Therapy of vascular dementia: perspectives and milestones

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Cerebrovascular disease is common in the elderly and can cause a wide spectrum of impairments that range from mild to severe. Sensitive and specific definitions of cerebrovascular cognitive impairment are hampered by the fact that cerebrovascular disease is not easily linked to cognitive syndromes, either clinically or pathologically, and the presence of coincident Alzheimer's disease is common. Importantly, however, it does appear that the dementia caused by brain vascular disease may share similar anatomical substrates with Alzheimer's disease, supporting the notion of a common substrate to dementia. Treatment of vascular cognitive impairment may need to emphasize primary or secondary prevention of cerebrovascular risk factors such as hypertension, but some symptomatic treatments are beginning to show modest success. Raised awareness of cerebrovascular disease as a cause for cognitive impairment is likely to result in better detection and treatment, leading to improved cognitive health for our aging population. Patients with vascular dementia (VaD) show cholinergic deficits that may result in characteristic clinical syndromes for different subtypes of the condition. Subcortical VaD is characterized by executive dysfunction and behavioral problems, reflecting deterioration of the frontal lobe. It is still under consideration whether cholinesterase inhibitors may have any effects on the typical symptoms of VaD. The authors' suggestion is that VaD is not a unique pathology: the etiopathogenesis of multi-infarct dementia and that of subcortical VaD are quite different. Future studies need to consider those entities separately to obtain good results, for a group of patients for whom, until now, there have been few therapeutic options.

Vascular dementia (VaD) is defined simply as the syndrome of dementia due to brain vascular disease. [1]. Numerous epidemiologic studies show a high prevalence of vascular brain injury amongst the elderly [2–3] and recent evidence supports a strong association between vascular risk factors and dementia [4,5]. Overall, in the Western world, vascular disease is the second most common cause of dementia [6]. However, in the very elderly, aged 85 years and older, there is a high risk of both stroke and Alzheimer's disease (AD), and the prevalence of VaD is reported to be slightly higher than that of AD (46.9 and 43.5%, respectively, with some patients possibly having mixed forms of dementia) [7]. In Europe, the prevalence of VaD is estimated to be 1.5 to 4.8% for individuals between the ages of 70 and 80 years [8].

VaD is not a disease unto itself, but a dementia that results from a panoply of cerebrovascular diseases affecting the brain. Current concepts of VaD, therefore, have focused on the notion of clinical and neuroimaging phenotypes that establish the presence of cerebrovascular brain injury that is believed sufficiently severe to contribute, if not fully explain the dementia [9]. Recently, O'Brien and colleagues proposed the use of the term 'vascular cognitive impairment', which is characterized by a specific cognitive profile, involving preserved memory with an impairment in attentional and executive functioning [10].

VaD is a heterogeneous syndrome, grouping together a broad category of patients in whom various manifestations of cognitive decline are attributed to cerebro- or cardiovascular disease. The National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS–AIREN) consensus criteria help to define it [11]. Furthermore, the NINDS–AIREN criteria list different pathologies, which help to identify patients with different subtypes of VaD:

- Multi-infarct dementia – multiple large and complete infarcts, hypoperfusion. According to NINDS–AIREN, complete infarction is the result of a necrosis of all tissue elements due to ischemic brain injury. It could be represented by a large artery infarct, which occurs in the distribution of major feeding arteries or their main branches, usually wedge-shaped,

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involving cortex and underlying white matter; on the other hand, a border zone infarct occurs in the terminal distribution of end arterioles (e.g., the 'parietal watershed' between anterior, middle and posterior cerebral arteries, periventricular white matter fed by long-penetrating end arterioles).

- Strategic infarct VaD – strategic single infarcts.
- Posthemorrhage dementia – according to NINDS–AIREN, hemorrhage is the result of a rupture of the blood vessel wall leading to extravasation of blood into the surrounding area/tissue
- Subcortical VaD – small-vessel disease, hypoperfusion. According to NINDS–AIREN this is mainly due to lacunar infarct, usually inferior to 2 mm in diameter, occurring in the distribution of small arterioles, usually in the white matter, basal ganglia, thalamus and pons; or to microinfarct – not seen on macroscopic examination, small area of cystic or noncystic necrosis surrounded by astrocytes. Incomplete infarct may also be present, due to a selective loss of neurons, myelin and oligodendrocytes, without cystic necrosis, occurring in the periphery of major artery distribution infarcts (e.g., penumbra) or in deep white matter. Incomplete white matter infarcts are associated with myelin pallor, astrocytosis and a variable degree of axonal loss. Pathologically, dilated perivascular spaces (spaces filled with cerebrospinal fluid surrounding arteries and veins), could be found. Their pathogenesis is still disputed: increased arterial permeability, perivascular inflammatory factors and mechanical pulsatility. They may be particularly prominent below the putamen and above the lateral portion of the anterior commissure.

As VaD is currently conceptualized, its pathologic diagnosis is problematic; not because it is difficult to make a pathologic diagnosis of cerebrovascular injury, but because it is difficult to determine post mortem whether a vascular lesion was causal, contributory, or coincidental to the dementia. No consensus has been reached regarding how to make a pathologic diagnosis of VaD. Typically, there is a requirement for vascular lesions, often of a certain size or volume, in the absence of degenerative lesions [12–14]. Joachim and colleagues considered strokes to have contributed to the clinical dementia if sufficiently remote or larger in size than lacune, or if the vascular lesions involved the hippocampus, amygdala, thalamus or basal forebrain [15]. In another schema, softening in the hippocampus and serum proteins in the perivascular parenchyma were additional requirements for a diagnosis of VaD [14]. Gold and colleagues defined VaD as cortical–subcortical infarcts in parietal, temporal or frontal lobes; subcortical infarcts alone were not considered sufficient for a pathologic diagnosis of VaD [16,17]. A pathologic diagnosis of Binswanger's subcortical arteriosclerotic encephalopathy can be made in the presence of severe white matter changes with demyelination and axonal loss plus severe and widespread changes of arteriolosclerosis [15]. In the Ischemic Vascular Dementia (IVD) project a scoring system was developed to rate the severity and extent of cerebrovascular brain injury (CVD-path and IVD-path scores) [18–20].

