antihypertensive agents (57). This study suggests that good control of blood pressure among hypertensives reduces the risk of severe WMH.

Austrian Stroke Prevention Study—From 1991 to 1994, 2007 individuals in Graz, Austria were enrolled in a study of genes and vascular risk factors in normal aging. Every fourth study participant or the next was invited to enter phase II of the study, which included MRI, Doppler sonography, SPECT, and neuropsychological testing (n= 509). Glycated hemoglobin A was identified as a risk factor for greater rate of MRI-measured brain atrophy over 6 years among normal subjects (n=201), explaining 13% of the variance (58).

Cardiovascular Health Study—In the CHS study, independent predictors of worsening WMG include cigarette smoking and infarct on initial scan (39). Among 622 elderly participants in the Cardiovascular Health Study (CHS), a linear trend was found between the top and bottom quintile of total homocysteine level with a combined MRI rating of infarcts and high white matter grade (odd ratio 3.3, 0.96-11.22) (59). In the CHS study among persons for whom lipid-lowering therapy was recommended, statin use was associated with 0.48 fewer points (95% CI 0.06, 0.89) decline per year in 3MS score compared to those who were untreated (60), a difference remaining after controlling for cholesterol level.

B. Primary Prevention: Clinical Trials That Include a Cognition Outcome Measure

In a follow-up to the original Syst-Eur trial (61,62), long-term antihypertensive therapy over 3.9 years, reduced the risk of dementia by 55%, from 7.4 to 3.3 cases per 1000 patient years (43 versus 21 cases, $P<.001$). Treatment of 1000 patients for 5 years can prevent 20 cases of dementia (95% CI, 7 to 33).

C. Secondary Prevention: Clinical Trials to Prevent Recurrent Stroke or TIA

In the PROGRESS trial, 6105 subjects with previous stroke or TIA were randomized to perindopril plus or minus indapamide versus placebo and followed for 3.9 years (63). The treatment group showed a 19% relative risk reduction versus placebo in cognitive decline as measured by the MMSE and a 43% reduction in new WMH (64).

D. Tertiary Amelioration

Randomized, double-blind, placebo-controlled trials have been conducted for a wide variety of compounds in patients with VCI, rarely distinguishing between the pathogenetic subtypes of VCI. The efficacy and safety of the calcium antagonist nimodipine versus placebo was studied in 230 patients with subcortical VaD (65). At 52 weeks, no significant differences were noted in the Sandoz Clinical Assessment Geriatric Scale, but fewer drop-outs and adverse events occurred in the nimodipine group, suggesting a possible beneficial effect on cardiovascular comorbidity.

Cholinesterase inhibitors have been studied in VCI (without distinction regarding subtype). Among patients with probable vascular dementia or AD plus CVD Erkinjuntti and colleagues (66) reported a 2.7-point difference in the Alzheimer Disease Assessment Scale, cognitive subscale for the galantamine (n = 396) versus placebo (n = 196) group. Similarly, among subjects with probable VCI (n = 616), Wilkinson and colleagues (67) reported a 2-point benefit in a randomized, double-blind, placebo-controlled, 24-week study of donepezil. By way of caveat, a meta-analysis undertaken by Schneider and colleagues (68) showed increased mortality associated with donepezil (OR 1.44; 95% CI, 0.68 to 3.02; $P=.04$) in two of three VaD trials. Cholinergic deficits have been demonstrated in Binswanger syndrome (69) and CADASIL (70), which provide a biochemical rationale for cholinergic enhancement in at least these subgroups of SIVD. Cholinesterase inhibitors have been approved for the treatment of VaD in some Asian countries, but not in the United States.

CONCLUSION

Epidemiological data suggests that prevention of SIVD is akin to the prevention of stroke. Identification and treatment of vascular risk factors, such as hypertension, diabetes mellitus, and hyperlipidemia, is a high priority (71). Overall, antihypertensive therapy is associated with a 35% to 44% reduction in the incidence of stroke. Only 70% of Americans with hypertension are aware of their condition, 60% are under treatment, and 34% are successfully controlled (72). Lack of diagnosis and undertreatment are more common among the elderly and minority populations. High priority must be given to reducing the vascular risk profiles.

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Figure 1.
Subcortical vascular dementia prefrontal subcortical circuits.

Figure 2.

Distribution of Lacunes. Frontal WM = 35%, Putamen = 16%, Caudate = 8%, Thalamus = 8% (Data from Dozono et al. Stroke 1991; 22: 993.) Figure from Ishii N, Nishihara Y, Imamura T. Why do frontal lobe symptoms predominate in vascular dementia with lacunes? Neurology 1986;36:340-345; with permission.

