Treating the symptoms of vascular dementia

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Abstract

Historically, the approach towards dementia associated with vascular disease has been to manage risk factors. Recent findings also suggest that symptomatic treatment is a realistic option, and cardiologists should be aware of treatments that are, or may soon be, available for their patients. Here, agents that have been evaluated for the symptomatic treatment of vascular dementia (VaD) are reviewed. In particular, the role of cholinesterase inhibitors is discussed. These agents are commonly used worldwide to treat the symptoms of Alzheimer's disease (AD). Since most patients with VaD have concomitant AD, cholinesterase inhibitors may provide some benefits in these patients. In addition, these agents have demonstrated some efficacy in patients with possible or probable VaD.

Key words: aspirin, donepezil, galantamine, rivastigmine, symptomatic treatment, propentofylline, pentoxyfilline, vascular dementia.

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Introduction

Vascular dementia (VaD) and Alzheimer's disease (AD) are the most common causes of dementia; in most patients these conditions coexist (figure 1).[1] They also share a number of risk factors, such as stroke, hypertension, diabetes, hypercholesterolaemia and the Apolipoprotein E (APOE) genotype.[1,2] Further examples include the relationship between cholesterol levels and amyloidogenesis,[4] and the presence of subtle attentional impairments in older hypertensive patients without dementia.[5,6] The debate over the relationships and commonalities of the two forms of dementia is ongoing, but it is becoming increasingly clear that it is unusual to find dementia in the context of cerebrovascular disease in the absence of at least some concurrent AD pathology.[7]

Patients with VaD and/or AD suffer from global cognitive deficits and behavioural problems. Vascular subcortical pathology damages fronto-subcortical circuits, leading to attention deficits, loss of executive function (higher-order thought processes such as decision-making or self-perception) and depression. These problems impair the performance of everyday activities of daily living, with related difficulties for patients and their caregivers.

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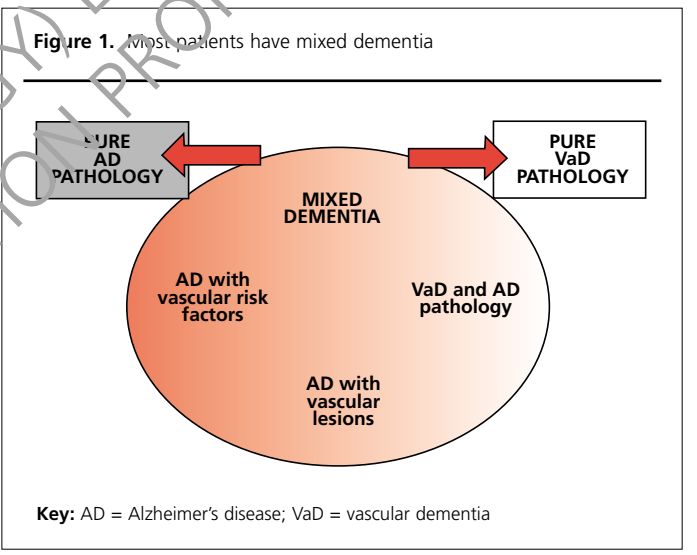


Figure 1. Most patients have mixed dementia

Key: AD = Alzheimer's disease; VaD = vascular dementia

Historically, the approach towards dementia associated with vascular disease has been to manage risk factors. Preventative measures and secondary stroke prevention must remain a key part of treatment. However, since the vast majority of patients with VaD will have additional AD pathology, comprehensive treatment should probably also target concurrent AD.[7]

Which patients develop VaD?

VaD encompasses dementia associated with single large cerebral infarcts, multiple small infarcts, lacunar infarcts or leukoariosis. Diagnostic criteria developed by the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) have identified different subtypes of the condition.[8]

- Multi-infarct dementia
- Strategic single-infarct dementia
- Small vessel disease with dementia
- Hypoperfusion leading to dementia
- Haemorrhagic dementia
- 'Other mechanisms' leading to dementia (combinations of the above lesions and/or other as yet unknown factors).