Clinical–pathologic and quantitative magnetic resonance imaging (MRI) correlations were analyzed for the first 20 and 46 autopsies in a prospective study of subcortical IVD, AD and normal aging [21]. The apolipoprotein e4 allele was rarely found in autopsy cases of pure cerebrovascular disease (9%), in contrast to AD (46%) or mixed AD/cerebrovascular disease (44%; $p = 0.03$). Conversely, hippocampal sclerosis was found more frequently in cerebrovascular disease (50%) or mixed AD/cerebrovascular disease (28%) cases, than AD (7%). Similarly, a large amount of white matter signal hyperintensity was found more frequently in mixed AD/cerebrovascular disease (86%) or cerebrovascular disease (75%) than AD (36%; $p = 0.08$). High white matter hyperintensities were associated with either arteriolosclerosis or cerebral amyloid angiopathy [20].

On the other hand, hippocampal and cortical gray matter atrophy were found in 88 and 80% of the dementia cases, irrespective of dementia subtype. These findings suggest that hippocampal and cortical gray matter atrophy may represent the *sine qua non* of the dementia syndrome. Other factors, however, may help to differentiate specific etiologic processes. The apolipoprotein e4 allele increases the risk of AD or mixed dementia, while high white matter hyperintensity increases the likelihood of cerebrovascular disease or mixed dementia. The pathologies that contribute to hippocampal atrophy in subcortical ischemic VaD (SIVD) include neurofibrillary degeneration and hippocampal sclerosis, while those contributing to cortical gray matter atrophy in SIVD are still unknown. Candidate mechanisms include a-β toxicity, micro- or incomplete-cortical infarcts, and secondary deafferentation of the cortex resulting from an underlying subcortical pathology [20].

The International Classification of Diseases tenth revision (ICD-10) criteria only recently identified subcortical VaD as a major subtype [22]. Subcortical VaD now incorporates the old entities 'lacunar state' and 'Binswanger disease' and relates to small vessel disease and hypoperfusion resulting in focal and diffuse ischemic white matter lesions and incomplete ischemic injury [23,24]. In addition to strategic infarct dementia and intracranial hematomas, dementia caused by cerebrovascular disease (commonly referred to as VaD) is often associated with subcortical ischemic vascular lesions caused by small-vessel disease. Patients with subcortical VaD are believed to represent a prevalent and homogeneous group [25,26]. Characteristic features of the condition include a subcortical syndrome comprising progressive cognitive impairment with frontal features and dysexecutive syndrome, and mood and personality changes such as depression and emotional lability [27–29]. Multiple studies consistently show significant associations between the extent of brain atrophy or white matter hyperintensity (WMH) volumes and diminished cognitive performance [30,31], including deficits in tests of attention and mental processing [32–35] and impairments in memory and general intelligence [33,34]. Other studies have also found significant associations between cognitive impairment – including incident dementia – and clinically silent cerebral infarctions [2,36,37]. The relationship of brain infarction to the clinical expression of AD has been assessed. The findings suggest that cerebrovascular disease may play an important role in determining the presence and the severity of the clinical symptoms of AD [38].

Treatment

Recognition that cerebrovascular disease causing dementia may be modified by treatment of cerebrovascular risk factors serves as an important tool for investigating various treatments aimed at secondary prevention of vascular cognitive impairment [39]. There is currently no approved symptomatic treatment for VaD, although daily aspirin treatment may improve or stabilize cognitive decline, compared with placebo [40], and nimodipine has been reported to provide some short-term benefits in the treatment of patients with this condition [41]. Therefore, some physicians prescribe aspirin and/or nimodipine for patients with VaD. These agents probably exert an effect via improved or stabilized cerebral perfusion, which may improve collateral circulation and/or improve impaired metabolism in the ischemic brain. A host of medications have been tried with limited success, including alkaloid derivatives, hemorheologics, metabolic enhancers and γ-aminobutyric acid antagonists [9].

Successful trials in patients with VaD are limited. One *post hoc* subgroup analysis of the 6-month Scandinavian Multi-Infarct Dementia Trial has shown that although a treatment effect was not observed in the total trial population, the subgroup of subcortical VaD patients receiving nimodipine performed better in the majority of tests and functional scales, compared with patients given placebo [42]. Pentoxifylline [43] and propentofylline [44], adenosine uptake/phosphodiesterase inhibitors that have been suggested to have neuroprotective properties, have shown promising results.

Most other previous clinical trials performed in patients with VaD have achieved unsatisfactory results [45], including a trial of the acetylcholinesterase (AChE)-selective inhibitor, galantamine [46,47]. In these studies, galantamine showed efficacy in patients with AD with cerebrovascular disease (mixed dementia), but not in isolated cases of VaD [46,47]. The drug's efficacy in mixed dementia may stem from its effects on the Alzheimer's aspect of the condition. As might be expected, identification of a suitable patient cohort complicates clinical trials aimed at symptomatic cognitive improvements for patients with VaD.

One reason for the failure of so many previous studies may be that most have been performed in patients with VaD as a whole, rather than in specific subtypes of the condition. As with any therapeutic area, studies evaluating the efficacy of new drugs in patients with VaD should be designed carefully to ensure that outcome measures used are appropriate to the condition being investigated. For studies involving patients with VaD, this means that studies should focus on individual subtypes of the condition, because the heterogeneity seen across the different subtypes may mask beneficial treatment effects. For example, the Scandinavian Multi-Infarct Dementia Trial failed to show a treatment effect with nimodipine in the total trial population, while a *post hoc* subgroup analysis demonstrated significant benefits in the subgroup of patients with subcortical VaD, compared with patients given placebo, over 6 months [42].

The rationale to employ cholinesterase inhibitors in vascular dementia

As with other types of dementia, the pathologic changes observed in patients with VaD appear to be associated with cholinergic deficits. Preclinical research using the spontaneously hypertensive

stroke-prone rat model of VaD has shown a significant reduction in the levels of the neurotransmitters acetylcholine (ACh) and choline in the cortex, hippocampus and cerebrospinal fluid compared with normal rats [48–50], which appear to correlate with impaired learning and memory [51].

In the latter study, the differences in cerebrospinal fluid levels between normal rats and stroke-prone rats increased with age, suggesting progressive deterioration of central cholinergic function in hypertensive stroke-prone rats. The cholinesterase (ChE) inhibitor epistigmine has been shown to improve blood flow in the Sprague-Dawley rat with the tandem occlusion of the left middle cerebral and common carotid arteries. Epistigmine also enhanced the ischemia-induced rostral shift of cerebral blood flow maximum in the contralateral hemisphere and the redistribution of cerebral blood flow, a phenomenon possibly related to recovery of function [52].

