



Stroke and Dementia: Overlap and Opportunity

Summary

The vascular system in the body is tasked with two functions: transport of materials that allow cells to function and elimination of cellular by-products that, if accumulated, could cause disease. Brain vessels have additional, distinctive anatomical and physiological characteristics owing to their role in exchanging substances between blood and brain. These facts begin to shed light on the emerging understanding of the vascular foundations of impaired brain function. Characterizing the connection between dementia and stroke in particular is important because of the potential for reducing dementia as a collateral benefit of preventing stroke.

One of the challenges involved with tracing an association between these two disease domains is that they represent multiple subtypes. Good arguments are presented in the paper for starting the discussion with the following broad categories: (a) stroke as most commonly understood (i.e., atherosclerotic infarct involving a large artery, producing manifest neurologic symptoms); and (b) dementia taken as a whole. However, a few subtopics are also worthy of consideration. These include silent (presumably minor) strokes and Alzheimer's disease (AD) and its related dementia. In the latter arena, vascular risk factors now appear to substantially influence the development of AD. This has led to the development of a new term reflecting the combined role of vascular and neurodegenerative mechanisms, namely, mixed dementia. A final preliminary matter involved recognizing that the concept of "connection" between medical conditions is itself fraught with complexity. In short, to say that stroke and dementia share *common risk factors* is not precisely the same thing as saying that stroke *causes* dementia. Both types of associations generate implications for prevention, but the second offers more dramatic and direct potential for reducing dementia by reducing stroke. Thus, the following question lies at the heart of the paper: *What is the evidence demonstrating a causal connection between stroke and dementia?* In this regard, the following pertinent insights are developed:

1. The brain tissue insult associated with stroke is commonly followed by dementia onset. Post-stroke dementia is a recognized subset of so-called vascular dementia.
2. But scientific investigation has gone further than the mere observation of dementia cases following stroke. Based on a January 2010 systematic review of 16 epidemiologic studies, stroke and dementia are in fact statistically associated; there is an *elevated risk* of dementia following stroke, with post-stroke dementia occurring at about double the rate expected in a general population.
3. This at least points to the reality of common risk factors between stroke and dementia, and thus the potential for reducing dementia through risk factor control. Although not all results have been encouraging in this regard, trials will continue to be pursued, in particular with respect to blood pressure reduction.
4. Careful control of confounding risk factors has allowed reviewers to push beyond the concept of common risk factors, demonstrating that there is a *causal* effect of stroke on dementia, and therefore more direct and robust preventive possibilities with respect to dementia incidence.
5. The serious cognitive impact of vascular factors and stroke may not be limited to vascular dementia. There are multiple indications of cerebrovascular mechanisms in the initiation and progression of Alzheimer's disease, suggesting that controlling the risk factors/symptoms

associated with acute cerebrovascular disease, as well as preventing recurrent stroke, could reduce the serious (and growing) societal burden related to dementia of the Alzheimer type.

Definition and Scope

The purpose of this document is to outline the emerging scientific evidence concerning the connection between stroke and dementia, a topic about which there continues to be lively discussion.¹ There are important consequences if the connection is found to be *causal* rather than merely coincidental.² It would offer an exciting pathway for prevention of a subset of dementia cases. Put differently, dementia prevention would become a *direct* collateral benefit of stroke prevention efforts, providing an extra incentive to mount those efforts in the first place.

The various meanings of the three key terms, *stroke*, *dementia*, and their *connection*, create challenges at the start of this paper. A related complication is the fact that both stroke and dementia are “moving targets” in science and medicine. An understanding of the complex and evolving nature of stroke and dementia will be explored below, leading to a restatement of the purpose and scope of the paper.

Which Stroke?

Stroke is a multifaceted disease, with more than 150 specific causes identified to date.³ The best known division within stroke is between the ischemic and hemorrhagic varieties. Ischemic strokes, accounting for about 85-90% of stroke cases,⁴ usually involve an interruption of blood supply due to an infarct (localized cell death resulting from obstruction of the blood supply). Hemorrhagic strokes usually entail a ruptured blood vessel followed by a bleed (hemorrhage) in brain tissues. *The focus of this paper will be on the predominant type, ischemic stroke.*

There are many typologies of **ischemic stroke** in the literature,⁵ usually classified according to one or more of the following dimensions:

