Diagnosis and Treatment of Subcortical Ischemic Vascular Dementia

The small-vessel variant of ischemic vascular disease appears to have been neglected in the vascular dementia (VAD) model and the overall cerebrovascular pathologic picture. Subcortical ischemic vascular dementia (SIVD) is quite difficult to identify and diagnose due to the difficulty of establishing a causal relationship between the changes and cognitive deficits seen by a primary-care physician, as well as identified through various brain-mapping techniques.

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Apoplectic dementia was the term utilized in the past when patients presented with sudden cerebral bleeding, softening or tumors that resulted in an abrupt change in cognition, which could be progressive and incurable. In the early 1900s, it was widely accepted that atherosclerosis caused gradual stenosis of the brain vessels, causing parenchymal lesions that lead to dementia. However, the differentiation between other dementias and VAD were not clear, and the association between clinical strokes and cognitive changes were not firmly established. Hardening of the arteries was a term applied to a number of different dementia syndromes, including at times, and erroneously, Alzheimer's disease (AD).

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Vascular Dementia

Modern concepts of VAD began to evolve in the 1970s when studies from Newcastle revealed that subjects with dementia and little, if any, AD pathology demonstrated a relationship between lost tissue volume from infarctions and the degree of global cognitive decline. Hachinski[1] subsequently introduced the term multi-infarct dementia (MID) in 1974, which includes a history of clinical strokes with focal neurologic signs and symptoms, and stepwise cognitive decline.

The medical community has perhaps over-focused on this model of VAD, neglecting the sizeable contribution from small-vessel disease to the overall cerebrovascular pathologic picture. Hence, this article pertains to the small-vessel variant of ischemic vascular disease: SIVD.

Subcortical Ischemic Vascular Dementia

The greatest challenge in diagnosing SIVD lies in establishing a causal relationship between the magnetic resonance imaging (MRI) changes and the cognitive deficit(s) from the viewpoint of a primary-care physician. One can argue that causality is irrelevant, but if a patient has SIVD, management of the vascular risk factors should be optimized, regardless of their exact role in causing the dementia syndrome. What is clear is that the etiology of SIVD involves hypertension and diabetes mellitus (DM), particularly if poorly controlled.

Although there are minor differences in wording, most dementia definitions share the following elements:

1) acquired intellectual decline despite a clear sensorium;
2) effects on multiple cognitive domains which usually include memory; and
3) sufficient severity to interfere with customary everyday activities.[2]

During the past five years, emphasis has been placed on identifying early stages of vascular cognitive impairment in order to administer treatments earlier in the disease. Three historic syndromes fall under the current rubric of SIVD:[3]

1) lacunar state, first described by Marie[4] and Perraud;[5]
2) thalamic or strategic infarction dementia; and
3) subcortical arteriosclerotic encephalopathy, or Binswanger's syndrome.

These syndromes are associated with frontal-type behavioral symptoms. A unifying hypothesis based on disruption of cortical and subcortical circuits has been proposed.[6] Three such circuits are relevant to non-motor behavior:

1) a dorsomedial prefrontal circuit related to executive function;
2) a medial prefrontal circuit related to initiation and drive; and
3) an orbital prefrontal circuit related to social behavior.

An alternate hypothesis is that deep white-matter lesions disrupt the white-matter tracts necessary for cognition and emotion. These include association and commissural, striatal and subcortical fibres that interconnect with 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 fibres. However, it should be remembered that such changes at times remain clinically silent, gradually exhausting the clinical reserve of affected individuals.

Clinical SIVD features include sudden hemiparesis, dementia, dysarthria, pseudobulbar palsy, and changes in affect including inappropriate laughing or crying, small-stepped gait, and urinary incontinence. Aphasia and hemianopsia are usually absent. The distribution of lacunes in the subcortical gray matter and diffuse softening of the white matter, particularly of the frontal lobes, have been noted. Behavioral symptoms include lack of volition and akinetic mutism, which were thought to be characteristic of prefrontal lobe lesions.[3]

Strategic infarct dementia (*e.g.,* thalamic dementia) typically involves distribution of the paramedian thalamic artery. This usually includes the dorsomedial nuclei, closely connected with the prefrontal lobes. Dementias associated with such strategic syndromes are featured by marked apathy, impaired attention and mental control, with anterograde and retrograde amnesia, as well as striking executive dysfunction.[3]

Binswanger's syndrome was first described by Otto Binswanger.[7] He outlined eight cases of slowly progressive mental deterioration and pronounced white-matter changes with secondary dilatation of the ventricles. Alzheimer 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 zones is postulated as the mechanism of injury.

