Vascular Dementia: Potential of Antiplatelet Agents in Prevention

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Abstract
The term ‘vascular dementia’ (VaD) corresponds to a clinicoradiological syndrome that can be defined with more or less restriction. VaD can result from: (1) cortical or subcortical ischemic lesions related to the occlusion of large vessels, (2) lacunar infarcts with or without white-matter lesions at the subcortical level related to small-vessel diseases, (3) ischemic lesions related to hypoperfusion or anoxic-ischemic encephalopathy or (4) hemorrhagic lesions. The prevention of VaD is based on stroke prevention which implies risk factor manipulation and use of antithrombotic drugs among which the most widely used are antiplatelet drugs. The efficiency of these drugs to prevent cognitive impairment and dementia is not proven. Prospective studies are needed to investigate their potential in patients at risk of VaD: after ischemic stroke, in the presence of cognitive impairment of vascular origin or when MRI shows ‘silent’ ischemic white-matter lesions and/or infarcts.

Table 1. DSM-IV criteria for VaD

| A1 | Memory impairment |
| A2 | One or more of the following cognitive disturbances |
|    | a Aphasia |
|    | b Apraxia |
|    | c Agnosia |
|    | d Disturbance in executive functioning |
| B  | Cognitive deficits due to criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning |
| C  | Factors judged to be etiologically related to the disturbance |
|    | a Focal neurological signs and symptoms |
|    | b Laboratory evidence indicative of cerebrovascular disease (e.g. multiple infarctions involving the cortex and underlying white matter) |
| D  | Not occurring exclusively during the course of delirium |

Key Words
Vascular dementia, prevention • Antiplatelet treatment
diagnostic criteria for dementia are focusing on memory impairment associated with alteration of at least one other cognitive domain leading to a significant impairment in social or occupational functioning. No specification concerning the underlying vascular disease is required for diagnosis which explains that one fifth of patients fulfilling the DSM-IV criteria can present without any abnormality on the CT scan. In contrast, the NINDS-AIREN criteria designed for research appear more specific (table 2). Executive dysfunction is a feature of both DSM-IV and NINDS-AIREN definitions; in contrast, visuospatial dysfunction is considered as a criterion only in the latter. Furthermore, the different etiological links with the underlying vascular disorder are foreseen using the NINDS-AIREN criteria [2]. Other definitions of VaD have been proposed, such as that of the Alzheimer’s Disease Diagnostic and Treatment Centers [3], that of the International Classification of Diseases, 10th revision [2] (table 3), or that derived from the Hachinski ischemic score [4]. This score, based on a 13-item scale (table 4), was initially proposed to differentiate multi-infarct dementia caused by multiple ischemic stroke (score ≥7) and Alzheimer’s disease (AD; score <4). However, it is now well established that the occurrence of multiple cerebral infarcts is not the only pathway to VaD. The occurrence of a single infarct in a strategic brain area can lead to de-
mentia [5, 6]. Intracerebral hemorrhages may also have similar consequences. Furthermore, imaging studies have shown that white-matter lesions [7] and so-called silent infarcts [8] could also contribute to the cognitive decline. On the other hand, evidence of brain lesions of vascular origin does not necessarily mean that they are responsible for the cognitive deficit in a given patient. Zekry et al. [9] have recently emphasized that the location, but not the volume, of ischemic or hemorrhagic lesions within the limbic or heteromodal association areas in the brain (cortical or white matter) was playing the primary role in the occurrence of dementia both in VaD and in mixed dementia which is an association of VaD and AD.

Finally, the concept itself of VaD is now reappraised not only because it covers various types of tissue lesions and different underlying vascular disorders, but also because the definition of dementia imposes an artificial categorical distinction on a continuous or stepwise progression of cognitive impairment. This is crucial to understand before establishing strategies for the prevention of cognitive decline [10]. It is also obvious that the risk of dementia in patients with cerebrovascular disease will largely differ according to the presence or absence of associated degenerative brain changes that occur frequently with aging since mixed dementia is probably the most frequent form of dementia [11]. Recently, the term ‘vascular cognitive impairment’ was proposed to better encompass the whole spectrum of cognitive alterations associated with cerebral lesions of vascular origin [12].

In large European population-based studies, the prevalence of dementia is 6.4% in subjects aged over 65 years [13], 4.4% for AD and 1.6% for VaD [14]. The prevalence of VaD increases considerably with age, from 0.3% between 65 and 69 years to 5.2% at the age of 90 years [14]. In the Rotterdam study, a large population-based study of 7,046 persons aged more than 55 years who were free of dementia at baseline, 395 new cases of dementia were observed after a mean follow-up of 5.7 years including 293 cases of AD and 57 cases of VaD. The corresponding incidence of VaD was estimated at 1.5 per 1,000 person-years and was found lower in women than in men (ratio: 0.57) [15]. Similar results were observed in other large cohorts [16]. Thus, the incidence of VaD, as well as that of stroke, is higher in men whereas the prevalence is higher in women [14] because of their 10-year-longer life expectancy.

