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Vascular Cognitive Impairment: An Overview

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Dementia is a huge and growing global problem, with up to 25 million cases worldwide and a new case developing every seven seconds (Ferri *et al.*, 2005). Numbers are set to double in the next 25 years and double again in the next 25, thus showing an exponential rise. Costs to health and social care are enormous, with a recent UK Alzheimer's Research Trust report estimating that annual costs of dementia care were five times as high as people with other common diseases such as stroke, heart disease or cancer (ART, 2010). Dementia is age-related, with both prevalence and incidence rising with age. Around 5% of the over 65s are affected, rising to 20% of the over 80s and up to 50% of the very old old – in their 90s.

Dementia refers to a global cognitive decline which can have a number of causes. Once several other pathologies or potentially reversible causes (such as space occupying lesions, vitamin deficiencies, or psychiatric disorders) are excluded, the most common causes in late life are Alzheimer's disease, responsible for around 60% of cases, vascular dementia, responsible for 15-20% of cases, and dementia with Lewy bodies, responsible for around 15% of cases. Other causes include late onset frontotemporal dementia, dementia due to Huntington's disease, and a range of other less common degenerative, metabolic and infective causes. The importance of vascular factors is recognised by the presence of significant vascular pathology in a third of dementia cases acquired from community registers (MRC CFAS, 2001). Rates of vascular dementia rise with age, as for Alzheimer's disease, doubling approximately every 5.3 years as opposed to every 4.5 years for dementia (Jorm *et al.*, 1987). Dementia affects around 15-20% of people three months after stroke, and a further 20-25% develop delayed dementia after stroke, which may be vascular, but increasingly a degenerative component to such delayed dementia after stroke is recognised (Pendlebury and Rothwell, 2009).

Historical background to the concept of vascular dementia

Alzheimer described the first case of 'pre-senile dementia' in 1906 (Alzheimer, 1907) and throughout most of the 20th century Alzheimer's disease, as it became known, was thought to only occur in early (under age 65)

life. Later onset or 'senile' dementia was thought to be due to cerebral arteriosclerosis. Seminal studies undertaken in Newcastle upon Tyne, UK, in the 1960s, examined patients during life and correlated findings with neuropathology at autopsy (Blessed *et al.*, 1969). These studies inclusively showed that Alzheimer's disease, rather than cerebral arteriosclerosis, was the main determinant of dementia in later life. Vascular dementia was therefore thought to occur when there were multiple infarcts in the brain and Hachinski (1974) coined the term 'multi infarct dementia'. Subsequent classification systems such as the ICD and DSM were based on this. Subsequently it became clear that though multi infarct dementia was an important type of dementia, vascular dementia was a more heterogeneous concept and, for example, subcortical ischaemic vascular dementia was as common, if not more common, than multi infarct dementia (O'Brien *et al.*, 2003).

Problems with definition and overlap between pathological causes of dementia

The field of dementia has always struggled with difficulties over terminology and definitions. One of these relates to the term dementia, particularly in relation to non-Alzheimer dementias. This is because most definitions of dementia include memory impairment as a central and prominent component. This is appropriate when the cause is Alzheimer's disease, because 90% of people with Alzheimer's disease have significant memory impairment as an early and predominant feature. However, in non-Alzheimer dementia such as vascular dementia, frontotemporal dementia or dementia with Lewy bodies, memory impairment is variable and may not occur until relatively late in the disease process. This can sometimes lead to some circularity in definition, in that a subject can be quite significantly cognitively impaired in a number of domains, but be classified as 'not demented' because memory may still be largely intact. To recognise the heterogeneity of cognitive features associated with vascular disease, as well as the problems inherent in the 'memory' dominant definition of dementia, a broader term of Vascular Cognitive Impairment has recently been proposed.