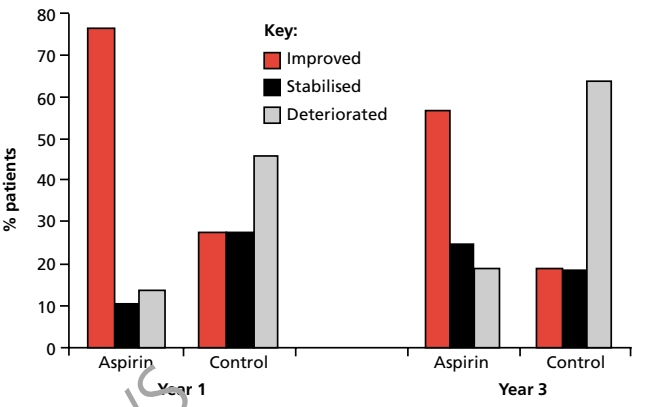
Examples of some of the different underlying processes may be useful. About 26% of patients suffering from ischaemic stroke have been reported to develop dementia,[9] whilst small vessel disease is an important substrate of VaD in many patients[10] and concurrent neurodegenerative pathology is particularly important in people with small strokes.[11] In addition, risk factors for stroke, including hypertension, high cholesterol or fibrinogen levels and diabetes mellitus, have been related to AD or cognitive decline.[5,6,12-14] The presence of cerebrovascular disease is thought to have an additive effect on Alzheimer's pathology – dementia symptoms appear to develop earlier for a given level of AD pathology.[15,16] It has been hypothesised that cerebrovascular disease may trigger a cascade leading to increased neurodegeneration.[17]

Patients with coronary heart disease may also be at risk of VaD. A range of cardiac disorders may give rise to cardiogenic embolisms, placing patients at risk of cortical and subcortical infarcts.[18] Patients with symptomatic atherosclerosis in the coronary arteries often have disseminated disease[19] and may have a prior history of cerebrovascular disease or be at risk of subsequent ischaemic events in the cervico-cranial arteries. Cognitive decline is also known to follow coronary artery bypass grafting (CABG) in up to 40% of patients, possibly due to decreased cerebral perfusion during cardiac manipulation or to release of microembolic plaque material following unclamping of the aorta.[18]

Agents that may improve the symptoms of VaD

Cardiologists have been adept at reducing the risk of ischaemic events. Large studies have shown that controlling risk factors such as cholesterol may reduce the prevalence of AD,[20,21] while treatment with antihypertensive agents reduces the risk of further strokes and cognitive impairment in stroke survivors.

Figure 2. The benefits of aspirin in preventing the symptoms of vascular dementia. Percentages of patients (n=70) showing improved, stabilised or deteriorated cognition over the long term[23]



However, the symptomatic treatment of dementia has not been common practice. Recent findings suggest that this no longer need be the case, and cardiologists should be aware of treatments that are, or may soon be, available for their patients.

Aspirin

Aspirin is widely used in the secondary prevention of ischaemic events, including stroke.[22] It has also been evaluated for the treatment of VaD. Probably the best known study of the drug for this indication is that of Meyer *et al*.,[23] in which 70 patients diagnosed as having multi-infarct dementia received aspirin 325 mg/day or placebo for three years. Both groups had comparable risk factors for stroke, which were treated similarly, as well as comparable initial cerebral blood flow values. Daily aspirin treatment appeared to improve or stabilise cognitive decline, compared with placebo (figure 2).[23]

These benefits were probably due to improved or stabilised cerebral perfusion in patients receiving aspirin.[23] Such effects may improve collateral circulation and/or improve impaired metabolism in the ischaemic brain.

However, a systematic assessment of all trials investigating the effects of aspirin in VaD stated that further research is needed to confirm the effects of aspirin on cognition, and to assess its effects on other outcomes such as behaviour and quality of life.[24]

Peripheral and cerebral activators

Pentoxyfilline is indicated in cases of cerebrovascular disease where blood flow is impaired in the microvasculature. It is also used to increase tissue oxygen levels in patients with peripheral arterial disease. One double-blind, placebo-controlled trial evaluated the efficacy of this drug in 289 patients with VaD.[25] Patients received pentoxyfilline 400 mg or placebo three times daily for nine months. Pentoxyfilline provided significant benefits, improving global, intellectual and cognitive functions.

It seems likely that these benefits were due to improved or stabilised cerebral perfusion in patients receiving pentoxyfilline.

Adenosine uptake/phosphodiesterase inhibitors

Propentofylline was the first of a new class of dementia drugs for which regulatory approval was sought for use in dementia of vascular origin. In a randomised, placebo-controlled trial, 260 patients with AD and/or VaD received propentofylline 300 mg or placebo three times daily.[26] After 12 months, propentofylline-treated patients showed modest benefits in global function, cognitive function and activities of daily living. The precise mode of action responsible for these benefits remains uncertain, although a neuroprotective role was suggested. Unfortunately, further work pertaining to propentofylline was discontinued as a consequence of disappointing results in a later study.

