Alzheimer Disease as a Vascular Disorder
Nosological Evidence

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Background—The main stumbling block in the clinical management and in the search for a cure of Alzheimer disease (AD) is that the cause of this disorder has remained uncertain until now.

Summary of Review—Evidence that sporadic (nongenetic) AD is primarily a vascular rather than a neurodegenerative disorder is reviewed. This conclusion is based on the following evidence: (1) epidemiological studies showing that practically all risk factors for AD reported thus far have a vascular component that reduces cerebral perfusion; (2) risk factor association between AD and vascular dementia (VaD); (3) improvement of cerebral perfusion obtained from most pharmacotherapy used to reduce the symptoms or progression of AD; (4) detection of regional cerebral hypoperfusion with the use of neuroimaging techniques to preclinically identify AD candidates; (5) presence of regional brain microvascular abnormalities before cognitive and neurodegenerative changes; (6) common overlap of clinical AD and VaD cognitive symptoms; (7) similarity of cerebrovascular lesions present in most AD and VaD patients; (8) presence of cerebral hypoperfusion preceding hypometabolism, cognitive decline, and neurodegeneration in AD; and (9) confirmation of the heterogeneous and multifactorial nature of AD, likely resulting from the diverse presence of vascular risk factors or indicators of vascular disease.

Conclusions—Since the value of scientific evidence generally revolves around probability and chance, it is concluded that the data presented here pose a powerful argument in support of the proposal that AD should be classified as a vascular disorder. According to elementary statistics, the probability or chance that all these findings are due to an indirect pathological effect or to coincidental circumstances related to the disease process of AD seems highly unlikely. The collective data presented in this review strongly support the concept that sporadic AD is a vascular disorder. It is recommended that current clinical management of patients, treatment targets, research designs, and disease prevention efforts need to be critically reassessed and placed in perspective in light of these important findings. **(*Stroke*. 2002;33: 1152-1162.)**

Key Words: Alzheimer disease ■ dementia ■ microcirculation ■ risk factors ■ vascular disorders

Alzheimer disease (AD) is an insidious disorder that progressively ravages the brain, destroying its memory, intellect, and dignity in the process. The main stumbling block in the clinical management and in the search for a cure of AD is that the cause of this disorder has remained uncertain until now. For more than 30 years, AD has been classified and managed as a neurodegenerative disorder,[1,2] following a report by Roth in 1955[3] that suggested that dementia should be classified into 2 distinct disorders according to the variable mental changes caused by each: vascular dementia (VaD), caused by vascular lesions, and AD, resulting from a neurodegenerative process.

Most investigators in the field have supported Roth's notion that dementing processes will differentially affect brain structures, resulting in a consistent pattern of neuropsychological deficits. Even if this notion were correct, it does not explain the clinicopathological similarities between 2 apparently different disorders, namely, AD and VaD, despite the fact that the latter originates from a cerebrovascular insult and the former through some less obvious mechanism.

Consequently, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), the presence of cerebrovascular disease in a demented individual paradoxically excludes the diagnosis of AD, and the condition is classified instead as VaD.[2] These 2 sets of criteria for differentiating AD from VaD and their respective diagnoses have been based on "expert opinion" rather than a critical review of the scientific evidence.[4]

Since the first description of this disorder more than 90 years ago,[5] there has been little clarity in the pathogenic evolution of AD, despite an enormous amount of basic and clinical research. This situation has deferred attention to the reduction of risk factors, optimal patient management, and development of effective therapy that can alter the course and the outlook of this disease. Physicians' attitudes toward modifying the course of AD have consequently been fatalis-

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tic, and little effort has been made to reshape the thinking that "nothing can be done" about this illness.

More recently, however, a substantial and ever-growing amount of evidence, discussed below, indicates that nongenetic AD is initiated by vascular factors that precede the neurodegenerative process. This conclusion seems consistent with most of the basic and clinicopathological data reported thus far for AD and is not inconsistent with other findings that may favor a neurodegenerative process as the cause of this disorder.