The concept of Vascular Cognitive Impairment also recognises the fact that there is no strict cut-off between cognitive impairment and dementia, more a graduation and also that vascular factors are important in dementias apart from vascular dementia. For example, an important interaction between vascular pathology and Alzheimer's disease has been shown (Snowdon *et al.*, 1997). People with Alzheimer's disease who have additional vascular pathology exhibit a greater cognitive impairment during life than those with a similar degree of Alzheimer change but without vascular

pathology. This important interaction between vascular and Alzheimer's disease, already recognised as very common by the MRC CFAS study (MRC/CFAS, 2001), was further developed in the 1990s, when it was recognised that several vascular risk factors were also risk factors for Alzheimer's disease. These included hypertension, smoking, possession of the ApoE protein E4 allele, ischaemic heart disease, hypercholesterolemia, raised homocysteine, diabetes, obesity and atrial fibrillation (O'Brien *et al.*, 2003). Imaging evidence of subcortical vascular change in the form of white matter lesions was also demonstrated to be more common in people with degenerative dementia than similarly aged controls (Barber *et al.*, 1999). More recently, additional genetic factors for late onset Alzheimer's disease have been described beyond possession of the ApoE4 protein allele (see www.alzforum.org for updated list of genetic risk factors) including possession of the angiotensin-converting enzyme gene and factors along the inflammatory and vascular pathways (see Table 1). It is, therefore, increasingly recognised that vascular factors play an important role in primary degenerative dementias such as Alzheimer's disease and their modification may therefore be of relevance for slowing or preventing non vascular types of dementia as well as vascular causes.

Genetic Factors in AD

• Early onset AD	
– APP	
– PS1	
– PS2	
• Late onset AD	
– ApoE4 (Cholesterol transport)	3.68
– ACE (angiotensin/blood pressure)	0.83
– ILIbeta (inflammation)	1.18
– TFAM (mitochondrial transcription factor)	0.82
– CLU (clusterin, A processing)	0.86
– PICALM (vesicle protein trafficking)	0.86
– TNK1 (kinase signalling)	0.86

Table 1. www.alzforum.org, 2010.

Post stroke cognitive impairment

In hospital-based studies rates of dementia three months after stroke approach 30% of which around 10% is pre-stroke dementia (Pendlebury and Rothwell, 2009). Post stroke cognitive impairment and dementia is an important clinical syndrome which slows recovery, increases length of stay, increases the risk of subsequent institutionalisations and increases the risk of recurrent stroke as well as increasing mortality. The rates of dementia after stroke continue to rise in a relatively linear fashion (Pendlebury and Rothwell, 2009), illustrating that stroke, or risk factors associated with it, continue to place the brain at increased risk of vulnerability to dementia in the longer term. Risk factors for post stroke dementia include vascular risk factors, the presence of atrophy and white matter lesions on imaging as well as features of stroke itself, such as large lesion size, bilaterality. Correlates of dementia after stroke remain to be fully determined, but it seems likely that both vascular and, especially in older people, Alzheimer-type changes both play a role, especially in delayed dementia after stroke (Firbank *et al.*, 2007a).

Imaging findings of white matter lesions have been consistently associated with the presence of executive and attentional disturbances, including after stroke (Burton *et al.*, 2004). Lesions are also more common in those with dementia than cognitively intact controls but the prognostic significance of lesions in those without symptoms has been unclear. However, recent findings from a large European study, the Leukoaraoisis and Disability (LADIS) study, which followed 639 subjects with mild, moderate or severe white matter lesions over three years, found that in this non disabled population, increasing burden of white matter lesions (especially those with the more severe confluent lesions) significantly increased the risk of progression to disability or death, with rates of transition to disability or death 30% per year in those with severe lesions compared to 15% of those with moderate, only 11% in those with mild lesions (Inzitari *et al.*, 2009). Although it is not yet clear how such white matter lesions should be treated, their adverse prognostic significance has now been established, opening a way for preventative studies.

Treatment of vascular cognitive impairment

Unfortunately, only a relatively limited amount of research has been done in this area. Studies of aspirin in terms of cognitive benefit are inconclusive. An early study (Meyer *et al.*, 1989) allocated 70 people with multi infarct dementia either to aspirin or no treatment. Subjects were followed annually for three years and those treated with aspirin showed higher cognitive performances compared to those receiving no treatment. However, this study has been criticised because of the small sample size, the high dropout rate, the lack of

placebo and the lack of true randomisation. Other controlled studies in vascular dementia have not been undertaken, but aspirin studies of large community cohorts or those with Alzheimer's disease have consistently failed to demonstrate any clear benefit in terms of cognition of aspirin treatment over placebo. Other putative treatments for vascular dementia including hydergine, propentofylline, nimodipine, pentoxifylline, nicergoline, posatirelin, have largely been negative. Some benefits of nimodipine in subcortical vascular dementia have been described (Pantoni *et al.*, 2005), but effects are modest and primary outcomes are not clearly positive, meaning that it is unlikely nimodipine produces clinically significant benefits. Studies of memantine show a small cognitive benefit but no change in global or functional outcomes (Orgogozo *et al.*, 2002; Wilcock *et al.*, 2002).