In humans, postmortem studies have shown that choline acetyltransferase (ChAT) activity is reduced in VaD patients, compared with controls [53,54]. Furthermore, clinical studies have indicated that patients with subcortical VaD have significantly lower concentrations of ACh in the cerebrospinal fluid, and that these decreases are strongly correlated with cognitive deficits [54,55]. In the human brain, ACh plays a pivotal role in the autoregulation of cerebral blood flow through the parasympathetic innervation of the circle of Willis and of the pial vessels [56], and causes significant arterial relaxation by promoting the synthesis of vasodilator agents [57]. A 50 to 60% reduction in hippocampal ChAT activity is observed in the brains of patients with both AD and VaD [58]. The number of muscarinic cholinergic receptors is also markedly reduced in VaD and mixed dementia patients [58]. In addition, the level of ACh in the cerebral fluid of VaD patients is significantly lower than in controls, but is similar to the level observed in AD patients [59].

Cholinesterase inhibitors: an overview

Three ChE inhibitors are commonly prescribed for the symptomatic treatment of AD – the AChE-selective inhibitors, donepezil and galantamine, and the dual AChE and butyrylcholinesterase (BuChE) inhibitor, rivastigmine. A fourth agent, tacrine, is no longer routinely prescribed due to a high incidence of hepatotoxicity at therapeutic doses [60–62]. Although all ChE inhibitors share the same basic mode of action (inhibition of AChE), their pharmacokinetic characteristics differ substantially [63–75]. Cholinergic neurotransmission occurs when ACh released from the presynaptic neurone binds to nicotinic or muscarinic postsynaptic ACh receptors. Mammalian brains contain two major forms of ChEs – AChE and BuChE – both of which possess the capacity to hydrolyze ACh. These two enzymes differ genetically, structurally and kinetically [75]. AChE is located in the synaptic cleft (soluble form) and synaptic membranes (membrane-bound form) [74], and BuChE is mainly associated with glial cells [76].

An important feature differentiating ChE inhibitors is specificity for the ChE enzymes inhibited. All three agents inhibit AChE, which is the main enzyme responsible for the breakdown of ACh in the normal brain. In contrast, rivastigmine acts differently from donepezil and galantamine in targeting both AChE and BuChE [73]. Although BuChE represents only 10% of total ChE activity in the temporal cortex of the healthy human brain [77], recent results using sensitive histochemical techniques indicate that the enzyme is capable of hydrolyzing ACh and plays a greater role in normal cholinergic transmission than previously thought [78]. The importance of BuChE in cholinergic neurotransmission is likely to increase in AD because as the disease progresses, AChE activity decreases by up to 45%, and BuChE activity increases by 40 to 90% [77–79]. Results with rivastigmine show that cognitive improvements (measured using the computerized neuropsychologic test battery) correlate independently with the inhibition of AChE and BuChE in the cerebrospinal fluid [80], suggesting that inhibition of both enzymes is a highly desirable feature of AD therapy. The ChE inhibitors also differ in selectivity for different forms of ChE. Both AChE and BuChE exist in a series of globular forms, including the G1 and G4 forms [81]. In the AD brain, a selective reduction in the level of the G4 form occurs, whereas the level of the G1 form remains unchanged or increases [79–82]. This effect is most pronounced in the cortex and hippocampus, which are severely affected in AD. Therefore, a preferential affinity for G1 AChE, as seen with rivastigmine, may contribute to greater activity in the brain areas most affected in AD [83]. A lower affinity for G4 AChE, which predominates in the peripheral nervous system, may lead to improved safety over the course of AD [84,85].

In addition, levels of the G1 form of AChE and BuChE are particularly high in neuritic plaques, a characteristic neuropathologic feature of AD [77]. Recent success with ChE inhibitors in AD has stimulated similar work in VaD with

some success [86–92], suggesting the possibility of further work in this area. Two of the four licensed ChE inhibitors, galantamine and donepezil, have recently featured in published work, describing their action in dementia associated with cerebrovascular disease. To do this, a recent review explores the relationship between AD, for which this group of compounds originally received licensing approval, and vascular pathology within the brain, highlighting the significant overlap in risk factors and the frequent coexistence of the two conditions in the patients that are studied [93]. Whether they are interrelated or separate entities is discussed, followed by a description of the current classifications of AD with cerebrovascular disease, and the three subtypes of 'pure' VaD – subcortical, cortical and strategic infarct. Understanding these entities allows more accurate diagnostic and prognostic information to be given to patients, and leads towards matching the published clinical evidence discussed with more predictable clinical syndromes. This distinction is particularly relevant in terms of the studies conducted thus far. A recent review concluded that 'from a public health viewpoint, recognition of vascular cognitive impairment before the development of dementia and the correction of vascular burden on the brain, may lead to a global decrease of incident dementia' [94].

However, galantamine has been studied in a placebo-controlled study of patients with AD and cerebrovascular disease, as well as patients with VaD [45], whereas donepezil has been studied exclusively in patients with VaD. Differences in the way the placebo groups acted in these studies confirmed the fact that these are actually two distinct groups. Galantamine showed efficacy across the combined groups studied, with placebo deterioration similar to previous AD studies. Erkinjuntti and colleague provides convincing evidence that the AChE-selective inhibitor galantamine is effective in patients with AD with cerebrovascular disease (mixed dementia) [45]. However, galantamine failed to provide significant benefits over placebo in patients with pure VaD. The authors suggest that this was because the study was not powered to detect statistical significance in the pure VaD subgroup and because there was a slow placebo decline. However, the results will inevitably be interpreted by some critics as suggesting that the efficacy of galantamine in mixed dementia stemmed only from the drug's effects on the Alzheimer's aspect of the condition.

Donepezil produced a positive effect in VaD – with the placebo group relatively unchanged. The symptomatic improvements seen were not really surprising, as cholinergic deficits are a common factor across all of these syndromes. Wherever this is the predominant biologic finding, it would be expected that ChE inhibitors would have a similar effect, whatever the condition causing it [93].