The question of whether AD is first provoked by a neurodegenerative process, as the prevailing paradigm maintains, or by premorbid vascular-related events, such as those listed in the Table, which then propel neurodegenerative changes mostly in the elderly, is of crucial importance. Establishing the correct pathogenesis for this dementia could, for example, help to unravel the exact mechanisms responsible for the cognitive failure and, in so doing, target specific therapy to overcome or treat this disorder more effectively.

If, as we have proposed,[6–11] AD is a vascular disorder that initiates its pathology through cerebral microvascular abnormalities, then its origin, clinical signs, diagnosis, and potential treatment should revolve around a "vasculopathic complex" that provides its defining qualities. This vasculopathic complex would be expected to be identified with the following: (1) epidemiological evidence linking vascular factors to cerebrovascular pathology that can set in motion metabolic, neurodegenerative, and cognitive changes in Alzheimer brains; (2) evidence that AD and VaD (defined here as a "poststroke hypoperfusion" dementia) share similar risk factors; (3) evidence that therapy that improves cerebrovascular insufficiency also improves AD symptoms; (4) evidence that preclinical or prodromal detection of potential AD is possible from direct or indirect regional cerebral perfusion measurements; (5) evidence that AD clinical symptoms arise from cerebromicrovascular pathology; (6) evidence of matching clinical symptomatology in AD and VaD; (7) evidence showing overlap of cerebrovascular and neurodegenerative pathology in AD and VaD; (8) evidence that cerebral hypoperfusion can trigger hypometabolic, cognitive, and degenerative changes; and (9) evidence that AD is a heterogeneous and multifactorial disorder due to a variety of vascular risk factors or indicators of vascular disease.

Reported Risk Factors for AD Compiled From Epidemiological Studies of Elderly Subjects

• Aging	• Thrombogenic factors
• Atherosclerosis	• ApoE4
• Stroke	• High serum homocysteine
• Diabetes mellitus	• Hypertension
• Smoking	• Hypotension
• Alcoholism	• High fibrinogen levels
• High HDL cholesterol	• Head injury/loss of consciousness
• Cardiac disease	• Menopause
• Migraine	• Lower education
• High serum viscosity	• Transient ischemic attacks
• Depression	• Microvessel pathology
• Fat intake	

Note that despite the discrete etiogenesis, pathological course, and clinical outlook of each risk factor, all are linked by 2 activities: (1) all are vascular related and (2) all impair or reduce cerebral perfusion. It should be noted that most of the risk factors listed are also risk factors for VaD. See text for details.

It is not the purpose of this review to be exhaustive or to profoundly interpret all the findings in support or contradiction of its main thesis, a chore that would require considerably more space than allowed here. Instead, this review will attempt to crystallize the most relevant clinical and basic findings that indicate that sporadic AD should be classified as a vascular disorder.

Epidemiological Studies

A growing number of prospective, population-based epidemiological studies have evaluated aged demented subjects and nondemented age-matched controls with the goal of identifying risk factors that might clarify the pathological process leading to AD. A reassuring feature in most of these epidemiological studies, especially the large-scale ones, is their ability to transcend cultural barriers and historical disease biases and generally to arrive at quite similar conclusions. Most of the epidemiological data discussed here have been reported within the last decade and deal only with nongenetic risk factors. As a reference point, the only suspected risk factors for AD in 1988 were aging, Down syndrome, and persons with 1 or more relatives affected with this disorder.[12]

One of the most important of the epidemiological studies, as judged by cohort population size, duration of follow-up, and determinants of various risk factors associated with AD, is the Rotterdam Study. More than 7000 elderly subjects have been studied since 1990 in a series of reports consisting of demented subjects and nondemented, age-matched controls.[13] The dementia group was further divided into vascular and Alzheimer's dementia with the use of accepted neurological, neuroimaging, and psychological screening techniques.[13,14]

