Is the distinction between Alzheimer's disease and vascular dementia possible and relevant?

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Advances in epidemiological, clinical, imaging, and neuropathological studies have undermined the clear distinction between vascular and Alzheimer-type dementia, which has characterized the last two decades of research in dementia. A significant degree of overlap between the two entities was demonstrated in terms of clinical expression, risk factors, and postmortem brain autopsy. In this article, we propose mechanisms by which cardiovascular risk factors might affect the manifestation of Alzheimer's disease, suggest possible explanations for the overlap with vascular dementia, and discuss the implications this might have on future differential diagnosis and treatment strategies.

Dialogues Clin Neurosci. 2003;5:7-15.

Keywords: *Alzheimer's disease; vascular dementia; cardiovascular risk factor; cholesterol; apolipoprotein E; diabetes; hyperhomocysteinemia*

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"Brain atherosclerosis" was the term historically used in an attempt to provide a rational explanation for the progressive cognitive decline observed in many—but not all—elderly people. The term was derived from the observation that the vasculature of the brain was disrupted in the elderly, like that of the rest of the organs, and that many—but not all—demented individuals showed brain infarcts at postmortem examination. Despite the fact that Alois Alzheimer published his description of a demented individual with no significant underlying vascular pathology 100 years ago, the efforts to distinguish between vascular and nonvascular dementia were mostly undertaken in the 1970s.[1-3] The impetus to distinguish between the two types of dementia, Alzheimer's disease (AD) and the entity initially termed multi-infarct dementia (MID) and later on vascular dementia (VD), had both scientific and pragmatic underpinning (the change from MID to VD was necessary, since the term MID did not cover the full range of cerebrovascular pathology).

Reasoning for differentiation between AD and VD

The scientific reasoning for the distinction between AD and VD was based on evidence collected during the 1970s and 1980s, leading investigators to conclude that a vascular pathology was not the main underlying pathology for most demented individuals. First, many demented individuals had diffuse amyloid deposits or plaques and neurofibrillary tangles as the predominant postmortem pathology, with no or minimal vascular pathology or infarcts.[1] Second, in some of these demented individuals with predominantly plaques and tangles, the counts of the cholinergic cells in the nucleus basalis of Meynert were diminished, as was the activity of the neurotransmitter acetylcholine in the cortex.[4-8]

Selected abbreviations and acronyms

AD	*Alzheimer's disease*
AGE	*advanced glycation end-product*
ApoE	*apolipoprotein E*
APP	*amyloid precursor protein*
HDL	*high-density lipoprotein*
IDE	*insulin-degrading enzyme*
MCI	*mild cognitive impairment*
MID	*multi-infarct dementia*
VD	*vascular dementia*

Taken together, these findings convinced researchers that AD was a unique and discrete disease entity with well-defined histology (presence of plaques and tangles) and neurochemistry (cholinergic deficiency), thus leading a sustainable hypothesis regarding its pathophysiology.[9] On the other hand, as VD was conceptualized as a "matter of strokes large and small,"[10] the Hachinski Ischemic Score was developed in order to differentiate it from AD. The scale is based on presence of risk factors for VD, such as hypertension, history of strokes, and evidence of associated atherosclerosis, and on the clinical characteristics of strokes (abrupt onset, stepwise deterioration, fluctuating course, focal neurological signs, and symptoms). Additional support for a vascular origin of dementia according to the Hachinski Ischemic Score were the presence of nocturnal confusion, relative preservation of personality, depression, somatic complaints, and emotional incontinence. The items making up the scale reflect the conceptualization of vascular risk factors as exclusively associated with brain infarcts, which, in turn, are responsible for the clinical manifestations of MID (and later VD).

The pragmatic reasoning for the distinction between AD and VD was the assumption in the late 1970s and early 1980s that specific treatments for AD exist. This assumption was based on the apparent finding that increasing cholinergic activity by pharmacological manipulations could improve symptoms in demented individuals.[11-13] In order to increase the likelihood of demonstrating an effect for drugs enhancing cholinergic activities, it was believed to be essential to identify patients affected by a cholinergic deficit, ie, AD patients, and distinguish them from VD patients, who were not expected to benefit from cholinergic enhancement.

However, since the late 1990s, this distinction has been challenged by clinical, neuropathological, epidemiological, and even therapeutic studies. The following paragraphs will elaborate on this challenge, attempt to explain the role of cardiovascular risk factors in the AD syndrome, and propose possible interactions between AD and VD.