The increasing number of demented patients (particularly in well-developed countries) represents an important challenge for health care and social support systems. However, little is known concerning the actual cost for society of this tremendous issue [17]. At the caregiver level, the burden of dementia has different aspects: general strain, isolation, disappointment or emotional disturbances [18]. Interestingly, the relatives of patients with VaD might be more stressed by the disturbing behavior and the memory impairment of the patients whereas, for AD, the most stressful part of caring is the social behavior [19].

### Main Causes and Risk Factors

VaD results from ischemic and/or hemorrhagic cerebral lesions that can manifest as different clinical syndromes (table 5). Most often, four categories of lesions can be detected on MRI or CT scan in VaD patients: (1) cortical or subcortical ischemic lesions related to the occlusion of large vessels, (2) lacunar infarcts with or without white-matter lesions at the subcortical level related to small-vessel diseases, (3) ischemic lesions related to hypoperfusion or anoxic-ischemic encephalopathy or (4) hemorrhagic lesions [20].

The occlusion of large vessels secondary to atherothrombosis or caused by cardiac emboli can lead to the so-called multiple-infarct dementia related to the accumulation of large infarcts at the cortical and/or subcortical level [4]. In some cases, only a single infarct in functionally critical areas of the brain (angular gyrus, thalamus, basal forebrain or territory of the posterior or anterior cerebral artery) can lead to a ‘strategic-infarct dementia’ [6]. Atrial fibrillation is a major cause of stroke; in the Rotterdam study, dementia was more than twice as common in subjects with atrial fibrillation than in those without [21].

| Table 5. Main causes of stroke (modified from Albers et al. [77]) |
|-------------------|--------|
|                    | Percent |
| **Primary hemorrhage** | 15     |
| Atherothromboembolism | 20     |
| Intracranial small-vessel diseases | 25     |
| Cardiac source of embolism | 20     |
| Cerebral venous thrombosis | 0.5    |
| Miscellaneous unusual causes | 5      |
| (e.g. dissection, arteritis, drug abuse) |       |
| **Undetermined cause** | 30     |
related with cognitive impairment even in the absence of stroke events possibly through the occurrence of silent cardioembolic infarcts [22, 23].

Small-vessel diseases of the brain lead to a large spectrum of lesions in the subcortical regions supplied by the perforating arteries: lacunar infarcts (small deep infarcts of diameter less than 15 mm), white-matter demyelination and rarefaction (called ‘leukoaraiosis’) and microhemorrhages. The contribution of these different lesions in the cognitive deficit largely varies according to their type (complete or incomplete infarcts, demyelination), extent and location [9]. The most frequent small-vessel disease of the brain is the hypertensive arteriosclerotic angiopathy, mainly detected in elderly patients. In the majority of cases, the subcortical ischemic lesions are associated with more or less severe degenerative lesions (as observed in AD) in so-called mixed dementias. Only in few cases are the widespread deep infarcts and diffuse white-matter lesions isolated and responsible for a ‘pure VaD’ previously called ‘Binswanger’s disease’ [24]. The term ‘subcortical ischemic VaD’ is now preferred for this category of dementia related to small-vessel diseases in general [20], a group including hereditary small-vessel diseases such as ‘cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy’ [25] caused by mutation of the Notch3 gene on chromosome 19 [26].

Ischemic lesions related to hypoperfusion of the brain are rare. They include the diffuse anoxic-ischemic encephalopathy [27] secondary to acute diffuse cerebral hypoperfusion (after cardiac arrest for example) and focal lesions in cerebral regions of selective vulnerability promoted by the presence of severe atherothrombotic stenosis or occlusion of large arteries [28].

Finally, the accumulation of hemorrhagic lesions is another cause of VaD. Hypertension modifying the wall of the perforating arteries of the brain is the most frequent cause of deep cerebral hematomas in the elderly and thus of VaD due to hemorrhagic lesions. Other risk factors include high alcohol intake and the male sex according to Ariesen et al. [29]. In contrast, severe forms of amyloid angiopathy predominating in leptomeningeal and short cortical perforating arteries are mainly responsible for recurrent cortical hemorrhages in elderly patients that can also lead to VaD or mixed dementia [30]. Familial forms of amyloid angiopathy secondary to different mutations in several genes (Amyloid Precursor Protein, protein Bri, Gelsolin, Cystatin C) are extremely rare [31].