On the basis of the collective data gathered by the Rotterdam Study, it was concluded that vascular risk factors and indicators of vascular disease, particularly in elderly subjects, have an established association with AD.[15,16] The risk factors for AD reported thus far in the Rotterdam Study, many of which have been confirmed by other independent studies, include the following: (1) diabetes mellitus,[17] (2) thrombotic episodes,[18] (3) high fibrinogen concentrations,[19] (4) high serum homocysteine,[20] (5) atrial fibrillation,[16,21] (6) smoking,[22,23] (7) alcoholism,[24] (8) low level of education,[25] and (9) atherosclerosis[26] (Table). All these conditions have a vascular involvement and are known to reduce cerebral perfusion.[27]

Two compelling sets of data from the Rotterdam Study and the Honolulu-Asia Study indicate that AD can develop from vascular pathology involving atherosclerosis or hypertension. In the Rotterdam Study, a group of 284 dementia patients (207 with AD and the rest with VaD), all diagnosed with varying severity of atherosclerosis (determined noninvasively), were compared with 928 nondemented age-matched controls. It was found that AD and VaD severity correlated significantly with the severity of atherosclerosis in these

patients.[26] Using Occam's razor, 2 possible conclusions can be drawn from these findings: (1) AD or VaD caused both the atherosclerosis and the degenerative vessel wall damage observed in these patients, or (2) atherosclerosis provoked the development of AD or VaD, and as the vessel pathology worsened, cognitive function deteriorated. Since the diagnosis of dementia had been recently made in these patients and it is well known that atherosclerosis often requires several decades or more to unfold, it is more likely that atherosclerosis was present before AD and VaD and sparked the gradual cognitive loss that later progressed into either dementia. Moreover, it was observed that the frequency and severity of AD and VaD were associated with the degree of atherosclerosis. The conclusion from this study that atherosclerotic carotid artery flow (which is known to result in chronic brain hypoperfusion) can lead to cognitive decline much later in life is further supported by cerebral function studies in humans in which 1 common carotid artery is occluded for 30 minutes. In this acute clinical test, the degree of cognitive performance wanes in direct relation to reduced cerebral blood flow (CBF) after carotid occlusion, a dysfunction that is reversed when occlusion is removed.[28]

It has long been suspected that raised blood pressure in midlife may precede the development of AD. Until the last few years, little evidence had been gathered to support this notion. A study of Japanese-American men (the Honolulu-Asia Aging Study) with elevated blood pressure and a mean age of 53 years reported that these individuals have a higher risk for AD when followed for 25 years.[29,30]

Elevated midlife blood pressure has been shown to increase the risk of mild cognitive impairment (MCI) in older subjects to the same degree as the presence of apolipoprotein E-ε4 (apoE4) genotype, a genetic marker for AD and for vascular pathology of the brain and heart.[31–38] It is important to note that MCI is presently considered by many in the field to be the first stage of AD when it is routinely discovered in elderly patients. MCI is suspected in patients presenting with only memory difficulties but no other cognitive disability.[39–41]

In another longitudinal Honolulu-Asia Aging Study, midlife hypertension was seen to be associated 36 years later with a significantly greater number of neurofibrillary tangles in the hippocampus and with brain atrophy in postmortem AD brains compared with age-matched AD brains with a history of normal blood pressure.[30]

More recently, the FINMONICA study examined midlife blood pressure and cholesterol concentrations in the development of MCI and AD. The FINMONICA study, which included 1449 subjects and a 21-year follow-up, reported that people with raised systolic pressure or high serum cholesterol levels in midlife had a significantly higher risk of developing MCI and, later in life, AD.[42,43] The risk for MCI or AD was higher when both blood pressure and cholesterol levels were high, suggesting that AD prevalence may be accelerated as the level of cerebral perfusion decline becomes more marked.[42] Blood pressure and cholesterol increases are also prominent in the development of VaD.[30,44–47]

Cross-cultural studies that have investigated the incidence of hypertension in genotypically similar population groups residing in Africa or the United States conclude that lifestyle rather than genetics plays a more important role in the development of high blood pressure and the risk of AD.[48]