Evidence for overlap between AD and VD

Clinical and pathological evidence

The traditional characterization of AD (an insidious and gradual progression with no focal neurological signs) and VD (an abrupt onset with stepwise progression and focal neurological signs) was not unequivocally supported by data.[14-19] Significant numbers of patients were described who had predominantly brain infarcts, but an AD-like course, and vice versa.[20] Also, the availability of advanced imaging methods lead to the recognition of diverse neuroanatomical vascular brain lesions (thromboembolic stroke, small lacunar infarcts, and white matter lesions), whose implication and etiology are still debatable but are probably the result of hypoperfusion to brain tissue.[21-23] It was also recognized that many of the infarcts identified by imaging techniques or at postmortem examination are silent infarcts, which do not necessarily contribute to clinical expression in terms of focal signs or symptoms or cognitive impairment. Furthermore, for some VD subtypes, namely subcortical microvascular disease, mild cognitive impairment (MCI) can precede dementia and thus mimic the clinical course of AD.[24]

Neuropathologically, the seminal "Nun Study," which followed 102 elderly nuns to postmortem, demonstrated that, among those who met neuropathological criteria for AD, those with brain infarcts had higher prevalence of clinically expressed dementia than those without infarcts.[25] Similarly, the complex interaction between AD and vascular pathology was demonstrated in a 3-year follow-up study of stroke patients who were not demented before the stroke.[26] One third of the patients who developed poststroke dementia were diagnosed as suffering from AD.[26] Finally, a substantial proportion of brains who meet neuropathological criteria for AD show lesions such as cerebral amyloid angiopathy, microvascular degeneration, periventricular white matter lesions, and other vascular pathology,[27,28] further complicating the neuropathological distinction between the two disease entities.

Epidemiologically, it has been demonstrated that individuals affected by vascular risk factors during midlife[29-42]

are more likely to manifest dementia associated with AD-like brain pathology in old age. Hence, it appears that most of the risk factors for cardiovascular disease, such as diabetes, hypertension, abnormal plasma cholesterol, high intake of saturated fat, thromboembolic episodes, high fibrinogen concentrations, high serum homocysteine, atrial fibrillation, smoking, alcoholism, atherosclerosis, and apolipoprotein E4 (ApoE4) allele, are also risk factors for AD and not exclusively for VD.

Therapeutically, it was recently shown that drugs enhancing cholinergic activity are as effective in patients suffering from VD as they are in AD patients,[43] hence eliminating the pragmatic justification for the distinction.

The simple solution to the challenge brought to the distinction between AD and VD is to invoke the "mixed dementia" notion, by which dementia is caused by the concomitant presence of both AD-like pathology (plaques and tangles) and infarcts, which contribute to the manifestation of dementia in a cumulative fashion. This explanation has much face validity, since both AD pathology and VD pathology are age-dependent manifestations, hence the idea that they converge to manifest dementia is a plausible one. A corollary explanation is that the incidence of cardiovascular risk factors, such as diabetes and hypertension and additional constituents of the metabolic syndrome (hyperlipidemia, central obesity), progressively increase after the fifth and sixth decades of life,[44,45] and contribute to a pathway during the seventh and eighth decades of life leading to VD, which, together with AD-like pathology, reaches the threshold for clinical manifestation of dementia. However, the high prevalence of demented individuals whose neuropathological examination reveals both AD and VD pathology[28,46-48] does not necessarily prove a synergetic relationship between the two types of lesions to produce dementia. It is conceivable that either the neurodegenerative or the vascular lesions do not contribute to the clinical manifestation until a certain load of pathology is reached. Thus, in some patients with cooccurrence of both types of lesions, one type of lesion could be regarded as an "innocent bystander." Indeed, the correlations between clinically diagnosed mixed dementia and neuropathological examination remain poor.[49]

Cardiovascular risk factors

A more interesting hypothesis of heuristic value would indicate that the risk conferred by the presence of cardiovascular risk factors, such as diabetes, hypertension, or hyperlipidemia, toward AD disease is independent of the risk conferred by the same risk factors toward VD. The following paragraphs will review this possibility, provide suggestions for mechanisms by which cardiovascular risk factors contribute directly to AD pathology, and discuss possible ways for interaction and overlap between AD and VD. Finally, treatment and prevention implications based on the overlap between the two pathologies will be briefly discussed.