- Presumed cause or etiology, such as large artery infarct, minor infarct, cryptogenic (unknown)
- Site, or the type and localization of the vascular lesion
- Temporal features, such as completed, evolving, transient
- Neurologic symptoms, such as asymptomatic or “silent,” mild cognitive impairment, severe

The various types of ischemic stroke demonstrate specific connections with dementia. Two overlapping categories deserve special mention in this regard. First, there is disease in single penetrating arteries that leads to **minor stroke** (sometimes known as lacunar stroke, after the lacuna or “empty” space left behind in the brain following an infarct). This subtype accounts for up to one-third of cerebral ischemic events.^{6,7} The other (overlapping) stroke category of interest is where symptoms are not manifest.⁸ The concept is that some brain damage due to stroke is minor enough to escape clinical notice. This condition, traditionally described as **silent stroke**, occurs frequently, as highlighted by Royall:⁹

...it is important to distinguish between “stroke” as a clinical presentation and ischemic cerebrovascular disease (ICVD), its presumed cause. ICVD, as measured by ischemic changes on magnetic resonance imaging (MRI), or at autopsy, is far more common than are the clinical conditions recognized by clinicians as “stroke.”

After unpacking the topic of dementia following stroke in general, the neurologic consequences of silent (mostly minor) stroke will also be briefly noted in the paper.

Which Dementia?

Dementia is not a disease per se, but a group of symptoms¹⁰ that characterize a large number of different diseases and conditions.^{11,12} As suggested by its root meaning (literally “deprived of mind”), the key mark of dementia is an irreversible decline in intellectual functioning (such as memory loss) that is severe enough to interfere with the ability to perform routine activities at home or work. Just as stroke is at one end of the range of cerebrovascular diseases (with minor strokes or transient ischemic attacks at the other end), dementia occupies one end of the “neurologic deficit spectrum” (with mild cognitive impairment at the other end).

As noted above, different diseases can lead to dementia. Alzheimer’s disease is one of the main identified causes; many other dementia cases have a vascular basis.¹³ The usual term for the latter type has been vascular dementia (VaD). To better distinguish any neurological symptoms from the underlying pathology of AD, a term parallel to vascular dementia has been introduced: dementia of the Alzheimer type (DAT).

Alzheimer’s disease has been thought to account for up to 70% of dementia cases,¹⁴ though this proportion is likely to undergo revision as dementia causation is better understood. The association of AD with dementia is notoriously difficult to characterize. This is partly because proof of AD depends on pathology, that is, on physical markers discovered post-mortem. The best a clinician can do with a live patient is diagnose “probable AD,” traditionally indicated by the lack of evidence of vascular involvement. In other words, AD has been considered to be a purely neurodegenerative phenomenon that is separate from the vascular arena represented by stroke. However, this distinction seems to be eroding, so much so that the practice of using signs of cerebrovascular disease to differentiate AD-related and non-AD-related dementia has lately been called into question.^{15,16}

As noted above, **vascular dementia** is defined in terms of dementing symptoms that can be traced to a vascular cause. While this presumed etiology is the ultimate basis of differentiation, VaD and AD do vary in clinical presentation as well. VaD is marked in particular by a loss of executive function, while showing milder memory deficits than those found in AD.¹⁷ Furthermore, AD is typified by slow onset and “relentless progression to complete incapacitation,” whereas VaD generally appears more abruptly and demonstrates an unpredictable progression pattern.¹⁸ It is beyond the scope of this paper to describe the evolving picture of VaD description and classification. However, it is important to underline one development. Signs related to VaD have increasingly been found alongside classic AD disease. When this is demonstrated, a different classification term is now applied: *mixed dementia*. It now seems that **mixed dementia** “could be responsible for a large number of cases currently diagnosed as probable AD.”¹⁹

With this background, it is possible to further scope the broad focus of the paper. The fundamental question is whether routinely-diagnosed, symptomatic ischemic stroke is a condition connected to dementia. At the start, the paper will not concentrate on dementia subtypes. In fact, from an epidemiological perspective, dementia is typically considered as a whole, regardless of presumed causes. There are three reasons for this approach:

1. As explained above, from a clinical perspective all dementia may be considered to be “non-AD,” since the presence of lesions characteristic of AD generally is not proven until after death!
2. There are important age groups, such as those over 70 yrs of age, where mixed dementia may actually be the dominant form of dementia.²⁰
3. Generally, the classic categories are beginning to have less validity—cases of “pure AD” (or even “pure VaD”) may be very infrequent, especially among the elderly.