The effect of chronic cerebral hypoperfusion on human cognition has been studied primarily in patients presenting with carotid artery stenosis of long duration and in those who have undergone surgical treatment to improve blood flow by carotid endarterectomy (CEA). A review of the literature with respect to the effects of CEA on brain function remains controversial because CEA can promote cerebral microemboli even when reversing carotid artery stenosis and increasing cerebral perfusion. However, it would appear that when global brain hypoperfusion after CEA is reversed without microembolic sequelae, cognitive ability generally improves, but when microemboli are generated or the hypoperfused state is not corrected after CEA, cognitive performance often remains unchanged.[49,50]

It now appears that coronary artery bypass grafting (CABG) surgery may induce cognitive loss in as many as 50% of patients undergoing this procedure.[51] This high prevalence of cognitive decline after CABG continues for at least 5 years after surgery.[51] With more than 150 000 new patients electing CABG surgery every year in the United States,[52] the problem warrants considerable efforts in the prevention and identification of patients at risk for postoperative cognitive dysfunction.[53,54] Prospective population studies could determine whether CABG is a major risk factor for Alzheimer's and other dementias.

One vascular event that has received little epidemiological attention in relation to its clinical gravity is the development of silent stroke. It has been estimated that approximately 11 million Americans experience a silent stroke (defined as a focal stroke without acute symptoms) every year.[55] Silent stroke shows a higher prevalence in cigarette smokers and subjects with atherosclerosis, conditions that are linked to AD and to cerebral hypoperfusion.[13,14,16,22,26,56] Silent stroke may be a "sleeping giant" in the development of AD since cerebral perfusion is often found to be reduced in association with an increased oxygen extraction fraction (misery perfusion) during an attack,[57] a hemodynamic presentation typically found in AD patients.[58,59]

Additional vascular-related risk factors have been reported for AD: migraine,[60] high intake of saturated fat,[61] presence of apoE4 allele,[33,47,57,62] transient ischemic attacks,[63] high serum cholesterol levels,[13,16,47] depression,[64,65] alcoholism,[24,63] high serum homocysteine levels,[20,66] menopause,[67,68] high fibrinogen concentrations,[19,69–71] hypotension,[72–74] ischemic stroke,[75,76] head injury,[77–79] cardiac disease including arrhythmias,[80–86] and, most importantly, aging.[7,87] Most of these risk factors are present not only in the early stages of AD but often decades before any cognitive symptoms develop.[18,22,25,26,29,42,43,46]

The main point is that despite the discrete pathologies involved in each of these risk factors (Table) and their differential clinical course and outlook, all share 1 common action: the reduction or impairment of optimal cerebral perfusion.[88] When elementary statistics are used, the possibility that these reported AD risk factors share a single, common biological pathology that is due to chance alone is highly improbable. A secondary point is that most of the

aforementioned risk factors for AD are also risk factors for VaD (Table). This relationship, if considered only by itself, strongly suggests that these 2 dementias share a common origin. When it is considered that approximately 30% of all AD brains show some form of cerebrovascular pathology, and pratically all AD brains reveal either periventricular white matter lesions, microvessel degeneration, cerebral amyloid angiopathy, or combinations of these lesions,[89–91] the connection between AD and VaD appears more than mere chance. The reverse of this relationship is equally intriguing, because approximately 40% of brains meeting the criteria for clinical VaD diagnosis have concurrent AD pathological deposits involving senile plaques and fibrillary tangles.[92] Moreover, difficulties in differentiating AD from VaD on clinical grounds alone are well known,[93–96] creating the suspicion that their pathophysiological roots are nearly identical.