The relationships between vascular risk factors and dementia have been demonstrated in different cohorts, most frequently without distinction between VaD, mixed dementia and AD. Most data from longitudinal studies emphasized the crucial role of hypertension in the occurrence of dementia [32, 33]. In a large cohort of 3,703 Japanese-American men included in the Honolulu Heart Program, the risk of dementia was increased by a factor of 4 for a diastolic blood pressure above 90 mm Hg and by 4.8 for a systolic blood pressure above 160 mm Hg by comparison with normotensive subjects. In France, in a longitudinal population-based study of 1,373 French elderly individuals (EVA study), the risk of cognitive decline after 4 years (defined as a 4-point drop on the Mini-Mental State Examination, MMSE) was 4.3 times greater in patients with high blood pressure measured at baseline. This risk was increased by 6-fold in untreated hypertensive patients at the 2-year assessment [32].

The risk of VaD related to the lipid profile has been investigated longitudinally only in a few studies. Moroney et al. [34] found that the risk of dementia with stroke was weakly associated with high levels of low-density lipoprotein cholesterol in their large prospective study but not in their cross-sectional analysis. Elsewhere, different authors reported that a low level of high-density lipoprotein cholesterol was associated with an increased risk of VaD [35–37]. In the longitudinal study performed by Reitz et al. [37], the impact of drugs used to reduce the cholesterol level on the risk of dementia was not significant. Prospective studies are warranted to assess the promising effects of statins on the risk of dementia.

Smoking was found to increase the risk of both VaD and AD. In the recent study of Juan et al. [38] of 2,820 participants aged 60 years, the relative risk of VaD was found to be nonsignificant in past smokers but at 1.98 in current smokers. Interestingly, Ott et al. [39] have recently reported that the MMSE score of persons who never smoked on average declined 0.03 points/year but that this decline was 0.03 and 0.13 points greater in former and current smokers.

Hyperhomocysteinemia was previously associated with VaD in different case-control or cross-sectional studies [40, 41]. Various data suggest that hyperhomocysteinemia is mostly associated with small-vessel diseases, white-matter lesions or silent deep infarcts in the brain [42, 43]. Longitudinal studies are lacking to estimate the actual risk of dementia related to increased homocysteinemia.

The recent data from the Women Health Initiative showed that estrogen + progestin therapy increased the risk for dementia in postmenopausal women aged 65 years or older, also possibly by increasing the risk of vascular insults to the brain [44].
A decreased risk of dementia or cognitive decline was reported with a moderate consumption of wine both in the Paquid study [45] and in the EVA cohort as observed in general for vascular diseases. This protective role of moderate alcohol consumption (1–6 drinks weekly) has recently been confirmed in a nested case-control study of patients recruited from the Cardiovascular Health Study cohort [45]. Diabetes is slightly increasing the risk of dementia in general [46, 47] with a relative risk estimated at 1.66 by Leibson et al. [46] for both AD and VaD.

Besides these modifiable vascular risk factors, numerous markers of the cardiovascular risk have recently been identified such as biochemical markers (e.g. C-reactive protein, fibrinogen, interleukin 6), morphological markers (e.g. intima-media thickness, coronary calcifications, silent cerebral infaracts) and genetic markers (e.g. phosphodiesterase) [48]. Only a few of them have been studied in relation with VaD; they are mostly markers of early atherosclerosis.

In the Atherosclerosis Risk in Communities cohort, a large biracial, longitudinal investigation of 10,963 individuals, no significant relationship was detected between the carotid intima-media thickness and the risk of cognitive decline measured 6 years after the entry in the study [49]. In contrast, the severity of atherosclerosis (measured with indicators such as wall thickness, plaques, ratio of ankle-to-brachial systolic blood pressure) was found to be strongly associated with both VaD and AD in the Rotterdam study [50]. This is possibly related to the increased risk of ischemic stroke, silent infarcts and white-matter lesions in the presence of atherosclerosis. In the Framingham study, the occurrence of a first stroke doubled the risk of dementia at 10 years [8]. Recently, silent brain infarcts (asymptomatic lacunar infarcts on MRI) were found to double the risk of dementia at 3.6 years in the elderly patients included in the Rotterdam study [8]. The severity of aortic [51], carotid [52] and vertebral [53] atherosclerosis was previously shown to increase the risk of ischemic stroke, which is further amplified when atherosclerosis involved the intracranial arteries [53, 54]. The intima-media thickness and plaques at the carotid level are associated with the occurrence of silent cerebral infarcts on MRI [55]. Finally, in the EVA cohort, the presence of carotid plaques at baseline was associated with severe MRI white-matter hyperintensities observed 4 years after the entry in the study after adjusting for age, gender and hypertension [56].