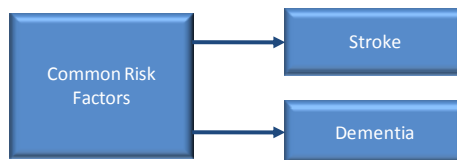
However, given the different presentations of DAT and VaD, and because AD pathology continues to be of paramount interest among the public and in science as a contributor to dementia, it will be useful to end with a discussion of the vascular connections with DAT in particular.

Causal Connection?

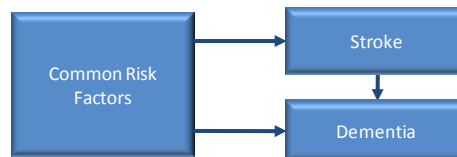
Finally, the heart of the *connection* question is whether any association found between stroke and dementia may be simply attributed to *common risk factors*, or whether a component may be traced to stroke actually *causing* dementia. Identifying a stroke event as a direct causal factor of dementia would offer a robust and predictable prevention pathway. By contrast, it is less certain that the indirect approach of reducing common risk factors will lower both stroke rates and dementia rates. This subtle distinction catapults the paper into the complex world of causation in medicine, a topic that often creates great confusion. For the present purpose, three broad categories for interpreting an association between stroke and dementia are diagrammed below.

Association Between Stroke and Dementia: Possible Explanations

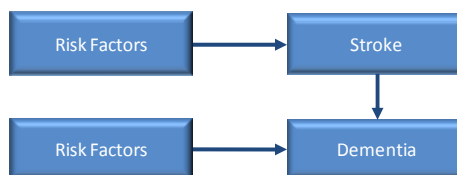
A. Common Risk Factors



B. Combination of Common Risk Factors and Causal



C. Causal



It should be reiterated that the presence of common risk factors does not prove anything about etiology. In short, there would still not be clarity about the extent to which stroke actually causes dementia “as opposed to there being common underlying risk factors for both in certain cases.”²¹ In other words, more layers must be added to the argument, from epidemiologic to biologic. Overlapping biological mechanisms in particular will be explored within the final comments specific to AD.

Plausibility of a Causal Connection

In summary, the most pertinent issue in this paper is whether there is evidence to support shifting the understanding of the stroke-dementia connection from possibility A to possibility B in the diagram

above. This is the same as asking the following about dementia as a whole: *Is there truly a causal association with stroke?*

The hypothesis that there is in fact such an association must be tested, but it already may be seen to be plausible. “Face validity” of the stroke-dementia connection begins with understanding that all VaD cases are already part of the biological world of stroke. The neurologic deficits that have a clear vascular connection are generally created by a temporary or permanent reduction in blood flow (=ischemia) that leads to a blood supply deficit (=hypoperfusion) within brain tissues; this in turn is directly related to reduced oxygen supply (=hypoxia) in brain cells that can produce an infarct (=an event, and the related area of cell death).

Stroke is of course a severe and abrupt form of cerebral blood flow interruption; thus it is not too surprising that this type of event is followed in the first few months by the onset of dementia symptoms.^{22,23} Three months after a stroke, one-quarter to one-third of patients have been found to meet operationalized criteria for dementia, and an even greater proportion have cognitive impairment short of dementia. A significant number of these patients had mental deterioration before the stroke, implying the possibility of underlying neurodegenerative processes.²⁴ However, pre-existing biological processes do not explain the whole story. While the prevalence of post-stroke dementia varies between studies, it averages to about 28% at 3 months in hospital-based research where pre-stroke dementia is *not excluded*; on the other hand, it still stands at 18% in hospital-based studies that *exclude* pre-stroke dementia.²⁵ Furthermore, the strong association of post-stroke dementia with multiple (recurrent) strokes underlines the potential beneficial “effect of optimum stroke care and secondary prevention in reducing the burden of dementia.”²⁶

These data only are *suggestive* of a causal connection, because it is not clear to what extent the risk of dementia immediately following stroke is different from the risk “in stroke-free but otherwise comparable individuals.”²⁷ Thus, plausibility arguments are helpful, but ultimately not enough. The next sections of the paper will briefly trace a more complete stroke-dementia causation picture, building the classic layers of evidence one atop the other, as follows:

- A. *Epidemiology (I)*: An association between one condition and another, suggesting at least common risk factors that place both conditions in a similar “biological arena.”
- B. *Intervention*: Reducing a common risk factor reduces both conditions.
- C. *Epidemiology (II)*: The association cannot be explained *solely* by common risk factors, suggesting some form of true causal effect from one condition to the other; prevention effects become more predictable.
- D. *Biology*: Plausible causal mechanisms, backed up by biological evidence.

