Vascular dementia – a suitable case for treatment

ROGER BULLOCK

Abstract

Vascular dementia (VaD) and Alzheimer's disease (AD) are often described as distinct entities. Recent literature suggests that they may be part of a continuum, where pure VaD is quite rare, Alzheimer's disease is only 40% of the total and AD with cerebrovascular disease makes up the majority of cases that present to memory clinics. This relationship between VaD and AD is highlighted by their common risk factors – especially cardiovascular. Pure VaD is a heterogeneous entity, now separated clinically and radiologically into cortical, subcortical and strategic infarct subtypes. The treatment of VaD includes the primary and secondary prevention of cardiovascular and cerebrovascular disease; and early signs of a dementia may not always involve memory loss. This can lead to late presentations of patients when the more obvious signs and symptoms occur. Consequently, dementia services should work more closely with cardiology and stroke services in order to detect early cases of VaD. This will be increasingly important as new treatments become available.

Key words: vascular dementia, Alzheimer's disease, cerebrovascular disease, cardiovascular risk factors.

Br J Cardiol (Heart Brain) 2003;**10**:HB 20–HB 23

Introduction

The two commonest dementias are reported to be Alzheimer's disease (AD) and vascular dementia (VaD). VaD prevalence is quoted at 20% in many population case studies.[1] However, the diagnostic criteria used may have been loose, leaving VaD over-represented. One third of VaD patients have significant AD pathology[2,3] along with presynaptic cholinergic deficits in basal forebrain neurones. A post-mortem series of ageing nuns[4] found only a 3% incidence of pure VaD. Thus, the true frequency of VaD may be less than 10% and what is commonly reported as VaD may really be a combination of AD and cerebrovascular disease (CVD).

Kingshill Research Centre, Victoria Hospital, Okus Road, Swindon, SN1 9PU.
Roger Bullock, Clinical Director and Consultant
Correspondence to: Dr R Bullock
(email: roger.bullock@kingshill-research.org)

Roger Bullock

Two studies support that view. Nolan[5] looked prospectively at patients diagnosed as having VaD in a dementia clinic, finding 87% of those entered had either AD (58%) or AD plus CVD (42%). The Stockholm memory clinic found that 37% of its dementia patients had pure AD, 60% had both AD and CVD and only 3% had VaD or other dementia.[6]

The relationship between AD, CVD and VaD

As age is a risk factor for both AD and CVD, both frequently co-exist. Many AD cases have vascular pathology, with a third having actual cerebral infarction.[7] The nun study[4] found brain infarction predicted the severity of expression of the clinical AD syndrome in those with Alzheimer pathology, rather than the hallmark pathology of plaques and tangles. The Rotterdam study[8] showed similar findings, suggesting perhaps that the co-existence of AD and CVD is not just a chance finding.

The known risk factors for AD and VaD enforce this relationship. While many have considered that a history of generalised vascular pathology would usually predispose to VaD, table 1 shows that this is equally true for AD. This makes it difficult to make a clear diagnosis from the clinical history alone; and in mixed cases of dementia it is problematic to ascertain what the relative contributions of AD and CVD might be in a single patient with cognitive decline.

Table 1. Risk factors for Alzheimer's disease and vascular disease

Alzheimer's disease	Vascular dementia
Age	Age
Carotid artery atherosclerosis	Carotid artery atherosclerosis
Atrial fibrillation	Atrial fibrillation
Diabetes	Diabetes
Smoking	Smoking
Genetic factors – APOE ε4	Genetic factors – APOE ε4
Hypertension	Hypertension
Stroke	Stroke
High cholesterol	High cholesterol
High homocysteine	High homocysteine
Ventricular dysfunction	

Table 2. NINDS-AIREN criteria for the classification of vascular dementia

I. 1. Presence of dementia
2. Presence of cerebrovascular disease
3. Temporal relationship between the two

II. 1. Gait disturbance 2. Unsteadiness and falls
3. Urinary symptoms 4. Pseudobulbar palsy
5. Personality, mood and executive functional change

III. Slow memory loss, lack of focal signs and absence of CVD on imaging make VaD less likely

IV. Possible VaD may be a) dementia with focal signs but no CVD on imaging or b) dementia with no temporal relationship, a variable course and CVD on imaging

V. Definite VaD requires clinical criteria for probable VaD, plus histopathologic evidence of CVD, with no marked amount of plaques and tangles or other features of other dementias

Key: NINDS = National Institute of Neurological Disorders and Stroke; AIREN = Association Internationale pour la Recherche et l'Enseignement en Neurosciences; VaD = vascular dementia; CVD = cerebrovascular disease

Hypertension is common, and is a risk factor for both AD and VaD. Two large hypertension treatment studies have shown that the lowering of blood pressure in the treatment arms led to a significantly reduced incidence of both AD and VaD compared to the placebo group.[9,10] As only a third of hypertension cases are picked up, better screening and more aggressive treatment may contribute to an overall reduction in the incidence of dementia in the future. These, along with other secondary preventative measures such as smoking cessation and weight control, are important targets for primary care.