Demonstration of a cholinergic deficit in Alzheimer's disease and dementia with Lewy bodies has led to the development of a generation of compounds to boost cholinergic function, the cholinesterase inhibitors (Perry *et al.*, 1978). Licensed treatments in most countries include donepezil, rivastigmine and galantamine, and all produce a modest benefit in people with Alzheimer's disease (O'Brien, 2006). Several studies indicated that a cholinergic deficit may also exist in vascular dementia, though this has recently been questioned (Perry *et al.*, 2005). Early trials of cholinesterase inhibitors in vascular dementia produced mixed benefits, with some suggestions of an improvement (Erkinjuntti *et al.*, 2001). However, several large studies of galantamine, donepezil and rivastigmine have been largely negative. These studies have produced a small cognitive benefit but generally no significant change in terms of global outcome scales, activities of daily living or behavioural features (see Table 2). A study of donepezil in 168 subjects with a rare but relatively pure genetic form of vascular dementia (cerebral autosomal dominant arteriopathy with subcortical ischemic leucoencephalopathy or CADASIL) showed no significant benefit of donepezil treatment on primary outcome, though there were some benefits on secondary endpoints consistent with the fact there may be cholinergic deficits in CADASIL (Dichgans *et al.*, 2008). However, overall meta analyses of cholinesterase therapies for vascular dementia have concluded that, whilst they have produced small benefits in cognition, these are of uncertain clinical significance and the data are insufficient to support widespread use of the drugs (Kavirajan and Schneider, 2007). However, those with mixed Alzheimer and vascular pathology do appear to benefit (Erkinjuntti *et al.*, 2001) and this is consistent with the findings of Perry *et al.* (2005) from autopsy studies who report that cholinergic deficit is as great in those with mixed Alzheimer/vascular pathology as in Alzheimer's disease, but cholinergic function is intact in those with more pure vascular dementia.

RCTs of CHEI in Vascular Dementia				
	Cognition	Global	ADL	Behaviour
Galantamine (Gal-INT-06) (n=121) Erkinjuntti *et al.*, 2001	No (p=0.06)	No	No	No
Galantamine (Gal-INT-26) (n=788) Auchus *et al.*, 2007	Yes	No	No	No
Donepezil (307) (n=603) Black *et al.*, 2003	Yes	No	Yes	n/a
Donepezil (308) (n=616) Wilkinson *et al.*, 2003	Yes	Yes	No	n/a
Donepezil (319) (n=974) (press release 16.3.06)	Yes	No	No	n/a
Rivastigmine (VantageE) (n=710) Ballard *et al.*, 2008	Yes (p=0.028)	No	No	No

Table 2.

Prevention of vascular dementia

Clearly this would be the goal of management, either modifying risk factors or using pharmacotherapy. One recent study reported a risk index for developing dementia (Barnes *et al.*, 2009), which is reproduced in Table 3. As can be seen, several of the risk factors including body mass index, MR findings of white matter disease, carotid artery thickening, history of bypass surgery, slow physical performance and lack of alcohol consumption are all potentially vascular risk factors. However, translating such relatively consistent findings from epidemiological studies that vascular risk factors are important risk factors for dementia into preventative studies has not been straightforward. Two well-conducted studies of modification of cholesterol, the PROSPER and the heart protection study (Shepherd *et al.*, 2002; Rea *et al.*, 2005) describe including between 6,000 and 20,000 people with follow-up for five to six years showed no benefits in terms of cognition or prevention of dementia between those allocated to statin therapy and those allocated to placebo. Since the emergence of hypertension as an important risk factor for Alzheimer's disease, there has been great interest in whether treating hypertension will prevent dementia. Findings from the SYST-EUR study showed that nitrendapine treatment significantly reduced the number

Late-Life Dementia Risk Index

(Risk 4% to 56% over 6 years)

