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Pharmacological prevention and treatment of vascular dementia: Approaches and perspectives

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ABSTRACT

Vascular dementia (VaD) is a common dementing illness. There are no pharmacological agents with a regulatory approval for its treatment or prevention. Review of published clinical trial reports indicates that early treatment of hypertension, a risk factor for stroke, reduces VaD risk and slows progression. However, unlike stroke, treatment of hyperlipidemia with statin class drugs or treatment of blood clotting abnormalities with acetylsalicylic acid do not appear to have an effect on VaD incidence or progression. Pharmacological agents for treatment of Alzheimer's dementia (AD) such as memantine or acetylcholinesterase inhibitors have small positive effects on cognition in VaD, which are likely due to their action on co-existing AD-related neuropathology. Drug development efforts using novel approaches such as patient stratification by their genotype are needed in order to address the increasing need for effective VaD therapeutics.

1. Introduction

Vascular dementia (VaD) is defined as the loss of cognitive function resulting from ischemic, ischemic-hypoxic or hemorrhagic brain tissue lesions due to cardiovascular disease and cardiovascular pathological changes (Roman, 2002; Seitz et al., 2011). It affects 1 to 4 of every 100 individuals by age 65 (Malouf and Birks, 2009) with the prevalence doubling every 5 years to the age of 90 (McShane et al., 2009). It is believed that VaD is a clinical and pathological entity that is distinct from Alzheimer's dementia (AD), Lewy body dementia, or fronto-temporal dementia, although elements of vascular disease may be present in all of these conditions. A number of excellent reviews have been written on diagnosis, pathogenesis, and epidemiology of VaD (Gorelick et al., 2011; Kirshner, 2009; Pendlebury and Rothwell, 2009) and detailed analyses of its neuropathology, genetics, imaging and other relevant topics can be found in this Special Issue. There are several diagnostic criteria for VaD, including Diagnostic and Statistical Manual of Mental Disorders; DSM-IV-TR, International Classification of Disease; ICD and National Institute of Neurological Disorders and Stroke — Association Internationale pour la Recherché et l'Enseignement en Neurosciences; NINDS-AIREN. These diagnostic criteria have 3 common elements. They require: (i) cognitive impairment or dementia syndrome demonstrated by neuropsychological testing, (ii) clinical history of stroke or other manifestations of cerebrovascular disease demonstrated by neuroimaging and (iii) temporary association between the cognitive symptoms and cerebrovascular disease (Gorelick et al., 2011). There are several clinical and pathological types of VaD, including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Binswanger's disease, lacunar state and miscellaneous other vascular cognitive syndromes (Kirshner, 2009). A recent consensus conference has developed a concept of vascular cognitive impairment (VCI), as a syndrome with evidence of clinical stroke or

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subclinical brain injury and cognitive impairment affecting at least one cognitive domain (Gorelick et al., 2011), however, analysis of these variants falls beyond the scope of this review. Among the predictors of VaD are demographic factors that include sex (VaD is more prevalent in women), age (VaD is more common in older individuals), low educational attainment, family history of dementia, previous cognitive decline, premorbid conditions including diabetes, atrial fibrillation, previous stroke or transient ischemic attacks, hypertension, and hyperlipidemia or dyslipidemia (Gorelick et al., 2011; Pendlebury and Rothwell, 2009). Prevention and treatment of VaD has received extensive coverage (Baskys and Hou, 2007; Birks and Grimley Evans, 2009; Craig and Birks, 2009; Kavirajan and Schneider, 2007; Malouf and Birks, 2009; McGuinness et al., 2009b; Muangpaisan and Brayne, 2010; Sharp et al., 2011; Williams et al., 2008). The prevailing conclusion of these reports is that most pharmaceutical clinical trials pertaining to VaD have produced disappointing results. It is necessary to note that so far no drug has been approved by any regulatory agency to prevent or treat VaD (Gorelick et al., 2011). This is a paradox because causes of VaD encompass ischemic stroke — a highly preventable condition. Because of substantial costs associated with dementia, efforts to address the problem of VaD treatment and prevention are well justified. This review will briefly summarize available VaD prevention and treatment clinical trial data.

2. Prevention of VaD

Stroke is an essential element of VaD. A question arises whether modifications of risk factors for stroke such as hypertension, hyperlipidemia or dyslipidemia, atrial fibrillation, or diabetes have any impact on disease risk or improve cognition in individuals with VaD.