A recent work reports positron emission tomography findings of patients with VaD: it has been showed that frontal lobe hypoperfusion and hypometabolism play important roles in dementia caused cerebral infarctions and also in asymptomatic strokes and patients with chronic cerebral circulatory insufficiency [95]. Further to recent data indicating that patients with VaD show a cholinergic deficit, and a specific frontal hypoperfusion [95,96], there have been differing attempts to determine whether rivastigmine, a dual inhibitor of AChE and BuChE, has any effects on the symptoms of VaD. Since the frontal lobe in particular is known to be associated with executive function and behavioural changes, the brain region selectivity of rivastigmine may also explain its efficacy in patients with subcortical VaD, since it acts upon particularly relevant areas of patients' brains. Rivastigmine has shown particular activity in regions of the cortex associated with attentional processes and executive function [97–100], and significant correlations have been observed between AChE and BuChE inhibition and functions of frontal and temporal brain regions associated with attention for up to 12 months in patients with AD [100–102].

The first attempt to evaluate the effects of rivastigmine in patients with subcortical VaD was a preliminary 12-month analysis [103], which indicated that long-term rivastigmine treatment is effective and safe in this patient population, and it has been confirmed by another study [88]. This study only involved subcortical VaD patients (inclusion criteria for clinical studies should be as clear and unequivocal as possible). The results demonstrate that long-term treatment with rivastigmine resulted in a general stability of cognitive performance and daily function, a slight improvement in executive function and planning behaviour (as demonstrated by ten point clock test scores), and a general improvement in behaviour and social conduct, included in the so-called frontal executive dysfunction [27].

To confirm the previous, though limited, observations, another study indicated an amelioration of behavioural alterations in patients with VaD, treated with rivastigmine [104]. Moreover, in that study it was found that there was a reduction in sleep disturbances in patients taking rivastigmine [104]. This statement has no anatomic or biochemical foundations, but it may in part reflect the described reductions in anxiety, agitation and hallucinations in patients treated with rivastigmine.

Another study indicated an amelioration on the Ryden Scale for aggression in patients treated with rivastigmine [105]. Very recently, another study aimed to determine whether rivastigmine has any effects on delirium in VaD. The results from this follow-up study suggest that delirium is frequent in elderly and cognitively impaired patients; it might not be a simple consequence of acute disease and hospitalization, but it can be considered as being secondary to brain damage and to metabolic disturbances. It may be induced by a lack of ACh in the brain, if one relies on the Lewy Body dementia model. Rivastigmine, with its brain selectivity, may help in reducing the event frequency and can help to shorten their duration [106]. To avoid any bias, it must be underlined that all the data on rivastigmine are from open label and not controlled trials. However, these are the only studies to have been conducted in this selected population, suffering from subcortical VaD.

Perspectives

Details regarding VaD are still obscure. The potential role of blood pressure in VaD is not clear. A number of epidemiologic studies show strong associations between elevations in middle-life blood pressure and the prevalence of later life cognitive impairment and dementia [104–107]. Early evidence suggests that treatment of hypertension in the elderly may be quite successful in reducing the incidence of dementia [108–110]. In the Systolic Hypertension in Europe (Syst–Eur) trial [108], cognition was primarily assessed by the Mini-Mental Examination [111]. Treatment with a calcium-channel blocking antihypertensive was associated with a nearly 50% reduction in the incidence of dementia amongst approximately 2000 elderly people with isolated systolic hypertension [108]. Given the high percentage of elderly people suffering from untreated hypertension [112], secondary prevention treatment trials such as Syst–Eur may have a substantial impact on cognitive impairment amongst the elderly. Very recently, another work assessed the relationship between concurrently and previously measured blood pressure levels, hypertension, its treatment, and severe white matter lesions in ten European cohorts [113]. In total, 1805 nondemented subjects aged 65 to 75 years were sampled from ongoing community-based studies that were initiated 5 to 20 years before the MRI. White matter lesions in the periventricular and subcortical regions were rated separately using semiquantitative measures. Concurrently and formerly assessed diastolic and systolic blood pressure were associated with more severe periventricular white matter lesions. An increase in systolic blood pressure levels were associated with more severe periventricular and subcortical white matter lesions. People with poorly controlled hypertension had a higher risk of severe white matter lesions than those without hypertension; however, a potential negative effect of decreasing diastolic blood pressure level on the occurrence of severe periventricular white matter lesions should be taken into account.

The potential role of other vascular risk factors are also not clear; for example, hypercholesterolemia in VaD. The potential role of statins has not been confirmed in the literature [114,115]. The new data suggest that much of the prior epidemiologic data may be flawed in the properly conducted longitudinal studies, in the sense that they do not bear out the protective relationship that was observed in earlier cross-sectional studies.

Even more intriguing is the potential role of the ChE inhibitors in the three types of VaD: many studies have been conducted in subcortical VaD and as seen, some have been conducted generically in VaD, not considering the differences between subcortical vascular, multi-infarct or single strategic infarct dementia. No data have been collected on the potential different roles of the three drugs in multi-infarctual dementia, compared with subcortical VaD and in post-hemorrhagic dementia.

Tightly bound to the potential role of ChE inhibitors, is the concept of the peculiar vulnerability of specific brain regions in VaD. For example, lacunes correlate with metabolic rates in the dorsolateral frontal cortex. In fact, white matter lesions substantially reduce metabolic rates throughout the cortex, most strongly so in dorsolateral frontal cortex. Regional cerebral glucose metabolism and normalized activity in dorsolateral frontal regions correlated with executive function, memory and global executive function [118]. There is no clear reason for the

Highlights

- Vascular dementia (VaD) is not a disease unto itself, but a dementia that results from a panoply of cerebrovascular disease.
- Etiopathogenesis of VaD is different, and must be taken into account.
- Treatment of VaD may need to emphasize primary and secondary prevention.
- Cholinesterase inhibitors should be considered for a potential benefit in the treatment of VaD.
- Future studies should be conducted to better define targets and strategies.

particular vulnerability of this selectivity, the significance of which might be important for the development of specific therapeutic strategies, at least for subcortical VaD.