In regard to the correlations that appear to fuse these 2 dementias, a reasonable explanation for the cerebrovascular component seen in some AD brains is that it is likely due to "mixed" dementia, that is, pathological lesions characteristic of AD and VaD existing comorbidly and as a separate entity from a "pure" dementia in which only neurodegenerative lesions (AD) or cerebrovascular lesions (VaD) are present. However, this argument does not explain why pure AD still retains a powerful vascular basis. For example, as shown in the Table, many of the risk factors reported for AD, such as atherosclerosis, cardiac disease, and diabetes, are not in themselves cerebrovascular events characteristic of VaD. In fact, these reported risk factors appear to convert just as easily to VaD as they do to AD.[13–26,60–87] It should be recalled that VaD usually arises from immediate ischemic, hemorrhagic, hypoxic, or anoxic events, and, as seen in the Table, AD can develop from many other conditions that might not give exclusive rise to VaD. How AD develops from these risk factors is controversial, but we have presented a "hemodynamic model" in the past that offers a possible explanation of this process and the evidence in support of its position.[6–11,88] Since it is almost certain that additional risk factors for AD will be reported in the near future, it will be of interest to see how many of these will exert an influence similar to those already known to promote a reduction of cerebral perfusion.

In summary, considerable epidemiological evidence supports the concept that AD is a heterogeneous and multifactorial disorder with a definite vascular basis.

Pharmacological Treatments for AD

No drug treatment at the present time is truly effective in the treatment of AD or in altering the course of this disorder. Only 3 drugs are available in the United States for prescriptive use in AD: tacrine(Cognex), donepezil (Aricept), and rivastigmine tartrate (Exelon). All 3 act to slow the synaptic breakdown of acetylcholine, a neurotransmitter important in memory and learning. A fourth drug, galantamine hydrobromide (Reminyl), targets "mixed" dementia, that is, VaD or AD complicated by cerebrovascular pathology.

These treatments generally provide modest damage control at the early stages of AD and offer minor to no improvement at later stages of the disease. For this reason, other drug therapies for AD have been tried. These include nonsteroidal anti-inflammatory agents,[97,98] ginkgo biloba,[99,100] estrogen during menopause,[67,68,101] dimethyl sulfoxide,[102] aspirin,[97,103] vitamin E,[104–106] acetyl-L-carnitine,[107,108] antihypertensive drugs,[109] statins,[110,111] and selegiline.[112] While the biological activity and pharmacokinetics of these compounds differ from one another and their effect in reducing the symptoms or delaying the progress of AD is debatable, they all share to a degree 1 common effect: to improve or increase cerebral perfusion.[10,113] Most (although not all) of these agents are not known to exert a direct protective or a salvaging effect on neural tissue after nonvascular damage of the brain. In other words, whatever beneficial effect is obtained from their administration in AD is not exclusively due to nerve cell rescue or protection.

Prodromal Diagnosis of AD

Prevention of brain damage and cognitive disability in AD patients is entirely dependent on the ability to diagnose this disorder as early in the disease process as possible. This strategy can salvage neurons not yet destroyed from irreversible damage and death by applying treatments that direct their action at early neuronal protection. Such treatments need not be strictly pharmacological (see Reference 113 for review).

There is now good evidence that the first stage of AD begins with MCI, defined as memory deficits with preservation of other cognitive and functional activities.[39–41] Recognition of MCI means that AD diagnosis and preventive treatment can be applied much earlier than previously practiced. One technique that offers such preclinical assessment of AD during the MCI stage is based on detection of cerebral hypoperfusion patterns with the use of single-photon emission CT (SPECT) or positron emission tomography among individuals complaining only of memory problems. In 1 study, subjects with memory complaints not meeting criteria of the Alzheimer's Disease and Related Disorders Association for AD had their regional CBF measured with SPECT and were separated into 2 groups. The majority of the subjects with significant hypoperfusion of the hippocampal-amygdaloid complex (areas linked to memory function) converted to AD within a 3-year follow-up, while patients with normal cerebral perfusion in these and other brain areas did not.[114,115]

Other neuroimaging studies have supported the aformentioned findings. In MCI patients who later converted to AD, the presence of temporoparietal (including hippocampal) hypoperfusion,[116] hippocampal-parahippocampal hypoperfusion,[117] and posterior cingulate hypoperfusion[118] distinguished this population group from non-MCI subjects.

Other markers indirectly reflecting reduced cerebral perfusion are used with equal success. Positron emission tomography, when used to measure cerebral glucose metabolism, shows specific decline of glucose metabolic rate utilization in the hippocampus in subjects with MCI[119,120] and in the brains of subjects who later convert to MCI.[121] Cerebral hypometabolism is often due to a lowering of cerebral perfusion.