Figure 3. Regional vulnerability to global ischemia. Less vulnerable are the (1) cerebral cortex , (2) the corpus callosum , (3) the subcortical cortical u-fibers, and (4) the external capsule. More vulnerable are (5) the deep white matter and (6) basal ganglia and thalamus.

Figure 4.
Cardiovascular health study white matter grading scale.

Figure 5.
Quantitative MRI measures (% intracranial volume): SIVD program project.

Figure 6.

Annualized changes in 3MS and digit symbol substitution by groups of participants defined by worsening white matter. A, Scores on the modified mini-mental state examination (maximum score 100). B, Digit-symbol substitution test (number correct) for each year of study from initial to follow-up scans.

Figure 7.
A priori hypotheses: SIVD Program Project.

Figure 8.
Model-derived cognitive trajectories for hypothetical cases.

Figure 9.
Summary of SIVD project.

WMH in temporal pole
T2-weighted MRI

Lacunar
infarcts
FLAIR

Microbleeds
T2*
weighted
gradient
echo planar

Figure 10.
Cerebral autosomal dominant arteriopathy subcortical infarcts and leukoencephalopathy (CADASIL).

Figure 11.
Cognitive profile in Cadasil. Pronounced deficits in attention and processing speed.

Figure 12.
Frequency of risk factors by ischemic stroke subtype.

Table 1
Criteria for Subcortical Vascular Dementia
 From Erkinjuntti T, Inzitari D, Pantoni L, et al. Research criteria for subcortical vascular dementia in clinical trials. *J Neural Transmission* 2000; 59(Suppl 1): 23-30.

-
- I.** The criteria for the clinical diagnosis of subcortical vascular dementia include all of the following:
- A. COGNITIVE SYNDROME including both
 DYSEXECUTIVE SYNDROME: Impairment in goal formulation, initiation, planning, organizing, sequencing, executing, set-shifting and maintenance, abstracting
 and
 MEMORY DEFICIT (may be mild): Impaired recall, relative intact recognition, less severe forgetting, benefit from cues.
 and
 Deterioration from a previous higher level of functioning, interfering with complex (executive) occupational and social activities not due to physical effects of cerebral disease.
 - B. CEREBROVASCULAR DISEASE including both, EVIDENCE OF RELEVANT CEREBROVASCULAR DISEASE BY BRAIN IMAGING
 and
 PRESENCE OR HISTORY OF NEUROLOGIC SIGNS consistent with subcortical cerebrovascular disease (such as hemiparesis, lower facial weakness, Babinski sign, etc.).
- II.** Clinical features supporting the diagnosis of subcortical vascular dementia include the following:
- a. Episodes of mild upper motor neuron involvement such as drift, reflex asymmetry, incoordination.
 - b. Early presence of a gait disturbance (small-step gait or marche à petits-pas magnetic, apraxic-ataxic or Parkinsonian gait).
 - c. History of unsteadiness and frequent, unprovoked falls.
 - d. Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease.
 - e. Dysarthria, dysphagia, extrapyramidal signs (hypokinesia, rigidity).
 - f. Behavioral and psychological symptoms such as depression, personality change, emotional incontinence, psychomotor retardation.
- III.** Features that make the diagnosis of subcortical vascular dementia uncertain or unlikely include:
- a. Early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills.
 - b. Absence of relevant cerebrovascular disease lesions on brain CT or MRI.
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Table 2
Brain imaging criteria for subcortical vascular disease
From Erkinjuntti T, Inzitari D, Pantoni L, et al. Research criteria for subcortical vascular dementia in clinical trials. J Neural Transmission 2000; 59(Suppl 1): 23-30.

A. COMPUTED TOMOGRAPHY (CT)

Extensive periventricular and deep white matter lesions: patchy or diffuse symmetrical areas of low attenuation (intermediate density between normal white matter and cerebrospinal fluid)

AND

Absence of hemorrhages, cortical and/or cortico-subcortical non-lacunar territorial infarcts and watershed infarcts (large vessel disease stroke). No signs of normal pressure hydrocephalus

B. MAGNETIC RESONANCE IMAGING (MRI)

Binswanger type white matter lesions: Hyperintensities extending into periventricular and deep white matter; extending caps (>10 mm as measured parallel to ventricle) or irregular

OR

Lacunar cases: Multiple lacunes (e.g. > 5) in the deep gray matter **and** at least moderate white matter lesions: extending caps or irregular halo or diffusely confluent hyperintensities

AND

Absence of hemorrhages, cortical and/or cortico-subcortical non-lacunar territorial infarcts and watershed infarcts, signs of normal pressure hydrocephalus, and specific causes of dementia