Possessing an APOE ε4 allele is a consistent risk factor for dementia, as it is for coronary artery disease.[11] The APOE ε4 allele is a well-documented risk factor in AD, but also has been implicated in dementia following stroke[12] and vascular dementia.[13] AD patients with an APOE ε4 allele are three times as likely to have concomitant cardiovascular disease.[13] Since APOE ε4 is involved in cholesterol metabolism and is associated with high levels of low-density lipoproteins – which in turn may affect amyloid deposition – then cholesterol-lowering drugs may have an important role to play. Two studies have shown a relationship between taking statins and a reduction in the expected number of dementia cases.[14,15] However, a prospective study on the use of statins that included simple cognitive measures did not show significance in terms of cognition at three years.[16] Though disappointing, this may be a reflection of the instruments chosen to measure cognition, learning effects and the time scale needed to demonstrate a clear effect. Current evidence is not sufficient to recommend statins for either the prophylaxis or treatment of dementia, but their mode of action suggests that properly designed studies may soon demonstrate their value.

Classification of vascular dementia

To qualify as a case of vascular dementia, the criteria for dementia must be fulfilled, and vascular lesions related temporally to the cognitive deficits need to be present. Several clinical criteria have been used since the 1970s, the most widely used being the National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria.[17] These emphasise the heterogeneity and variability of the clinical course of vascular dementia. The criteria also list specific factors that support a vascular rather than degenerative course, along with imaging and neuropsychological findings. The criteria are briefly summarised in table 2. If satisfied they give a diagnosis at three levels of certainty – possible, probable and definite.

There is a wide range of potential vascular causes of dementia, not just the multiple infarcts described by Hachinski in 1972.[18] These include large and small vessel disease, cardiac embolic events and haemodynamic mechanisms.[19] Grouping the collective clinical spectrum under the umbrella of vascular cognitive impairment (VCI)[20] is perhaps more useful. Within this broader classification, three subtypes of VaD/VCI then emerge: cortical vascular dementia, subcortical vascular dementia and strategic infarct dementia.

Cortical vascular dementia

Focal cortical lesions that produce lower facial weakness, typical upper motor neurone lesions and gait abnormalities are the main feature of cortical vascular dementia. Memory impairment combined with loss of executive control and slowing of information processing are the common cognitive findings. Clinically, there is often an acute onset, followed by a varied course, with a slow stepwise progression that has plateaus. The declines are related to further strokes. This is the subtype commonly understood as multi-infarct dementia, with a WHO 10th revision international classification of diseases (ICD) code FO1.1.[21]

Subcortical vascular dementia

Subcortical vascular lesions usually take the form of lacunar infarcts or extensive periventricular white matter changes

(leukokaryosis). The latter were considered to be normal findings associated with increasing age, but now leukokaryosis greater than 25% is considered pathological. Cognitive loss here produces a progressive dysexecutive syndrome, with mental slowing and reduced ability to set and reach goals. Memory loss is not a prominent feature so the mini mental state examinations (MMSE) may be relatively preserved in spite of marked disability.[22] Depression is often a concomitant finding, along with subtle personality change, making frontotemporal dementia (FTD) a differential diagnosis. Two thirds of cases have a slow insidious onset, which is similar in both AD and FTD. Imaging will make the necessary distinction. This subtype has the ICD F01.2.

Strategic infarct vascular dementia

Thirty percent of those who have a single stroke over the age of 70 develop a post-stroke dementia.[23] The cognitive syndrome is varied, including severe memory impairment, apathy and loss of spontaneity, perseveration, mild aphasia and fluctuating consciousness and confusion. Symptoms are often associated with acute onset, but may resolve initially before returning in either a stepwise or progressive way. The infarct seems to affect a critical pathway that triggers a progressive disorder; though it is clinically similar to cortical vascular dementia, it is a distinct entity. The most appropriate ICD code is F01.0.