Emission tomography is also useful in diagnosing very-early-stage AD. With the use of SPECT image-reconstruction technique, elderly individuals with very mild AD (or MCI)

symptoms showed significant hippocampal hypoperfusion compared with age-matched nondemented subjects.[122]

Reduced hippocampal volume secondary to ischemic atrophy has been used successfully in MCI patients to identify a population group more likely to initiate conversion to AD.[123] These studies indicate that hippocampal perfusion levels may be a useful marker in predicting very early diagnosis of AD. The hippocampal region is known to contain the highest density of neurofibrillary tangles in the advanced stage of AD and is the most damaged brain region in these patients found at autopsy.[93]

By focusing on abnormal CBF patterns or their pathological end products, these neuroimaging techniques are becoming more reliable and sensitive in detecting prodromal clinical features predictive of progressive cognitive loss and possible unfolding of Alzheimer's dementia. Neuroimaging techniques used for the detection of chronic cerebral hypoperfusion in regions linked to memory and learning are consequently becoming a common diagnostic tool to identify the earliest possible stage of disorders that may later convert to AD. These techniques are medically attractive because they are noninvasive, cost-effective, easily performed, informative and, in the proper hands, provide a quantitative measure of disease progress and the relative merit of ongoing clinical management or treatment benefits.

AD Capillary Degeneration and Basic Considerations

Cerebral capillary degeneration has been shown to be present in practically all AD brains examined postmortem and in cortical biopsy material from pathologically confirmed AD.[124–132] The variety of these brain microvascular aberrations has been catalogued since 1967[133] and may have been first described by Tuke[134] in 1873, even before the clinical description of AD by Alzheimer in 1907.[4]

The capillary changes recorded in AD brain with the use of light and electron microscopy consist of (1) basement membrane thickening, (2) endothelial compression, (3) luminal "buckling" and narrowing, and (4) pericyte degeneration. These cerebral microvessel aberrations have been consistently observed in AD brain tissue by a considerable number of investigators using a variety of histological techniques.[135–143] The degenerate capillaries appear more prevalent in the hippocampus,[136,139,142] a region that is linked to memory and learning and is an initial target for neurofibrillary tangle formation in AD.[144] Microvessel changes in AD brains show no correlation to the stage of the disease (Braak I to VI), a finding that suggests that such capillary anomalies are not a consequence of AD pathology.[145]

Brain capillary distortions do not appear to be significantly targeted by amyloid angiopathic deposition. Ultrastructural examination of AD tissue reveals that cerebral amyloid angiopathy is mainly deposited in smooth muscle cells involving cerebral arterioles but often spares capillary endothelium and blood-brain barrier damage.[146–148]

The exact causes of the capillary structural changes, however, are unknown and would be difficult to demonstrate in humans since they may involve a series of interacting factors. Nonetheless, experiments in rodents undergoing chronic brain hypoperfusion (with the use of bilateral carotid artery occlusion) for 1 year have revealed that capillary changes almost identical to those described in AD brains also develop in these animals, with a distinct prevalence toward the CA1 hippocampal region.[147]

With the use of similar models of chronic brain hypoperfusion in rodents, a state mimicking MCI can be induced in which the only behavioral outcome observed after weeks or months is visuospatial memory impairment.[149] Rodent studies have reported cerebral metabolic changes after chronic brain hypoperfusion consisting of hippocampal cytochrome oxidase decline (a marker of energy metabolism),[149] microtubule-associated protein-2 loss in CA1 (a marker of protein synthesis),[150] changes in monoamine neurotransmitter turnover,[151] reduction of postsynaptic cholinergic activity,[152] decreased brain glucose utilization,[153,154] reactive gliosis,[155] heme oxygenase expression (a marker of oxidative stress),[156] and increase in matrix metalloproteinase-2 (a marker of vessel calcification).[157] All these changes occurred many weeks to months before any neuronal damage or spatial memory dysfunction was recorded, suggesting that chronic brain hypoperfusion induces important metabolic changes, mostly in the hippocampal area, which eventually trigger MCI-like memory loss in rats. In these studies animals were not observed to develop brain microinfarcts, hemorrhage, white matter changes, or high blood pressure, but CBF, when measured, was reduced to 25% to 33% of baseline.[158,159]