The idea that abnormal lipoprotein metabolism in general, and cholesterol in particular, affects the risk for AD derives from long-term follow-up of cohorts from middle age into senescence. Some,[38,41] but not all,[50] long-term follow-up studies have demonstrated a positive relationship between plasma hypercholesterolemia in midlife and rates of AD in old age. Furthermore, high plasma levels of high-density lipoprotein (HDL) cholesterol in midlife were found to be associated with a greater load of plaques and tangles in some,[51] but not all,[52] studies. The simple assumption would be that, in the same way as a high blood level of cholesterol damages the vascular endothelium in the periphery, it also damages the brain vasculature, hence increasing the risk for VD. However, it is also possible that abnormal cholesterol metabolism has a direct effect on the brain not mediated by its effect on the cerebral vasculature. This is supported by data showing that brain cholesterol metabolism and transfer is at least partly independent of systemic cholesterol metabolism. The main source of brain cholesterol is de novo synthesis in the brain itself, rather than transport from plasma,[53,54] which possesses a distinct set of lipoproteins.[55,56] Furthermore, it is assumed that the major role of the apolipoproteins implicated in AD in the brain is redistribution of cholesterol between different brain compartments rather than transfer to and from the plasma.[57]

There exist a number of hypotheses explaining the direct effect of cholesterol on the brain and on brain pathological processes. The degree of activity of the different amyloid precursor proteins (APPs) cleaving enzymes varies according to the surrounding lipid moiety: environments richer in cholesterol promote β- and γ-secretase, which produce insoluble amyloid plaques. Furthermore, β-amyloid also acts as a seed for the amyloid plaque in a lipid-rich membrane.[58] On the other hand, conditions poorer in cholesterol promote α-secretase activity, which does not create plaques.[59-61] Hence brain cholesterol metabolism

has an independent effect on amyloid plaque formation, not mediated by vascular pathology, thus potentially directly contributing to AD pathology.

Interestingly, recent studies have shown a decrease in AD prevalence among patients treated with cholesterol-lowering drugs from the statin group.[62,63] Statins are compounds that inhibit HMG CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase, a enzyme central to the process of de novo cholesterol synthesis. Studies have shown that statins lower the risk of developing dementia independently of their effect on plasma lipid levels[63,64] or exposure to other lipid-lowering drugs.[63] These results suggest that statins have properties additional to their systemic lipid-lowering effect, some of which are probably associated with central nervous system (CNS) protection.[65] Taken together, these lines of evidence suggest that, apart from its atherogenic effect, cholesterol is involved in several metabolic pathways in the brain, some of which may be relevant to the pathological process associated with plaque and tangle formation.

The relationship between AD and apolipoprotein E (ApoE) also indicates a direct role for abnormal lipoprotein metabolism on AD pathology that is not mediated by vascular lesions. ApoE is a protein involved in lipid transport and has three isoforms: ApoE2, ApoE3, and ApoE4.[66] The protein's polymorphism affects hepatic binding, uptake, and catabolism of chylomicrons, chylomicron remnants, very-low-density lipoprotein cholesterol, and subspecies of HDL cholesterol.[67] In the brain, ApoE is a major lipid-binding protein.[68] ApoE complex has a central role in neuronal repair and maintenance processes,[69] in which ApoE4 is less efficient than ApoE2 and ApoE3. These differences in the efficacy of neuronal repair will not be expressed clinically in a young healthy person with an intact brain. However, when a brain disease such as AD develops, the presence of the ApoE4 isoform reduces repair efficacy, enhancing tissue and function loss.[68] In agreement with the theories presented above, some,[70] but not all,[71-76] population-based studies have shown the association between ApoE4 allele and AD to be independent of the lipoprotein's effect on systemic dyslipidemia and atherogenesis.

However, other data support the vascular mechanism in ApoE pathology, showing that ApoE4 is a risk factor for dementia with stroke—either VD or AD with stroke.[77] Neuropathological studies of AD brains demonstrated that ApoE4 frequency is higher in AD brains with some kind of cerebrovascular pathology. The frequency of the ApoE4 alleles was six times higher in AD brains with moderate-to-severe cerebral amyloid angiopathy, when compared with mild amyloid angiopathy, and the severity was correlated with ApoE4 load (one versus two alleles).[78]

Diabetes, like hypercholesterolemia, is a complex systemic metabolic disorder, traditionally regarded as a risk factor for stroke and consequently for VD.[79-81] Diabetic patients who suffer strokes are at greater risk for subsequent dementia than nondiabetic individuals who suffer strokes.[82] The association between AD and diabetes is supported by some,[29,83,84] but not all,[85-88] epidemiological studies. In middle-aged men followed until old age, for example, there is an association between diabetes and neuropathological finding of both AD and VD dementia.[84]