A. Evidence That Stroke and Dementia Are Associated

There is clear evidence that *stroke and dementia are indeed associated*. A systematic review published in January 2010 examined 16 epidemiologic studies; a summary analysis concluded that a history of stroke generally doubles the risk of incident dementia in those over 65 years of age.²⁸ This result points at least to the presence of common risk factors shared by the two conditions (see below). Consistent with this concept is the fact that individuals with an elevated stroke risk profile also have significantly more cognitive impairment.

Common Risk Factors

While the risk factors for stroke and for dementia are still being investigated, a great deal has been discovered, including multiple overlaps between the two conditions (see the following table).

| Common Risk Factors of Stroke and Dementia | | |
|--|--|---|
| | Stroke | Dementia |
| Non-modifiable | <ul style="list-style-type: none"> Older age Genetic factors <ul style="list-style-type: none"> Family history of stroke Race / ethnicity Male gender | <ul style="list-style-type: none"> Older age Genetic factors <ul style="list-style-type: none"> Family history of dementia Down's syndrome Female gender |
| Modifiable | <ul style="list-style-type: none"> Vascular factors <ul style="list-style-type: none"> Hypertension Dyslipidemia Atrial fibrillation Atherosclerosis <i>Hyperhomocysteinemia</i> Asymptomatic carotid stenosis Cardiovascular disease Type 2 diabetes Poor diet and nutrition Physical inactivity Cigarette smoke <i>Obesity and the 'metabolic syndrome'</i> <i>Sleep apnea</i> <i>Alcohol and drug abuse</i> | <ul style="list-style-type: none"> Vascular factors <ul style="list-style-type: none"> Hypertension Hyperlipidemia (Hypercholesterolemia) <i>Atrial fibrillation</i> Atherosclerosis Hyperhomocysteinemia Hypolipidemia Orthostatic hypotension Congestive heart failure Hyperfibrinogenemia Cardiac arrhythmias Type 2 diabetes Poor diet and nutrition Physical inactivity Cigarette smoke Obesity and the 'metabolic syndrome' Sleep apnea Cognitive factors <ul style="list-style-type: none"> Mild cognitive impairment Intellectual stimulation Lower education level Head injury Chronic inflammatory conditions <i>Clinical depression</i> Parkinson's Disease |

Italics denotes risk factor where the evidence is more limited.

Sources: Diamond, *A Report on Alzheimer's Disease and Current Research*, 2005; Duron and Hanon, *Vascular Health and Risk Management*, 2008; Kirshner, *Current Neurology and Neuroscience Reports*, 2009; Peters, *BMC Geriatrics*, 2008; Román, *Cerebrovascular Diseases*, 2005; Rundek and Sacco, *Neurologic Clinics*, 2008.

The most important non-modifiable factor shared between stroke and dementia as a whole is older age. This pattern seems to be confirmed by research suggesting that non-vascular dementia, including classic or pure AD, may in fact be more prevalent at younger ages.²⁹

The large number of overlapping vascular factors stands out in the modifiable list. Among these, hypertension is likely the most important contributor to cognitive impairment.³⁰ This raises the possibility of a powerful simultaneous effect on both stroke and dementia if blood pressure is controlled.^{31,32,33,34,35,36} In fact, hypertension is so important as a factor in cognitive decline that it is sometimes listed along with stroke and dementia as the most serious threats to the brain.³⁷ Evidence contrary to this point of view is suggested in the section below on risk factor interventions.

Silent Stroke and Dementia

Another piece of the scientific puzzle is offered by the phenomenon of asymptomatic stroke, or silent brain infarcts as confirmed by MRI (or sometimes by autopsy). Studies have shown that the presence of silent infarcts also more than doubles the risk of subsequent stroke and dementia development.^{38,39} Thus, when minor, subclinical strokes are observed as incidental findings in neuroimaging assessments, clinicians should “institute preventive strategies to avert these untoward outcomes.”⁴⁰