The clinical features of Binswanger's include an insidiously progressive dementia, persistent hypertension or systemic vascular disease, lengthy clinical course with long plateaus, and the accumulation of focal neurologic signs including asymmetric weakness, pyramidal signs, pseudobulbar

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Table 1

Diagnosis of Subcortical Ischemic Vascular Disease (SIVD)[3]

Findings that increase the likelihood of SIVD

1. History of sudden onset or stepwise decline in neurologic or cognitive function.
2. History of chronic hypertension or DM, especially if inadequately treated.
3. History of small stroke (pure motor or sensory).
4. Focal neurologic findings such as reflex asymmetry, pronator drift, Babinski sign, small-stepped or shuffling gait.
5. Evidence of hypertensive or diabetic end-organ disease (*e.g.,* retinopathy, LV hypertrophy, nephropathy).
6. Evidence of SIVD on structural neuroimaging study.

palsy, and gait disturbances. The neurobehavioral symptoms include apathy, lack of drive, depression, and alterations of mood. Of course, the periods of slowly progressive deterioration can mimic AD. Sensitivity for detecting vascular brain injury widened significantly with the advent of modern imaging: computed tomography (CT) in the 1970s, and MRI in the 1980s and 1990s. The previous threshold occurred at the level of symptomatic stroke. More recently, neuroimaging has revealed evidence of silent brain injury without a history of a corresponding clinical event.

However, we should be clear that evidence-based standards that address sensitivity and specificity of clinical criteria against a reference standard are limited. In contrast to AD, there is no gold standard agreed upon for the diagnosis of VAD. Several findings in the clinical history and examination increase the likelihood of SIVD (Table 1).[3] The versatility and power of MRI do offer exciting clinical and research opportunities. High-yield MRI at three or more tesla offer unprecedented anatomic resolution; functional MRI and perfusion MRI give excellent temporal resolution; and diffusion tensor imaging provides information about architectural integrity.

Epidemiology

After AD, cerebrovascular disease is the second most common type of dementia. The incidence and prevalence of SIVD, however, is unknown.[8]

Epidemiologic studies tend to focus on a broad category of VAD, often adapting different classifications, and being frequently unable to reliably identify mixed AD/VAD.[9] Furthermore, few epidemiologic studies employ neuroimaging, leading to underestimates or precluding SIVD. Among patients hospitalized for first stroke, the proportion of events attributed to SIVD is 10% to 30%.[8] In another study, the proportion of cases attributed to SIVD varies from 36% to 67%[10] among patients diagnosed with VAD.

Pathophysiology

Small arteries refer to arterioles within the brain parenchyma. These vessels range in size from 100 to 600 microns in diameter, and do not have an internal elastic lamina. Arteriolosclerosis refers to the progressive deposition of hyaline in the smooth-muscle wall of the small arteriole. Hypertension and DM accelerate this degenerative process. As the media of the small artery undergoes progressive lipohyalinosis, the lumen narrows and the vessel becomes more tortuous and coiled. Ultimately, the process leads to fibrinoid necrosis and increased risk of thrombosis or hemorrhage.

Two pathophysiologic pathways cause ischemic brain injury associated with small-artery disease. The first pathway involves an occlusion of an arterial lumen and leads to lacunar infarction. The second is characteristic of a generalized narrowing of small arterioles and hypoperfusion, which leads to incomplete infarction of the deep white matter. While both pathways share roots in common risk factors and small-artery disease, they differ in the anatomic location and pathologic extent of their injury, as well as the accompanying clinical symptomatology. The end stages of these two pathways are known as lacunar state and Binswanger's syndrome. At later stages, the two pathways often converge.

When the lumen of an artery is occluded, acute ischemic injury is centered in its primary irrigation territory. For small penetrating arteries, the resulting so-called

lacunar infarct is usually < 1.5 cm in diameter. Sites of predilection include the white matter, especially in the frontal lobe, followed by the putamen, thalamus, pons, and caudate. Arterial occlusion is associated with complete infarction of all tissue elements, eventually leading to cystic necrosis. Small, or non-strategically located infarcts may be completely asymptomatic or silent. Symptomatic lesions are recognized by the sudden appearance of neurologic dysfunction such as pure motor weakness, pure sensory loss, or behavior or cognitive change.

Clinical Treatment

The primary treatment and prevention of SIVD is to manage the vascular risk factors to prevent further strokes. Close attention should be paid to the lowering of blood pressure and the control of DM. Antiplatelet agents should be utilized depending on the exact details of the clinical situation. Several longitudinal community-based studies, including the Framingham Heart Study,[11] Rotterdam Scan Study,[12] and the Honolulu Asian Study,[13] provide evidence that identification and control of risk factors in midlife may reduce the risk for cognitive impairment late in life. Of note, there are very few long-term trials measuring treatment outcomes in SIVD.

In the follow-up of the Systolic Hypertension in Europe Study, long-term antihypertensive treatment over 3.9 years reduced the risk of dementia by 55%, from 7.4 to 3.3 cases per 1,000 patients.[14] Even though this study included more than simply SIVD, energetic treatment of those vascular risk factors can been seen to alter long-term outcomes favorably. On the other hand, previous cross-sectional studies have suggested that MRI-defined SIVD is associated with marked cognitive impairment and, specifically, deficits of mental speed, attention, and executive skills. The LADIS Study[15] revealed that SIVD subjects seemed to be vulnerable to a rapid period of cognitive decline in these domains.[15] Further work will be required to hone in much further on this particular subset.

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