Expert commentary

Cerebrovascular disease is common to the elderly and can cause a wide spectrum of impairments that range from mild to severe. Sensitive and specific definitions of cerebrovascular cognitive impairment are hampered by the fact that cerebrovascular disease is not easily linked to cognitive syndromes either clinically or pathologically and the presence of coincident AD is common. Importantly, however, it does appear that the dementia caused by brain vascular disease may share similar anatomic substrates with AD, supporting the notion of a common substrate to dementia. Treatment of vascular cognitive impairment may need to emphasize primary or secondary prevention of cerebrovascular risk factors such as hypertension, but some symptomatic treatments are beginning to show modest success. Raised awareness of cerebrovascular disease as a cause for cognitive impairment is likely to result in better detection and treatment, leading to improved cognitive health for our aging population. Our suggestion is that VaD is not a unique pathology: the etiopathogenesis of multi-infarct dementia and that of subcortical VaD are quite different. Future studies need to consider those entities separately to obtain good results, for a group of patients for whom, until now, there have been few therapeutic options.

Outlook

VaD is a heterogeneous syndrome, grouping together a broad category of patients in whom various manifestations of cognitive decline are attributed to cerebrovascualr disease. As with other types of dementia, the pathologic changes observed in patients with VaD appear to be associated with cholinergic deficits. Moreover, in the human brain, ACh plays a pivotal role in the autoregualtion of cerebral blood flow through the parasympathetic innervation of the circle of Willis and of the pial vessels.

Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer's disease in the US population: prevalence estimates using the 2000 census. *Arch. Neurol.* 60(8), 1119–1122 (2003).
2. Longstreth WT Jr, Bernick C, Manolio TA, Bryan N, Jungreis CA, Price TR. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. *Arch. Neurol.* 55(9), 1217–1225 (1998).
3. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke* 22(3), 312–318 (1991).
4. Wu CC, Mungas D, Petkov CI. Brain structure and cognition in a community sample of elderly Latinos. *Neurology* 59(3), 383–391 (2002).
5. Vermeer SE, Den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM; Rotterdam Scan Study. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke* 34(2), 392–396 (2003).
6. Chui HC. Dementia. A review emphasizing clinicopathologic correlation and brain–behaviour relationships. *Arch. Neurol.* 46, 806–814 (1989).
7. Skoog I, Nilsson L, Palmertz B *et al.* A population-based study of dementia in 85-year olds. *N. Engl. J. Med.* 328, 153–158 (1993).
8. Rocca WA, Hofman A, Brayne C *et al.* The prevalence of vascular dementia in Europe: facts and fragments from 1980–1990 studies. EURODEM-Prevalence Research Group. *Ann. Neurol.* 30, 817–824 (1991).
9. Chui H. Vascular dementia, a new beginning. *Neurol. Clin.* 18(4), 951–975 (2000).
10. O'Brien JT, Erkinjuntti T, Esiberg B *et al.* Vascular cognitive impairment. *Lancet Neurol.* 2(2), 89–98 (2003).
11. Román GC, Tatemichi TK, Erkinjuntti T *et al.* Vascular dementia: diagnostic criteria for research studies. Report of the NINDS–AIREN International Workshop. *Neurology* 43, 250–260 (1993).
12. Tomlinson BE, Blessed G, Roth M. Observations on the brains of demented old people. *J. Neurol. Sci.* 11, 205–424 (1970).
13. Alafuzoff I, Iqbal K, Friden H, Adolfsson R, Winbald B. Histopathological criteria for progressive dementia disorders: clinical–pathological correlation and classification by multivariate data analysis. *Acta Neuropathol. (Berlin)* 74, 209–225 (1987).
14. Tierney M, Fisher RH, Lewis AJ *et al.* The NINCDS-ADRDA work group criteria for the clinical diagnosis of probable Alzheimer's disease: a clinicopathologic study of 57 cases. *Neurology* 38, 359–364 (1988).
15. Joachim CL, Morris JH, Selkoe DJ. Clinically diagnosed Alzheimer's disease: autospy results in 150 cases. *Ann. Neurol.* 24, 50–56 (1988).
16. Gold G, Giannakopoulos P, Montes-Paixao JC *et al.* Sensitivity and specificity of newly proposed clinical criteria for possible vascular dementia. *Neurology* 49, 690–694 (1997).
17. Gold G, Bouras C, Canuto A *et al.* Clinicopathological validation study of four sets of clinical criteria for vascular dementia. *Am. J. Psych.* 159, 82–87 (2002).