B. Risk Factor Interventions

It is logical to assume that prevention of mixed dementia and the rare cases of pure VaD will primarily involve interventions related to vascular risk factors, that is, the same measures used to avoid strokes (and heart attacks).⁴¹ However, this is the first layer of evidence to be introduced that raises a problem about the stroke-dementia connection. It seems that studies of the effect on dementia incidence of interventions aimed at stroke prevention have been equivocal; the use of statins to lower cholesterol levels does decrease the risk of dementia, whereas antihypertensives have unexpectedly yielded mixed results.^{42,43} A Cochrane review of this topic could only locate four trials suitable to evaluate the effectiveness of blood pressure lowering on cognitive impairment and dementia; furthermore, even these studies had so many limitations that definitive conclusions could not be drawn.⁴⁴

C. Causal Association

Importantly, epidemiologic studies that seek to rule out various confounding factors demonstrate that the association between stroke and dementia cannot be explained by common risk factors alone.⁴⁵ While not final proof of causality, this is an important result that points to the likelihood of a direct effect of stroke on dementia development. In other words, to generate the fullest impact on dementia rates, *incident stroke* must be manifestly reduced, not just the risk factors common to dementia and stroke. Trials clearly demonstrating this have yet to be pursued.⁴⁶

D. Biological Mechanisms and Alzheimer’s Disease

To unpack the final layer of evidence concerning biological mechanisms, it is useful to shift the focus to the subtopic of AD in particular and its connection to vascular factors and stroke. After all, the cerebrovascular connections to VaD are not really in dispute; when people raise questions about stroke and dementia overlaps, it is likely that AD is the uppermost concern in their mind. By offering some biomedical background on AD in this section, an appreciation begins to form about how intertwined the vascular and neurodegenerative mechanisms are in the onset of DAT.

Although the fundamental causes of AD are still unknown (apart from the less than 10% of cases that have an inherited genetic basis), historically it has been linked to mechanisms that *do not* have an ischemia connection. At the microscopic level, AD is marked by so-called senile plaques (SPs)⁴⁷ and neurofibrillary tangles, first characterized by Alois Alzheimer in his original report on the disorder in 1907. Both features represent brain tissue rather than vascular lesions, and both are related to neurologic impairment (such as loss of neurons and synapses), and ultimately to dementia.

A great deal of the biochemistry related to these lesions has been elucidated. SPs in particular involve a type of amyloid protein, specifically amyloid-beta ($A\beta$). In the small percentage of AD cases that have a genetic foundation, a form of $A\beta$ has been detected that is predisposed to accumulation and therefore to the creation of lesions. However, an explanation for $A\beta$ accumulation in the great majority of AD cases is still unclear. One intriguing suggestion is that vascular dysfunction is involved, specifically an inability to drain solutes such as $A\beta$ from the intercellular brain matter. Such drainage problems related

to blood vessels is known to be a consequence of aging, a fact that may help to explain the prevalence of both AD and dementia in the elderly.

Another “theory” of AD focuses on the supply rather than the drainage aspect of the vascular system.⁴⁸ It suggests that a combination of age-related changes in blood vessels and alterations produced by lifestyle and other risk factors lead to reduced cerebral blood supply (=hypoperfusion); this in turn destabilizes neurons, synapses, and neurotransmission, and contributes to the formation of the neurodegenerative lesions characteristic of AD (described above) and the associated dementia.

Intriguingly, processes related to blood supply have another connection with the amyloid processes described above. As well as causing neuronal problems, excess A β also manifests in the lining of blood vessels; the effects of such accumulation, known as cerebral amyloid angiopathy (CAA), include small infarcts in the cortex of the brain.⁴⁹ Summing up, the concept of cerebral hypoperfusion as a cause of dementia “explains the heterogeneous profile observed in AD patients, because an extensive list of risk factors for AD are also reported to significantly diminish blood flow to the aging brain.”⁵⁰ Summing up the evidence so far, it is fair to say that all vascular (and thus stroke) risk factors are also risk factors for AD.⁵¹ Further evidence for a strong connection between acute cerebrovascular disease and dementia of the Alzheimer type will be outlined in the next subsection.