Reduction of CBF can also be obtained with the intravenous administration of freshly solubilized $A\beta_{1\text{-}40}$ in mice[160,161] but not with the use of the reverse peptide $A\beta_{40\text{-}1}$.[161] In addition to the cerebral hypoperfusion observed in these rodents, regional vasoconstriction and increased vascular resistance are also seen, particularly in brain cortex.[160] These findings could partly explain the negative role of amyloid angiopathy in cerebral perfusion when the peptide is deposited in AD cerebrovasculature.

These experimental findings form a basic understanding of what happens to brain metabolic activity when aging and cerebral hypoperfusion meld in an animal model and offer some insight into what might be happening during the early stages of AD, when advanced aging and brain hypoperfusion appear to play major roles.

AD-VaD Correlates

It is commonly known that the differential diagnosis of AD and VaD on the basis of clinical evidence is, at best, very difficult.[94,162–164] This problem exists because of overlapping features found in both disorders. For example, AD and VaD share features involving cerebral hypoperfusion, white matter changes,[165–167] pathophysiological markers,[168–172] genetic links,[173–176] overlapping symptomatology, and diagnostic criteria of dubious reliability.[177–185] Several objective clinical criteria are presently used to distinguish AD from VaD, such as the Alzheimer Disease Diagnostic and Treatment Centers, National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), *DSM-IV*, and the Hachinski Ischemia Score.[186] Of these, the most useful in differentiating VaD from AD appears to be the

Hachinski Ischemia Score,[187] if it is assumed that mixed pathology is minimally present.[188] The use of CT or MR neuroimaging contributes little to characterizing either dementia when white matter changes and medial temporal atrophy are involved.[189] These findings strongly argue in favor of the hypothesis that AD and VD are not mutually exclusive disorders.

The similarities of the clinical presentation, pathophysiology, and rate of cognitive decline between AD and VaD have led to the development of treatments that appear useful to both conditions at the level where risk factors are discovered or during the disease process.[109,110,177,190–192] For this reason, several pharmaceutical companies have targeted both dementias using a common drug application,[110,111,191] with the rationale that central cholinergic mechanisms are impaired in both AD and VaD.[192] However, it is also possible that cholinesterase inhibitors have another action aside from increasing acetylcholine stores: that of improving CBF modestly and transiently by their vasodilating innervation derived from the nucleus basalis of Meynert.[193,194]

The comorbidity of many vascular-related risk factors makes a compelling case for AD and VaD sharing a common origin. We and others have reviewed this phenomenon in the past; the Table lists a series of suspected and actual vascular risk factors found in AD and also generally in VaD.[9,15,45,96]

In addition to sharing vascular risk factors, a major study has reported the coexistence of similar neuropathological features of AD and VaD in elderly nuns.[76] That study also found that these elderly women required an 8-fold increase in neurofibrillary tangles to express the same severity of dementia when strategic cerebral infarctions were absent, suggesting that patients with previous strokes require considerably less AD pathology for dementia symptoms to appear.

Cerebral Hypoperfusion and Hypometabolism in AD: Chicken or Egg?