18. Chui H, Zarow C, Ellis W *et al.* Diagnosis of ischemic vascular dementia (IVD), clinical–pathological correlations. In: *1st International Congress on Vascular Dementia.* Korczyn A (Ed.). Monduzzi Editore, Bologna, Italy, 27–32 (1999).
•• **Very important for clinical–pathological correlations.**
19. Chui HC. Evidence-based diagnosis of dementia. In: *Evidence-based Dementia: A Practical Guide to Diagnosis and Management.* Qizilbash N, Schneider L, Chui H *et al.* (Eds). Blackwell Science, Oxford, UK (2002).
20. Chui HC. *Clinical–Pathological Correlations: New Findings From Prospective Studies*. American Academy of Neurology, San Francisco, CA, USA, 1–32 (2004).
21. Vinters H, Ellis W, Zarow C *et al.* Neuropathologic substrates of ischemic vascular dementia. *J. Neuro. Exp. Neurol.* 59, 911–945 (2000).
22. Wetterling T, Kanitz RD, Borgis KJ. The ICD-10 criteria for vascular dementia. *Dementia* 5, 185–188 (1994).
23. Erkinjuntti T. Vascular dementia: challenge of clinical diagnosis. *Int. Psychogeriatr.* 9, 77–83 (1997).
24. Pantoni L, Rossi R, Inzitari D *et al.* Efficacy and safety of nimodipine in subcortical vascular dementia: a subgroup analysis of the Scandinavian Multi-Infarct Dementia Trial. *J. Neurol. Sci.* 175(2), 124–34 (2000).
• **First analysis of a specific subgroup of vascular dementia (VaD).**
25. Erkinjuntti T, Inzitari D, Pantoni L *et al.* Limitations of clinical criteria for the diagnosis of vascular dementia in clinical trials. Is a focus on subcortical vascular dementia a solution? *Ann. NY Acad. Sci.* 903, 262–272 (2000).
• **Focus on subcortical VaD: clinical and diagnosis problems.**
26. Prins ND, van Dijk EJ, den Heijer T *et al.* Cerebral white matter lesions and the risk of dementia. *Arch. Neurol.* 61, 1531–1534 (2004).
27. McPherson SE, Cummings JL. Neurospychological aspects of vascular dementia. *Brain Cogn.* 31, 261–282 (1996).
28. Looi JCL, Sachdev PS. Differentiation of vascular dementia from AD on neuropsychological tests. *Neurology* 53, 670–678 (1999).
•• **First study that systematically reviews the subtle differences between VaD and Alzheimer's disease (AD).**
29. Chui H. *Dementia Associated with Subcortical Ischemic Vascular Disease*. American Academy, PA, USA (2001).
30. Longstreth WT Jr, Arnold AM, Manolio TA *et al.* Clinical correlates of ventricular and sulcal size on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Collaborative Research Group. *Neuroepidemiology* 19(1), 30–42 (2000).
31. Knopman D, Boland LL, Mosley T *et al.*; Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology* 56(1), 42–48 (2001).
32. Swan GE, DeCarli C, Miller BL *et al.* Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurology* 51(4), 986–993 (1998).
• **First study that investigates the relationship between blood pressure and vascular cognitive decline.**
33. Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Carmelli D. Biobehavioral characteristics of nondemented older adults with subclinical brain atrophy. *Neurology* 54(11), 2108–2114 (2000).
34. DeCarli C, Murphy DG, Tranh M *et al.* The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. *Neurology* 45(11), 2077–2084 (1995).
35. Breteler MM, van Amerongen NM, van Swieten JC *et al.* Cognitive correlates of ventricular enlargement and cerebral white matter lesions on MRI: the Rotterdam Study. *Stroke* 25, 109–115 (1994).
36. Price TR, Manolio TA, Kronmal RA. Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. *Stroke* 28(6), 1158–1164 (1997).
37. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N. Engl. J. Med.* 348(13), 1215–1222 (2003).
•• **Very important for the systematic revision of VaD.**
38. Snowdon DA, GReiner LH, Mortimer JA, Riely KP, Greiner PA, MArkesbery WR. Brain infarction and the clinical expression of Alzheimer's disease. The Nun Study. *J. Am. Med. Assoc.* 277(10), 813–817 (1997).
39. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am. J. Public Health* 88(9), 1337–1342 (1998).
40. Meyer JS, Rogers RL, McClintic K *et al.* Randomized clinical trial of daily aspirin in multi-infarct dementia. A pilot study. *J. Am. Geriatr. Soc.* 37, 549–555 (1989).
41. Lopez-Arrieta JM, Birks J. Nimodipine for primary degenerative, mixed and vascular dementia. *Cochrane Database Syst. Rev.* 3, CD000147 (2002).
42. Pantoni L, Rossi R, Inzitari D *et al.* Efficacy and safety of nimodipine in subcortical vascular dementia: a subgroup analysis of the Scandinavian Multi-Infarct Dementia Trial. *J. Neurol. Sci.* 175, 124–34 (2000).
43. European Pentoxifylline Multi-Infarct Dementia (EPMID) Study Group. European pentoxifylline multi-infarct dementia. *Eur. Neurol.* 36, 315–321 (1996).
44. Marcusson J, Rother M, Kittner B *et al.* A 12-month, placebo-controlled trial of propentofylline (HWA 285) in patients with dementia according to DSM III-R. *Dement. Geriatr. Cogn. Disord.* 8, 320–328 (1997).
45. Sachdev PS, Brodaty H, Looi JC. Vascular dementia: diagnosis, management and possible prevention. *Med. J. Aust.* 170, 81–85 (1999).
46. Erkinjuntti T, Lilienfeld S. Galantamine shows efficacy in patients with Alzheimer's disease with cerebrovascular disease or probable vascular dementia. *Poster presented at the 53rd Annual Meeting of the American Academy of Neurology*. Philadelphia, PA, USA, 2–6 May 2001.
47. Erkinjuntti T, Kurz A, Gauthier S *et al.* Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet* 359, 1283–1290 (2002).
48. Saito H, Togashi H, Yoshiaka M *et al.* Animal models of vascular dementia with emphasis on stroke-prone spontaneously hypertensive rats. *Clin. Exp. Pharmacol. Physiol.* 22, 257–259 (1995).
49. Togashi H, Matsumoto M, Yoshioka M *et al.* Neurochemical profiles in cerebrospinal fluid of stroke-prone spontaneously hypertensive rats. *Behav. Lett.* 166, 117–120 (1994).
50. Kimura S, Saito H, Minami M *et al.* Pathogenesis of vascular dementia in stroke-prone spontaneously hypertensive rats. *Toxicology* 153, 167–187 (2000).
51. Togashi H, Kimura S, Matsumoto M *et al.* Cholinergic changes in the hippocampus of stroke-prone spontaneously hypertensive rats. *Stroke* 27, 520–526 (1996).
52. Scremin OU, Li MG, Scremin AM, Jenden DJ. Cholinesterase inhibition improves blood flow in the ischemic cerebral cortex. *Brain Res. Bull.* 42, 59–70 (1997).

53. Gottfries CG, Blennow K, Karlsson I, Wallin A. The neurochemistry of vascular dementia. *Dementia* 5, 163–167 (1994).

•• **First study on the topic.**

54. Wallin A, Blennow K, Gottfries CG. Neurochemical abnormalities in vascular dementia. *Dementia* 1, 120–130 (1989).

55. Tohgi H, Abe T, Kimura M *et al.* Cerebrospinal fluid acetylcholine and choline in vascular dementia of Binswanger and multiple small infarct types as compared with Alzheimer type dementia. *J. Neurol. Transm.* 103, 1211–1220 (1996).

56. Vasquez J, Purve MJ. The cholinergic pathway to cerebral blood vessels. I. Morphological studies. *Pflugers Arch.* 379, 157–163 (1979).

57. Vanhoutte PM. Endothelium and control of vascular function. State of the art. *Hypertension* 13, 658–667 (1989).

58. Sakurada T, Alufuzoff I, Winblad B, Nordberg A. Substance P-like immunoreactivity, choline acetyltransferase activity and cholinergic muscarinic receptors in Alzheimer's disease and multi-infarct dementia. *Brain Res.* 521(1–2), 329–332 (1990).

59. Szilagy AK, Nemeth A, Martini E, Lendvai B, Venter V. Serum and CSF cholinesterase activity in various kinds of dementia. *Eur. Arch. Psychiatry Neurol. Sci.* 236, 309–311 (1987).

60. Grossberg GT. Cholinesterase inhibitors for the treatment of Alzheimer's disease: getting on and staying on. *Curr. Ther. Res.* 64(4), 216–235 (2003).