Assessment of vascular dementia

It is important to try to achieve as accurate an aetiological diagnosis as possible, as this will enable the correct selection of treatment options and inform the prognosis. The assessment follows the usual process:

a) Clinical history. The clinician looks for a temporal relationship between vascular symptoms and cognitive deficits. Acute onset is unusual in AD, and a history strongly suggestive of AD probably is just that – irrespective of the vascular findings on imaging. Early continence problems may suggest a vascular aetiology.
b) Physical examination. The clinician will look for supportive neurological signs.
c) Neuropsychology. Impaired executive control is often a feature of VaD. Slowing of choice reaction time compared to both normals and AD can be shown on computerised tests. MMSE may be normal as memory loss may be minimal.
d) Imaging. This is now essential to confirm the diagnosis accurately in dementia. CT scanning will show major lesions whereas MRI is best for demonstrating subcortical lesions. Focal atrophy is suggestive of vascular origin, and SPECT will show focal deficits in VaD.

Treatment options in VaD

The interaction between AD and VaD may be complex, but it is reasonable to assume that the primary and secondary prevention of vascular disease may help with AD as well as VaD. This applies especially in the treatment of hypertension, high cholesterol and atrial fibrillation. ACE inhibitors are the preferred antihypertensives in the elderly as they protect cerebral blood flow and provided the evidence of reduction in dementia in the Perindopril Protection against Recurrent Stroke Study (PROGRESS).[10]

Conversely, therapeutic strategies for AD may work for VaD. Animal models show cholinergic dysfunction in VaD.[24] In humans with VaD, post mortem studies have demonstrated a reduction in choline acetyl transferase in the cortex, hippocampus and striatum[25,26] while patients with subcortical VaD have significantly lower levels of acetylcholine in their cerebrospinal fluid than normal controls. This decrease correlates with the severity of the dementia[27] and suggests that restoration of cholinergic function, for example using cholinesterase inhibitors, will prove a legitimate treatment strategy.

Showing a treatment effect in VaD can be difficult, because the disease can remain stable for long periods. This means that stabilising the condition may not reflect an actual drug effect: in clinical trials, demonstrating efficacy can prove problematic as the placebo groups do not deteriorate, as they do in other dementias.

Prognosis

The life expectancy in VaD is shorter than in AD, and residual physical impairments can make the patients frail and prone to other diseases. Sudden death is not uncommon. Many patients have survived quite major cardiovascular and cerebrovascular events, making a good 'medical recovery'. However, there are often subtle and progressive cognitive impairments that can be overlooked, especially if there is no obvious memory loss. Executive control correlates closely to functional activity and plays an important part in ability to participate in rehabilitation programmes. Consideration of the cognitive status of the patient should therefore be part of the routine in cardiovascular and stroke programmes, as the subsequent recovery and future independence of patients may be further improved.

A feature of VaD is a relative increase in the behavioural symptoms seen in dementia, especially in the early evening. A particular problem is agitation and aggression, both of which particularly distress the carer and lead to an increased risk of institutionalisation. VaD patients are thus frequently treated with antipsychotic medication, sometimes injudiciously, and are overrepresented in nursing home populations. Careful non-pharmacological and pharmacological intervention can successfully manage most of these symptoms in the community.

Conclusion

The distinction between AD and VaD is not clearcut. Vascular disease clearly makes the clinical syndrome in AD more severe, while pure VaD is probably much less frequent than was thought to be the case. Distinct types of VaD do exist, with differing clinical features, and identifying them correctly aids management and prognosis. Once the type of dementia has been correctly identified, the numbers of therapeutic options available clearly demonstrate that VaD is indeed a suitable case for treatment.

Early detection of any dementia is now thought to offer the best prognosis, both in terms of disease management and because it results in better informed patients and carers. Given

Key messages

- VaD has been loosely characterised in the past and it may be that AD plus cerebrovascular disease (often mis-classified as VaD) is the commonest condition seen in memory clinics
- AD and VaD share almost identical risk factors that may reflect some common aspects to their aetiology
- Pure VaD may only represent 5–10% of all dementias; and is subdivided into cortical, subcortical and strategic infarct subtypes
- The presenting features of VaD do not always involve memory impairment, so dementia services should work with cardiology and stroke services to screen for the other cognitive deficits that would aid early detection

the relationship between AD, VaD and vascular disease, the cardiology and stroke services are obvious places where improved liaison with the dementia services may produce better results all round. This may be achieved through appropriate early clinical intervention and further research on a selected population.

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