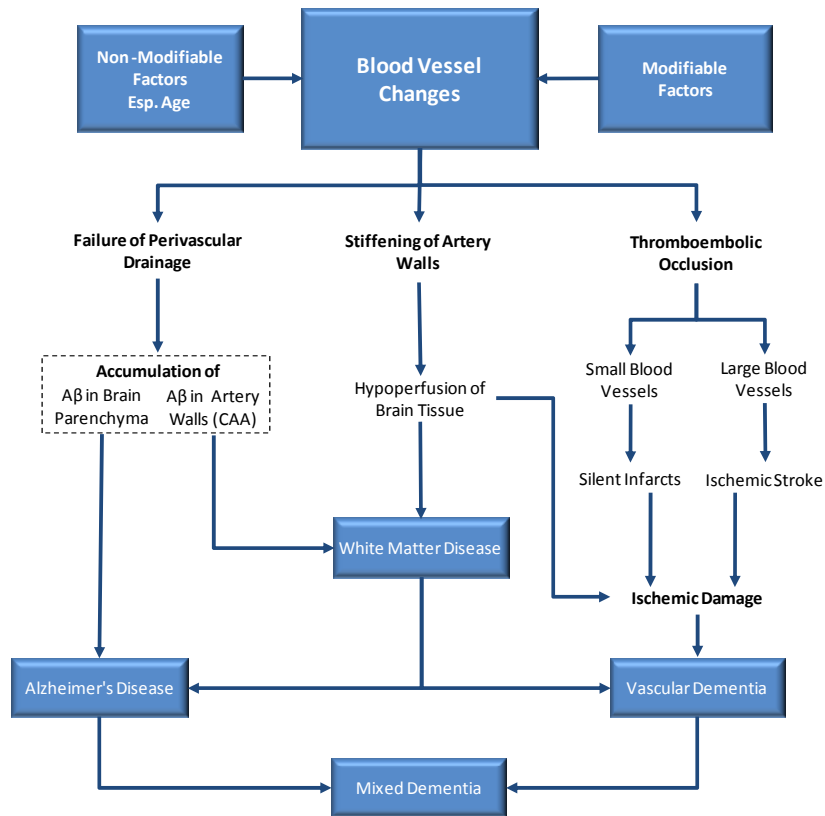
Evidence of an Association between Vascular Factors and AD

In the last decade, there has been a “confirmation of the heterogeneous and multifactorial nature of AD, likely resulting from the diverse presence of vascular risk factors or indicators of vascular disease.”⁵² Indeed, evidence has been steadily accumulating of the links between vascular factors and AD, even to the extent that some researchers now consider that AD is a vascular disorder with neurodegenerative consequence, rather than a neurodegenerative disorder with vascular consequence.⁵³ While this perspective remains controversial, the balance of evidence is compelling.^{54,55,56}

1. Some studies show that practically all reported risk factors for AD have a vascular component that specifically reduces cerebral perfusion
2. Detection of regional cerebral hypoperfusion with the use of neuroimaging techniques allows preclinical identification of AD candidates
3. Detection of cerebral hypoperfusion preceding hypometabolism, cognitive decline, and neurodegeneration in AD patients
4. Improvement of cerebral perfusion is one of the effects of most pharmacotherapy that is used to reduce the symptoms or progression of AD
5. Similarity of cerebrovascular lesions present in most AD and VaD patients
6. Detection of regional brain microvascular abnormalities before any cognitive and neurodegenerative changes in AD patients
7. Persons with stroke *and* AD confirmed post-mortem demonstrate more severe dementia

The preceding summary has shown how vascular factors may be centrally implicated in AD. In fact, the two main theories of biological causation of AD can be integrated in the following diagram, emphasizing the vascular linkages that point to pathways that are also related to ischemic stroke.⁵⁷

Vascular Factors and Dementia



A β = Ameloid Beta Protein
CAA = Cerebral Amyloid Angiopathy

A Paradigm Shift?

Cerebrovascular disease, which can lead to stroke, ultimately involves a failure of blood supply, whereas AD appears to involve in part a failure to eliminate certain molecules from the brain, a process which also normally occurs via blood vessels. It seems that these two conditions, both of which can lead to dementia, are “two sides of the same biological coin.” In short, both disease entities involve the vascular system. Adding to the mix are the degenerative changes to blood vessels that accompany aging, and that may be accentuated and/or accelerated in the presence of certain lifestyle-related factors. These blood vessel changes are definitely involved with cerebrovascular disease and, according to emerging research, may also be implicated in the initiation and/or progression of AD.

As is often true in medicine and the underlying basic science of human biology and pathology, the true picture of the connections between stroke and dementia (and, specifically, AD-related dementia) is likely even more complicated than any of the current concepts. The paradigm shift towards an integration of vascular and neurodegenerative mechanisms will need further testing before any consensus is achieved. If the role of cerebrovascular disease and stroke in dementia as a whole, and in AD-related cognitive impairment in particular, continues to be confirmed, then it will open the door to synergistic and efficient prevention opportunities that ought to be explored by public health planners.

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