Several mechanisms have been invoked to account for the direct relationship between diabetes and AD. Hyperglycemia causes high levels of advanced glycation end-products (AGEs), which have been found in high concentrations in neuritic plaques and neurofibrillary tangles.[89] AGEs have been shown to cause cross-linkage of extracellular proteins and promote aggregation of β-amyloid.[90] Alternatively, insulin at high levels (characteristic of some phases of type 2 diabetes) could be a competitive substrate for insulin-degrading enzyme (IDE). This enzyme has been found to be involved in the degradation of other substrates as well as insulin, amyloid being one of them. It is thus conceivable that high insulin levels cause competitive inhibition of amyloid degradation, thus leading to less effective dissolution of seeds for amyloid plaques.[91,92] Also, elevated levels of blood insulin have been suggested to impair cognitive performance,[93] leading to the hypothesis that serum insulin may alter cognitive function by affecting brain regions rich in insulin receptors, such as the hypothalamus, olfactory bulb, and hippocampus.[94-97]

Hypertension, like diabetes, has been directly implicated in AD by epidemiological studies in which midlife hypertension was associated with greater number of neurofibrillary tangles and neuritic plaques in the hippocampus and neocortex, and a more pronounced brain atrophy compared with midlife normotensive individuals.[98] Furthermore, the association between midlife hypertension and AD remained unchanged after controlling for vascular lesions, such as large infarcts or lacunar infarcts. Although hypertension exerts its deleterious effect through damage to blood vessels of all calibers and in all end organs by producing ischemia and infarcts, it is also plausible that hypertension causes

more subtle damage to very small blood vessels, which results in abnormal endothelial permeability and extravasation of plasma constituents.[99,100] These, in turn, could interact with amyloid or amyloid precursor to promote plaque formation.[19] A corollary possibility is that hypertension-induced vascular lesions, which lead to tissue ischemia, disrupt endothelial integrity. This enables interaction between plasma constituents or an effect on amyloid, thus promoting plaque formation.

White matter lesions are an additional phenomenon linking cardiovascular risk factors and AD pathology. Cardiovascular risk factors, such as hypertension, diabetes, and ischemic heart disease, have been found to be associated with white matter lesions by leading to a dysfunction of the blood–brain barrier, which, in turn, either through plasma component extravasation or brain cell reaction, promotes white matter changes.[101] White matter lesions have been suggested to be a common finding in AD and VD,[102] and have the same neuropathological appearance in the two disorders. It has been hypothesized that subcortical white matter lesions interact with AD pathology to produce dementia.[102]

Irrespective of the mechanism involved, midlife and late-life hypertension has been demonstrated to be positively associated with dementia in old age in several,[38,103-108] but not all,[109-111] population-based studies.

Hyperhomocysteinemia (higher than 14 micromolar), which reflects folic acid deficiency, has been associated with increased incidence of coronary artery disease, stroke, and cancer,[112-114] as well as impaired cognition and dementia in some[115,116] studies. However, in one study,[117] total levels of homocysteine were associated with silent brain infarcts and white matter lesions independently of each other and of other cardiovascular risk factors. The contribution of hyperhomocysteinemia to dementia could be thus mediated by periventricular white matter lesions, which, in their severe form, were found to be independently associated with cognitive decline at a three times faster rate than average.[118] Alternatively, studies supporting the direct effect of homocysteine on AD pathology have demonstrated that homocysteine causes neurotoxicity in cultured neurons by activating *N*-methyl-D-aspartate (NMDA) receptors[119] or causing DNA damage and thus triggering apoptosis.[120] Experiments in cell cultures and mouse models of AD suggest that folic acid deficiency and homocysteine impair DNA repair in neurons, which exposes them to oxidative damage induced by amyloid.[121]

Finally, in addition to the independent role of promoting AD pathology, all the risk factors presented above share the ability to promote atherosclerosis.[122] This raises the question of whether atherosclerosis itself is the final common pathway through which they are involved in the pathogenesis of AD. Supporting this possibility is a population-based study of newly diagnosed demented patients, in which the frequency of AD and VD was correlated with the severity of atherosclerosis. The odds ratio for AD in those with severe atherosclerosis compared with those without was 3.0. This association was stronger for those affected by atherosclerosis who were also ApoE4 carriers.[36] An alternative explanation for these results could be that dementia causes an aggravation of atherosclerosis by alteration in lifestyle and diet.