The collective findings discussed thus far imply that brain hypoperfusion probably precedes the hypometabolic and neurodegenerative state seen in AD. This is a reasonable assumption based on Darwinian laws of survival because it is less likely that neurons exposed to oxidative stress and impaired energy substrate delivery will reduce blood flow to them to accelerate their death. Moreover, the conclusion that brain hypoperfusion "pushes" oxidative stress, cognitive decline, and neurodegeneration is further reinforced by the following 6 findings. (1) Regional microvessel degeneration is independent of AD stage severity (Braak I to VI), a finding that indicates that these microvascular changes are not a consequence of AD pathology.[147] (2) Regional hypometabolism found in Alzheimer brains does not appear to result from neurodegenerative damage or senile plaque formation but is present before significant tissue pathology.[195,196] (3) Abundant density of senile plaques, neurofibrillary tangles, and neurodegenerative changes that met neuropathological criteria for AD have been found in a large percentage of cognitively normal, elderly brains at autopsy.[197] (4) The same structural capillary aberrations seen in AD have been also been observed in Down syndrome at a young age, when no senile plaque or neurofibrillary tangle formation has yet formed.[139] (5) Young patients with Down syndrome show abnormal patterns of cerebral perfusion similar to those found in AD at an age when senile plaques and neurofibrillary tangles are still absent from their brains and before any dementia symptoms are manifested.[198,199] (6) Oxidative stress seems to precede $A\beta_{1\text{-}42}$ deposition by many years in Down syndrome subjects who die in their teens and twenties,[200] a finding that indicates that AD-like pathology is not the trigger of neuronal metabolic disruption in these patients.

While it could be argued that hypometabolism in AD may elicit microvascular changes at some point, a considerable number of animal experiments have revealed that chronic brain hypoperfusion can trigger oxidative stress, energy metabolic deficits, and memory loss before any neuronal structural pathology materializes,[149–159] whereas we are aware of no data that demonstrate that the reverse process can or does occur. Moreover, the recent discovery of "neuroglobin" in rodent and human brain could partly explain why CA1 hippocampal neurons are exquisitely sensitive to hypoperfusion and hypometabolism.[201] Neuroglobin in brain appears to act much like myoglobin in cardiac muscle cells in that it aids in oxygen diffusion to the mitochondria. Lower resistance by CA1 to ischemia may be due to lower oxygen supply resulting from less available neuroglobin, whose lowest expression is in the hippocampus.[201]

For further reading on the role of vascular pathology in AD, the reader is referred to recently published volumes on the subject.[202–204]

Summary

Mounting clinical and experimental evidence indicates that AD can be caused by vascular-related factors that directly reduce cerebral perfusion to a critical level of dysfunction. This evidence can be summarized as follows: (1) epidemiological studies show that risk factors thus far described for AD have a vascular basis; (2) most of the risk factors for AD are also associated with VaD; (3) practically all drugs reported to slow the development of AD improve or increase cerebral perfusion; (4) development of AD can be predicted preclinically by measuring regional cerebral perfusion deficits; (5) clinical evidence exists that AD symptoms are related to brain microvascular hemodynamic pathology; (6) clinical symptomatology is similar in AD and VaD; (7) cerebrovascular pathological lesions often overlap in AD and VaD; and (8) evidence that cerebral hypoperfusion appears to precede the hypometabolic, cognitive, and degenerative pathology that is present in AD.

The wide range of potential vascular conditions that can develop into Alzheimer's dementia may help to explain the heterogeneous and multifactorial nature of this disorder. This review attempts to crystallize into a coherent clinical picture the major findings in support of the proposal that identifies AD as a vascular disorder.

Since the value of scientific evidence often revolves around probability and chance, it is fair to conclude that the data presented here pose a powerful statistical argument in support of the conclusion that AD has a vasculopathic origin. Rarely has so much verifiable information been available

from so many different sources that point so compellingly to the nosological origin of a disorder as in the case for AD.

This review also seeks to provide an alternative explanation to that offered by conventional wisdom, which has dominated research and clinical thinking and, through much self-investment, has delayed potential progress in the area of AD patient care for the past 25 years. Conventional wisdom has not appreciably improved AD course or disease outlook, nor has it engendered much hope that its extension into the future management and treatment of this disorder will result in a better quality of life for AD victims. It is the medical community's prime scientific responsibility, and it is in the patients' best interest, to recognize the possibility that conventional wisdom has been incorrect in the classification and management of AD.

It is now the task of investigators and others responsible for patient welfare to determine, in the immediate future, a course of action that includes proper examination of the findings presented in this review, with the intent of applying such information to the best advantage of AD patients.

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