Of note, the Apolipoprotein E4 gene allele which increases the risk of AD does not seem associated with the risk of VaD [57].

**Treatment**

Therapeutic options in patients with VaD are scarce. Various molecules have been evaluated to improve the cognitive deficit of patients with established VaD. The results obtained with vasodilators, nootropics and antioxidants or propentofylline in patients with VaD were disappointing. The beneficial effect of the calcium antagonist nimodipine initially detected in a subgroup of patients with subcortical VaD [58] has not recently been confirmed by a placebo-controlled study, although a trend for better performances in lexical production and less deterioration on the MMSE was detected in VaD patients under treatment [59]. Conversely, cholinesterase inhibitors have been found efficient in VaD. Three drugs approved in AD – donepezil, rivastigmine and galantamine – have been tested in VaD. Donepezil was evaluated in a total of 1,219 VaD patients diagnosed using the NINDS-AIREN criteria in two trials [60, 61]. In both trials, a significant benefit was detected in treated patients with the neuropsychological battery of the AD Assessment Scale cognitive subscale (ADAS-cog) after 24 weeks of treatment. Of interest, the cognitive decline was lower than that usually observed in AD patients during similar studies. In contrast to the mere reduction of cognitive decline obtained with this drug in patients with AD, some improvement of the baseline cognitive status was detected with this molecule in VaD. Galantamine is another acetylcholinesterase inhibitor that also modulates the central nicotinic receptors to increase the cholinergic transmission. In a large trial including both patients with mixed dementia and VaD, galantamine showed greater efficacy than placebo on the ADAS-cog and CIBIC-plus evaluation results [62]. Among patients with VaD, the mean change from baseline of the ADAS-cog was only 2.4 points; 31% patients under the treatment compared to 23% under the placebo had their global function improved or maintained at least up to 12 months. Rivastigmine was only evaluated in a small open-label study of patients with subcortical VaD showing some improvement in cognition, caregiver stress and behavior [62].

**Prevention**

After the diagnosis of VaD, some data suggest that the use of antiplatelet drugs may be beneficial to the patients. In a retrospective case-notes study, Devine et al. [63] observed that patients with VaD treated with aspirin discharged from the nonacute patient unit had a longer life...
expectancy and survival than patients without treatment. In a hospital-based cohort of African-American patients with VaD and AD, Freels et al. [64] also reported that VaD patients under antiplatelet treatment (or anticoagulation for cardiogenic embolism) were at lower risk of death. Controlled studies are however lacking to show how long the antiplatelet drugs should be administered to patients with VaD. The benefit/risk ratio may greatly vary in VaD patients according to the risk of hemorrhage which is increased by the presence of silent microhemorrhages on MRI often detected in the presence of diffuse ischemic white-matter lesions, by gait disturbances and falls, or by the lack of optimal control of blood pressure.

The relatively low efficacy of available drugs to improve cognition in patients with VaD emphasizes the crucial importance of prevention of vascular disorders which may lead to the development of dementia. The prevention of VaD is thus that of stroke which is based on risk factor manipulation for both ischemic and hemorrhagic stroke and on antithrombotic drugs for ischemic stroke.

Risk Factor Manipulation

The crucial role of hypertension in the development of dementia was confirmed by recent trials of antihypertensive drugs showing a reduction in the incidence of dementia by blood pressure lowering. The results of the Syst-Eur trial support the hypothesis that the treatment of 1,000 hypertensive patients aged >60 years for 5 years would prevent the occurrence of dementia in 19 cases [65]. In the PROGRESS trial, a secondary stroke prevention study [66] designed in hypertensive and nonhypertensive patients with a history of stroke or transient ischemic attack, a flexible regimen based on the angiotensin-converting enzyme inhibitor perindopril with the addition of the diuretic indapamide, was associated with a 34% risk reduction of dementia after 3.9 years. This effect was observed in association with the decreased risk of stroke under treatment and it was not significant in the absence of stroke recurrence [67]. Such results emphasized that the protective effect of antihypertensive drugs on cognition is probably related to the decreased frequency of cerebral insults.