- Older age (1–2 points)
- Poor cognitive test performance (2–4 points)
- Body mass index 18.5 kg/m2 (2 points)
- 1 Apolipoprotein E e4 allele (1 point)
- Cerebral MRI findings of white-matter disease (1 point) or ventricular enlargement (1 point)
- Internal carotid artery thickening on ultrasound (1 point)
- History of bypass surgery (1 point)
- Slow physical performance (1 point)
- Lack of alcohol consumption (1 point)

Table 3. CV Health Cognition Study, Barnes *et al.*, 2009.

of cases of dementia compared with placebo, with this effect persisting over the four-year follow-up period (Forette *et al.*, 1998; 2002). Interestingly, and consistent with the finding that hypertension is a risk factor for Alzheimer's disease, the main reduction was in cases of Alzheimer-type dementia. Several other studies have suggested that there is a signal from such therapy, the most recent being the HYVET study (Peters *et al.*, 2008) which examined those over 80 randomising them to indapamide or placebo. There was a non-significant trend for a reduction in dementia cases, but as with many studies of vascular risk the study was halted early because the primary end-point in terms of reduction in cardiovascular events was found. Overall, meta analyses either just show, or fail to show, a benefit of anti hypertensive treatment and firm conclusions about protective effect of anti hypertensive therapy in cognition cannot yet be made. Of interest, in a sub study of the study on cognition and prognosis in the elderly (SCOPE) which used the angiotensin to inhibit candesartan or placebo and a more detailed neuropsychological battery and repeat neuroimaging assessment, found evidence that a reduction in blood pressure with candesartan treatment was associated with a slowed rate of cognitive decline and a slowing of progres-

sion of white matter change, with a trend to slowed rate of overall brain atrophy (Firbank *et al.*, 2007b). Such studies combined with the known deleterious consequences prognostically of having a significant burden of white matter change (Inzitari *et al.*, 2009) would lend support to further large-scale studies investigating a variety of strategies which may potentially reduce or delay progression of white matter changes. This particular strategy in Alzheimer's disease may also be effective, given that vascular risk factors are common in people with Alzheimer's disease and that vascular pathology is a disparate additive to Alzheimer pathology in the expression of cognitive decline. A naturalistic study of 301 subjects with Alzheimer's disease (Deschaintre *et al.*, 2009) found that only 7% of those with Alzheimer's disease had no vascular risk factors. However, vascular risk factors were fully treated in 32%, partially treated in 43% and not treated at all in 26%. Although a naturalistic study, follow up over two and a half years show that those with treated vascular risk factors had significantly slower rate of cognitive decline compared to those without. However, support that treatment of vascular risk factors would slow cognitive decline in Alzheimer's disease was not provided by a randomised controlled trial by Richard *et al.* (2009) in which 130 subjects with Alzheimer's disease, with evidence of cerebrovascular disease on brain imaging, were randomised to vascular care (aspirin, folate, statin, pyridoxine and blood pressure lowering if BP>140/80) or usual care. At two-year follow-up there was no significant difference in rates of cognitive or functional progression to those allocated to vascular intervention group and placebo. However, although cholesterol was significantly lower in the intervention group compared to placebo, there was no significant difference in blood pressure between the groups (interestingly which dropped to a similar extent 15/5 mm of mercury) in both groups. Therefore, it is not clear whether the vascular package was ineffective as it failed to achieve a difference in blood pressure between groups. Further studies on the effect of intensive blood pressure lowering in preventing future cognitive decline are required.

Conclusions

Dementia is a huge and growing public health problem, with vascular dementia the second commonest cause of dementia and cognitive impairment. However, in addition, vascular factors are also important in Alzheimer's disease, there is still much to learn about the interaction between vascular and degenerative disease. Unfortunately, therapeutic strategies to date have been disappointing and neither the drugs used to treat Alzheimer's disease nor modification of vascular risk factors are clearly effective in preventing future

cognitive decline and dementia. There is a clear need for further mechanistic and therapeutic studies in the area, including preventative studies which should be undertaken in those with early disease, in those with particular vascular subgroups (for example those with post stroke dementia or subcortical ischaemic vascular dementia) and in those with white matter lesions. Because of the close interaction between vascular and Alzheimer pathology and the importance of vascular factors in Alzheimer's disease, successful strategies developed for the treatment or prevention of vascular dementia may also be useful for treating or preventing Alzheimer's disease.

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