Cholinesterase inhibitors

A major step forward in the understanding and treatment of AD was the proposal and confirmation of the 'cholinergic hypothesis'. This theory, originally suggested by Davies and Maloney[27] and Perry *et al*.,[28] has been substantiated by evidence that impaired acetylcholine (ACh)-dependent neurotransmission in key areas of the brain is a hallmark of AD. Cholinergic deficits have also been reported in patients diagnosed with vascular dementia.[29-31]

Three cholinesterase inhibitors are commonly used worldwide to treat the symptoms of AD – donepezil, rivastigmine and galantamine. These drugs target enzymes responsible for degrading ACh, essentially helping to make the most of remaining ACh levels in the diseased brain. Donepezil and galantamine inhibit acetylcholinesterase (AChE), and rivastigmine inhibits AChE and butyrylcholinesterase (BuChE).[32] The role of BuChE in glial cells may have some impact upon the development of concurrent AD pathology.[33] In addition, in animal models, cholinesterase inhibitors lead to vascular relaxation and improved cerebral blood flow in the ischaemic brain.[34-37] Such effects may be of particular importance in patients with vascular pathologies.

This review of cholinesterase inhibitor clinical studies will focus first on AD patients with vascular risk factors (VRF), and will then examine the evidence for patients with a diagnosis of VaD. Two large, placebo-controlled, 26-week studies involving patients with AD indicated that rivastigmine treatment was associated with greater cognitive and functional improvements in patients with concomitant VRF, compared with those without these risk factors.[38,39]

In addition, three large, placebo-controlled, 26-week studies have provided preliminary evidence of cognitive benefits in populations of patients with VaD. In the first study, galantamine demonstrated significant benefits on cognitive performance, activities of daily living and behavioural symptoms in patients with probable VaD, with and without concurrent AD.[40] In a subanalysis, patients with AD and cerebrovascular disease showed benefits similar to those seen in most 26-week studies of cholinesterase inhibitors in patients with AD, but the response to galantamine in probable VaD patients without AD did not attain statistical significance compared with placebo. Further studies are needed to clarify the value of galantamine in patients with probable VaD in the absence of AD.

The results of two donepezil studies are potentially encouraging but difficult to interpret as it is not clear whether some of these patients also met criteria for possible AD.[41,42] This is a particularly important point considering the galantamine study just described. Data from both overall study populations demonstrated modest, statistically significant, improvements in cognitive function. However, there were no significant improvements over placebo in activities of daily living in one of the donepezil studies, and behavioural symptoms were not assessed, leaving the clinical relevance of the study results uncertain. To date, these studies have only been presented in abstract form, and some of these issues may be clarified with full publication of the data.

Initial findings from a small, open comparison study in patients with 'pure' subcortical VaD indicated that rivastigmine provided significant long-term benefits over aspirin in terms of executive function, behaviour and depression (domains that characterise subcortical VaD).[43,44] A large, placebo-controlled trial is required to evaluate the role of rivastigmine in these patients.

Key messages

- It is possible to treat the symptoms of vascular dementia
- Presenting patients are likely to possess both vascular and Alzheimer pathologies, and it may be appropriate to target treatments at both conditions
- There is accumulating evidence to support the use of cholinesterase inhibitors in patients with vascular dementia or with Alzheimer's disease and concomitant cerebrovascular disease

Conclusions

Cardiologists should be thinking about the possibility of dementia in their patients and the potential benefits of symptomatic treatments. Since presenting patients are likely to possess both vascular and Alzheimer pathologies, it may be appropriate to target treatments at both conditions. Some treatments target the progression of vascular disease and others the dementia.

Although it is not yet conclusive, there is reasonable evidence to support the use of cholinesterase inhibitors in patients with AD with cerebrovascular disease or VaD. These agents have been approved for the treatment of AD (with or without cerebrovascular disease), although they are still under investigation for the treatment of the smaller group of patients with 'pure' VaD. Further studies are required to determine the effects of individual cholinesterase inhibitors on the underlying processes of AD and VaD and the clinical relevance of their effects. However, preliminary data indicate significant benefits at least in cognitive performance.

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