Conclusion

The data presented above lend themselves to several interpretations. It is possible that "pure" neurohistological vascular or "pure" plaques and/or tangles dementias constitute the extreme and rare end of a continuous process. In fact, a significant proportion of dementia cases present vascular lesions upon neurohistological examination—the location, extent, and clinical implications of which depend on the damaged vessel, and the insidious formation of plaques and tangles.[27] The cooccurrence of two pathological processes acting in parallel damages brain tissue, which, in turn, leads to a threshold of brain dysfunction viewed as clinical symptoms.[25] It is thus conceivable that cerebrovascular damage is caused in individuals affected in midlife by vascular risk factors, which later joins progressive and age-dependent formation of amyloid plaques, thus damaging brain tissue and being expressed as dementia. Conceptually, this would not be different from other aging processes leading to organ failure via several, concomitant processes, such as cardiac failure due to coronary ischemia and valvulopathy, or leading to functional failure, such as visual failure due to concomitant cataract and retinopathy.

Alternatively, rather than comorbidity of VD and AD-type dementia, part of the AD pathological pathway could involve a vascular component in which impairment of blood–brain barrier leads to disruption of selective permeability (by altering endothelial functioning), which, in turn, stimulates plaque and tangle formation.

An additional option for the conceptualization of the role of risk factors discussed above, and of other risk fac-

tors in AD, is that AD is a complex, multifactorial disease. At various points of the pathway towards amyloid plaque and neurofibrillary tangle formation, different contributing factors could pose their effect: the lipid milieu of the neuronal membrane could contribute to enhancement of APP-cleaving enzymes (β- and γ-secretase) leading to insoluble products; hyperinsulinemia could compete with amyloid for IDE and thus enable less dissolution of amyloid, competitive inhibition of amyloid-degrading enzyme, and promotion of cross-linkage of extracellular proteins by AGE; and the presence of the ApoE4 allele could be less effective in neuronal repair when disease processes exist. Thus, every risk factor discussed above could contribute to a different phase of plaque formation or consolidation. Although this theory provides an opportunity for an integrative conceptualization regarding the role of the various risk factors involved in the AD pathway, we are aware of the fact that it is still speculative in nature and demands further evidence.

Because some of the cardiovascular risk factors are modifiable, investigating the mechanisms by which they contribute to AD pathology and the manifestation of dementia has implications in prevention. This is particularly interesting, since in other multifactorial diseases, such as stroke, coronary heart disease,[123] and colon cancer,[124] modifiable environmental factors such as diet, physical activity, and smoking may account for over half of the variability leading to the disease. Not surprising therefore are studies demonstrating that physical and total activity in midlife,[125-127] diet,[40] and mild-to-moderate alcohol consumption[128] are protective against AD. However, these data should be seen with caution since there are not enough prospective studies to set clear guidelines regarding the medical and nonmedical strategies for dementia prevention or delay. ❑

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¿Es posible y relevante la distinción entre la Enfermedad de Alzheimer y la demencia vascular?

Los avances en los estudios epidemiológicos, clínicos, de imágenes y neuropatológicos han socavado la clara distinción entre demencia vascular y demencia de tipo Alzheimer, la cual ha caracterizado las últimas dos décadas de investigación en demencia. Se ha demostrado un grado significativo de sobreposición entre estas dos entidades respecto a la expresión clínica, los factores de riesgo y la autopsia cerebral postmortem. En este artículo se proponen mecanismos a través de los cuales los factores de riesgo cardiovascular pueden afectar la manifestación de la Enfermedad de Alzheimer, se sugieren posibles explicaciones para la sobreposición con la demencia vascular y se discuten las repercusiones que esto pudiera tener a futuro en los diagnósticos diferenciales y en las estrategias terapéuticas.

La distinction entre maladie d'Alzheimer et démence vasculaire est-elle possible et pertinente ?

Les progrès réalisés sur le plan des études épidémiologiques, cliniques, neuropathologiques et de l'imagerie ont estompé la distinction nette entre démence vasculaire et maladie d'Alzheimer qui avait caractérisé les 20 dernières années de recherche sur la démence. Un degré significatif de chevauchement entre les deux entités a été démontré en termes d'expression clinique, de facteurs de risque et d'autopsie cérébrale post mortem. Dans cet article, nous proposons des mécanismes par lesquels les facteurs de risque cardio-vasculaire peuvent affecter les manifestations de la maladie d'Alzheimer, suggérons des explications possibles pour le chevauchement avec la démence vasculaire et discutons les implications de ces réflexions sur le diagnostic différentiel futur et les stratégies thérapeutiques.

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