•• **Systematic review on the three cholinesterase inhibitors.**

61. Nordberg A, Svensson AL. Cholinesterase inhibitors in the treatment of Alzheimer's disease: a comparison of tolerability and pharmacology. *Drug Saf.* 19, 465–480 (1998).

62. Blackard WG Jr, Sood GK, Crowe DR, Fallon MB. Tacrine. A cause of fatal hepatotoxicity? *J. Clin. Gastroenterol.* 26, 57–59 (1998).

63. Sifton DW (Ed.). *Physicians' Desk Reference*. Medical Economics Company, NJ, USA, 1792, 2342, 2665 (2002).

64. Svensson AL. Cholinesterase inhibitors in Alzheimer's disease: an experimental study on mechanisms for interaction with muscarinic and nicotinic receptors and neuroprotection [published doctoral dissertation]. Huddinge, Sweden: Division of Nicotine Research, Department of Clinical Neuroscience and Family Medicine, Karolinska Institute, Huddinge University Hospital Publication no. 884, S-141 86 (1997).

65. Barnes CA, Meltzer J, Houston F *et al.* Chronic treatment of old rats with donepezil or galantamine: effects on memory, hippocampal plasticity and nicotinic receptors. *Neuroscience* 99, 17–23 (2000).

66. Svensson A, Nordberg A. Interaction of tacrine, galantamine, NXX-066 and E2020 with neuronal α4β2 nicotinic receptors expressed in fibroblast cells. In: *Alzheimer's Disease: Biology, Diagnosis, and Therapeutics.* Iqbal K, Winblad B, Nishimura T *et al.* (Eds.). Wiley, NY, USA, 751–756 (1997).

67. Bryson HM, Benfield P. Donepezil. *Drugs Aging* 10, 234–239 (1997).

68. Kasa P, Papp H, Kasa P Jr, Torok L. Donepezil dose-dependently inhibits acetylcholinesterase activity in various areas and in the presynaptic cholinergic and the postsynaptic cholinoceptive enzyme-positive structures in the human and rat brain. *Neuroscience* 101, 89–100 (2000).

69. Amici S, Lanari A, Romani R *et al.* Cerebrospinal fluid acetylcholinesterase activity after long-term treatment with donepezil and rivastigmina. *Mech. Ageing Dev.* 122, 2057–2062 (2001).

70. Davidsson P, Blennow K, Andreasen N *et al.* Differential increase in cerebrospinal fluid acetylcholinesterase after treatment with acetylcholinesterase inhibitors in patients with Alzheimer's disease. *Behav. Lett.* 300, 157–160 (2001).

71. Parnetti L, Amici S, Lanari A *et al.* Cerebrospinal fluid levels of biomarkers and activity of acetylcholinesterase (AchE) and butyryl cholinesterase in AD patients before and after treatment with different AchE inhibitors. *Neurol. Sci.* 23(Suppl. 2), S95–S96 (2002).

72. Darreh-Shori T, Almkvist O, Guan ZZ *et al.* Sustained cholinesterase inhibition in AD patients receiving rivastigmine for 12 months. *Neurology* 59, 563–572 (2002).

73. Weinstock M. Selectivity of cholinesterase inhibition. *CNS Drugs* 12, 307–323 (1999).

74. Samochocki M, Zerlin M, Jostock R *et al.* Galantamine is an allosterically potentiating ligand of the human α4-β2 nAChR. *Acta Neurol. Scand.* 176(Suppl.), 68–73 (2000).

75. Albuquerque EX, Alkondon M, Pereira EF *et al.* Properties of neuronal nicotinic acetylcholine receptors: pharmacological characterization and modulation of synaptic function. *J. Pharmacol. Exp. Ther.* 280, 1117–1136 (1997).

76. Giacobini E. Selective inhibitors of butyrylcholinesterase: a valid alternative for therapy of Alzheimer's disease? *Drugs Aging* 18, 891–898 (2001).

77. Perry EK, Perry RH, Blessed G, Tomlinson BE. Changes in brain cholinesterases in senile dementia of Alzheimer type. *Neuropathol. Appl. Neurobiol.* 4, 273–277 (1978).

78. Mesulam M, Guillozet A, Shaw P, Quinn B. Widely spread butyrylcholinesteras can hydrolyze acetylcholine in the normal and Alzheimer brain. *Neurobiol. Dis.* 9, 88–93 (2002).

•• **Potential effects of butyrylcholinesterase in AD.**

79. Arendt T, Bruckner MK, Lange M, Bigl V. Changes in acetylcholinesterase and butyrylcholinesterase in Alzheimer's disease resemble embryonic developmenta study of molecular forms. *Neurochem. Int.* 21, 381–396 (1992).

80. Giacobini E, Spiegel R, Enz A *et al.* Inhibition of acetyl- and butyryl-cholinesterase in the cerebrospinal fluid of patients with Alzheimer's disease by rivastigmine: correlation with cognitive benefit. *J. Neurol. Transm.* 109, 1053–1065 (2002).

81. Massoulie J, Bon S. The molecular forms of cholinesterase and acetylcholine in vertebrates. *Ann. Rev. Neurosci*. 37, 57–106 (1982).

82. Siek GC, Katz LS, Fishman EB *et al.* Molecular forms of acetylcholinesterase in subcortical areas of normal and Alzheimer's disease brain. *Biol. Psychiatry* 27, 573–580 (1990).

83. Poirier J. Evidence that the clinical effects of cholinesterase inhibitors are related to potency and targeting of action. *Int. J. Clin. Pract.* 127(Suppl.), 6–19 (2002).

84. Massoulie J, Pezzementi L, Bon S *et al.* Molecular and cellular biology of cholinesterases. *Prog. Neurobiol.* 41, 31–91 (1993).

85. Inglis F. The tolerability and safety of cholinesterase inhibitors in the treatment of dementia. *Int. J. Clin. Pract.* 127(Suppl.), 45–63 (2002).

86. Black S, Roman GC, Geldmacher DS *et al.*; Donepezil 307 Vascular Dementia Study Group. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke* 34(10), 2323–2330 (2003).

87. Wilkinson D, Doody R, Helme R *et al.* Donepezil in vascular dementia: a randomized, placebo-controlled study. *Neurology*, 61(4), 479–486 (2003).