2.1. Treatment of hypertension

To date, meta-analyses of several longitudinal trials have shown that hypertension is a potential risk factor for VaD and that antihypertensive medication use appears to reduce VaD risk (Chang-Quan et al., 2011; Shah et al., 2009; Sharp et al., 2011). However, population-based studies (Pendlebury and Rothwell, 2009) found that hypertension was only associated with the rates of pre-stroke dementia (odd ratio (OR = 1.4, confidence interference (CI 1.0–2.0; p = 0.04)), but not post-stroke dementia (OR 1.1, CI (0.9–1.3) ; p = 0.22), suggesting that treatment of hypertension should begin early in order to reduce VaD risk. Recent meta-analyses of randomized clinical trials (RCTs) addressed the issue of VaD risk and progression but produced inconsistent results (Ligthart et al., 2010; McGuinness et al., 2009b; Shah et al., 2009). This discrepancy could be explained by variable patient selection methods and inclusion of different RCTs in the meta-analysis. Use of different antihypertensive drugs such as angiotensin converting enzyme inhibitors, diuretics, calcium channel blockers, sympathetic nerve inhibitors, angiotensin II receptor antagonists or adrenergic antagonists, may also contribute to the inconclusive meta-analysis results. In addition, trials that had cardiovascular benefits set as their primary end-point were often terminated once the benefit became apparent, while it is possible that beneficial effects of antihypertensives on cognition could require more time to develop (McGuinness et al., 2009b). In contrast, meta-analyses of longitudinal studies, that yielded positive results, studied VaD patients taking antihypertensive drugs much longer than those in RCTs. Together these observations support the idea that data from longitudinal, retrospective or cross-sectional studies that support the usefulness of antihypertensives in VaD risk reduction could be considered reliable.

2.2. Use of statins

Elevated high-density lipid (HDL) cholesterol and non-HDL cholesterol levels have been associated with elevated VaD risk (McGuinness et al., 2009a, 2010). Statins are a class of drugs that upregulate LDL receptor activity and increase HDL cholesterol, by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase reduce formation and entry of low-density lipid (LDL) cholesterol particles into the circulation (McGuinness et al., 2009a). Three recent systematic reviews of clinical trials of statin use for VaD prevention (Ligthart et al., 2010; McGuinness et al., 2009a; Muangpaisan and Brayne, 2010) concluded that statins given in late life to individuals at risk for cerebrovascular disease have no effect in preventing any dementia including VaD. A Cochrane review (McGuinness et al., 2010) also found that there were no studies supporting the role of statins in treatment of VaD.

2.3. Aspirin

Aspirin (acetylsalicylic acid, ASA) is used for prevention of transient ischemic attacks, strokes and heart attacks. It inhibits thromboxane A2 (TXA2) and prostacyclin (PGI2), which promote aggregation of platelets and local vasoconstriction, and has analgesic, antipyretic and antiinflammatory properties. Although aspirin is widely prescribed for patients with VaD in order to slow the disease progression and improve cognition, there are no meta-analysis or RCT data to support this idea (Williams et al., 2008).

In conclusion, pharmacological treatment of hypertension, if started early, appears to reduce the risk and the progression of VaD. There is no conclusive evidence that other pharmacological approaches such as statins or ASA are of benefit. Besides of these pharmacological interventions, there is no convincing evidence that the so-called Mediterranean diet or smoking cessation could benefit those with cognitive impairment (Gorelick et al., 2011). However, a recently published meta-analysis based on 15 observational studies, suggest a significant and consistent protection against the cognitive decline by physical activity (Sofi et al., 2011).

3. Treatment of VaD

3.1. Memantine

Memantine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that has a regulatory approval for treatment of AD. It has been tested in two VaD studies that included 815 subjects with mild to moderately advanced disease. There was a small reduction in a behavioral disturbance scale (Nurse's Observational Scale for Geriatric Patients, NOSGER) (Kavirajan and Schneider, 2007; McShane et al., 2009; Orgogozo et al., 2002; Wilcock et al., 2002, see Table 1). In a study of a mixed patient population that included AD, VaD and mixed dementia patients (n = 168), there was a significant positive effect of memantine on Clinical Global Impression of Change (CGIC) scale (Kavirajan and Schneider, 2007; McShane et al., 2009). Similar findings indicating improvement in cognition and global function emerged from several smaller studies (n = 59-88) involving patients with unspecified dementia (McShane et al., 2009). These findings suggest that memantine could have a positive effect on cognition in patients with VaD.

3.2. Galantamine

Galantamine is a cholinesterase inhibitor that like other similar drugs of this class has a regulatory approval for treatment of AD. Two large RCTs involving VaD patients were selected for meta-analyses (Craig and Birks, 2009; Kavirajan and Schneider, 2007). One RCT included VaD and AD patients showing radiological and historical evidence of cerebrovascular disease. Galantamine at 24 mg/day for 24-weeks did not significantly change any of the outcome measures in the VaD subgroup of subjects. A combined analysis of VaD and AD patients showed a significant treatment effect on a variety of measures including ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive), CIBIC+ (Clinician's Interview-based Impression of Change with caregiver input), NPI (Neuropsychiatric Inventory) and DAD (Disability Assessment for Dementia) scales.

The second RCT included 788 subjects with VaD (Auchus et al., 2007; Craig and Birks, 2009; Kavirajan and Schneider, 2007, see