88. Moretti R, Torre P, Antonella RM, Cazzato G, Bava A. Rivastigmine in subcortical vascular dementia. An open 22-month study. *J. Neurol. Sci.* 203–204(C), 141–146 (2002).

89. Mendez MF, Younesi FL, Perryman KM. Use of donepezil for vascular dementia:

preliminary clinical experience. *J. Neuropsy. Clin. Neurosci.* 11(2), 268–270 (1999).
90. Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet* 359, 1283–1290 (2002).
91. Erkinjuntti T. Broad therapeutic benefits in patients with probable vascular dementia or Alzheimer's disease with cerebrovascular disease after treatment with galantamine. *Eur. J. Neurol.* 9(5), 545 (2002).
92. Erkinjuntti T. Treatment options. The latest evidence with galantamine (Reminyl®). *J. Neurol. Sci.* 203, 125–130 (2002).
93. Bullock R. Cholinesterase inhibitors and vascular dementia: another string to their bow? *CNS Drugs* 18(2), 79–92 (2004).
•• **Revision of the pharmaceutical properties of cholinesterase inhibitors.**
94. Erkinjunnti T, Roman G, Gauthier S, Feldman H, Rockwood K. Emerging therapies for vascular dementia and vascular cognitive impairment. *Stroke* 35(4), 1010–1017 (2004).
95. Okamoto K, Tanaka M, Kondo S. Treatment of vascular dementia. *Ann. NY Acad. Sci.* 977, 507–512 (2002).
96. Venneri A, Shanks MF, Staff RT *et al.* Cerebral blood flow and cognitive responses to rivastigmine treatment in Alzheimer's disease. *Neuroreport* 13, 83–96 (2002).
97. Sharma T, Kumari V, Mitterschiffthaler M *et al.* Cognitive effects of rivastigmine in Alzheimer's disease: an fMRI study. *Poster presented at the American College of Neuropsychopharmacology 40th Annual Meeting*. Hawaii, USA, 9–13 December 2001.
98. Adler G, Brassen S. Short-term rivastigmine treatment reduces EEG slow-wave power in Alzheimer patients. *Neuropsychobiology* 43, 273–276 (2001).
99. Nordberg A, Stefanova E, Almkvist O, Nilsson A, Wall A, Långstrom B. Improved cortical glucose metabolism in Alzheimer's disease (AD) patients treated with rivastigmine for 1 year. *J. Neurol. Sci.* 187(Suppl. 1), 142 (2001).
100. Giacobini E, Spiegel R, Enz A, Veroff AE, Cutler NR. Inhibition of acetyl- and butyryl-cholinesterase in the cerebrospinal fluid of patients with Alzheimer's disease by rivastigmine: correlation with cognitive benefit. *J. Neurol. Trans.* 143–147 (2003).
101. Almkvist O, Darreh-Shori T, Spiegel R, Nordberg A. Improved cognition and plasma cholinesterase (ChE) inhibition in AD patients receiving rivastigmine for 1 year: differential effects across time. *J. Neurol. Sci.* 187(Suppl. 1), P0143 (2001).
102. Nordberg A, Darreh-Shori T, Svensson A, Guan Z. Acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) activities in CSF of mild AD patients following 12 months of rivastigmine treatment. *J. Neurol. Sci.* 187(Suppl. 1), P0144 (2001).
103. Moretti R, Torre P, Antonello RM, Cazzato G. Rivastigmine in subcortical vascular dementia: a comparison trial on efficacy and tolerability for 12 months follow-up. *Eur. J. Neurol.* 8, 361–362 (2001).
104. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Rivastigmine in subcortical vvascular dementia: a randomized, controlled, open 12-month study in 208 patients. *Am. J. Alzheimers Dis. Other Demen.* 18(5), 265–272 (2003).
105. Moretti R, Torre P, Antonello RM, Bava A,Cazzato G. Rivastigmine superior to aspirin plus nimodipine in subcortical vascular dementia: an open, 16-month comparative study. *Int. J. Clin. Prac.* 58(4), 346–353 (2004).
106. Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G. Cholinesterase inhibition as a possible therapy for delirium in vascular dementia: A controlled, open 24-month study of 246 patients. *Am. J. Alzheimers Dis. Other Demen.* 19(1), 333–339 (2004).
107. Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. *Am. J. Epidemiol.* 138, 353–364 (1993).
108. Elias MF, D'Agostino RB, Elias PK, Wolf PA. Neuropsychological test performance, cognitive functioning, blood pressure, and age: the Framingham Heart Study. *Exp. Aging Res.* 21(4), 369–91 (1995).
109. Elias PK, D'Agostino RB, Elias PK, Wolf PA. Blood pressure, hypertension, and age as risk factors for poor cognitive performance. *Exp. Aging Res.* 21(4), 393–417 (1995).
110. Launer LJ, Masaki K, Petrovich H, Foley D, Havlik RJ. The association between mid-life blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *J. Am. Med. Assoc.* 274, 1846–1851 (1995).
111. Forette F, Seux ML, Staessen JA, Thijs L. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst–Eur) trial. *Lancet* 352, 1347–1351 (1998).
112. Hansson L. Antihypertensive treatment and the prevention of dementia: further insights from the Syst–Eur trial. *J. Hypertens.* 17(3) 307–308 (1999).
113. Birkenhager WH, Forette F, Seux ML, Wang JG, Staessen JA. Blood pressure, cognitive functions, and prevention of dementias in older patients with hypertension. *Arch. Intern. Med.* 161(2), 152–156 (2001).
114. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12(3), 189–198 (1975).
115. Barker WH, Mullooly JP, Linton KL. Trends in hypertension prevalence, treatment, and control: in a well-defined older population. *Hypertension* 31(1 Pt 2), 552–559 (1998).
116. van Dijck EJ, Breteler M, Schmidt R *et al.* The association between blood pressure, hypertension, and cerebral white matter lesions. *Hypertension* 44, 625–650 (2004).
117. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. *Lancet* 11(356), 1627–1631 (2000).
118. Reed BR, Eberling JL, Mungas D, Weiner M, Kramer JH, Jagust WJ. Effects of white matter lesions and lacunes on cortical function. *Arch. Neurol.* 61, 1545–1550 (2004).

Website

201. Breitner JCS. Studies reveal disappointing data on statin therapy for Alzheimer's disease. www.geri.com/geriatrics/article/articleDetail.jsp?id=127345 (Accessed June 2005).

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