Antithrombotic Drugs

In the presence of an identified vascular disorder, the use of antiplatelet drugs appears as the cornerstone of secondary stroke prevention [68]. The efficacy of antiplatelet drugs is largely demonstrated. The overview of 145 randomized trials of aspirin versus placebo clearly showed that the risk of vascular events is significantly reduced by aspirin in patients with acute or past myocardial infarction, angina, vascular surgery, angioplasty, atrial fibrillation, peripheral vascular diseases and in patients with a history of stroke or transient ischemic attacks with doses ranging from 75 mg to 1 g [69]. In stroke patients, the reduction risk of cerebral ischemic events with aspirin is between 20 and 30% [69]. After the occurrence of transient ischemic attack or stroke, the Ticlopidine-Aspirin Stroke Study showed that ticlopidine was slightly more effective than aspirin to prevent stroke with a cumulative event rate at 1 year for nonfatal stroke or death at 6.3% for patients under treatment and 10.8% for patients receiving aspirin [70]. However, ticlopidine has been shown to cause neutropenia in 2.4% treated persons. In the European Stroke Prevention Study, the combination of acetysalicylic acid and dipyridamole was found to reduce the risk of stroke or death by 24% in patients with prior stroke or transient ischemic attack [71].

Clopidogrel, a thienopyridine derivative similar to ticlopidine but with a superior effect in animals on adenosine-diphosphate-induced platelet aggregation [72], has been compared to aspirin in the CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events) trial. It was the largest prospective evaluation of antiplatelet agents and the first study to include patients with the three main clinical manifestations of atherothrombosis (recent ischemic stroke, recent myocardial infarction or symptomatic peripheral arterial disease). The intention-to-treat analysis showed that the relative risk reduction was 8.7% in favor of clopidogrel from an overall annual event rate of ischemic stroke, myocardial infarction or vascular death, ranging from 8.3% in the aspirin group to 5.3% in the clopidogrel group. Most importantly, the safety was comparable to that of aspirin without any increased risk of neutropenia. The results of the CAPRIE study suggest an overall relative risk reduction for stroke of 7.3% in favor of clopidogrel. Of interest, 59% of qualifying strokes were atherothrombotic and 40% lacunar. Furthermore, in patients included after the occurrence of a myocardial infarction, 20% of first outcome events were strokes; in those who had a symptomatic peripheral arterial disease, this frequency was close to 50%. These results suggest that clopidogrel is actually effective to reduce the risk of stroke not only in patients with a history of transient ischemic attack or ischemic stroke, but also in patients with a recent history of myocardial infarction or with symptomatic peripheral arterial disease. As the reduction of stroke plays a key role to decrease the risk of dementia (both VaD and mixed dementia), it can be inferred that antiplatelet drugs probably reduce the risk of cognitive de-
cline. Future trials including the occurrence of dementia or cognitive decline as a primary or secondary end point are, however, necessary to confirm this hypothesis. Such data will be particularly useful in elderly patients for whom the benefit/risk ratio of preventive strategies is regularly questioned.

Results from the Rotterdam study suggest that aspirin use in the elderly may increase the risk of stroke [73], possibly by increasing the risk of cerebral hemorrhage. Consequently, antiplatelet drugs cannot be recommended in the absence of an identified vascular disease to reduce the risk of VaD.

In prevention of stroke, cardiac arrhythmia due to atrial fibrillation and the existence of mechanical prosthetic valves are the only two indications of anticoagulants that have been demonstrated. The negative results of the Warfarin-Aspirin Recurrent Stroke Study trial support the concept that antiplatelet therapy is the preferred option for preventing recurrent ischemic stroke related to atherosclerosis [74].

Conclusion

VaD is a major health issue, firstly because it is the second leading cause of dementia either by itself or in association with AD, secondly because its prevalence is rising with the aging of the population, thirdly because of the lack of effective treatment once dementia is established. There are different varieties of VaD which are closely linked to the numerous etiopathogenic varieties of ischemic and hemorrhagic stroke.

Given the burden of VaD, its prevention is a crucial health priority. It is based on stroke prevention which implies risk factor manipulation and use of antithrombotic drugs among which the most widely used are antiplatelet drugs. Given the well-established efficacy of antiplatelet drugs, large use of these molecules and good tolerance in stroke prevention, it is likely that they may decrease the risk of VaD. Prospective studies are needed to investigate this potential in future therapeutic trials.

Finally, cognitive impairment and dementia should be considered now as major end points in studies devoted to stroke prevention. In future, the recognition of any vascular cognitive impairment and use of neuroimaging markers in the populations at risk will also be crucial to prevent VaD. In the elderly, a large spectrum of cognitive disturbances appear related to vascular cerebral lesions long before the occurrence of dementia. These lesions are easily detected on MRI. They can be observed even in the absence of stroke, coronary heart disease or peripheral arterial disease. In the general population, white matter lesions and/or ‘silent’ infarcts have been shown to increase both the risk of stroke and dementia [8, 75, 76]. The benefit of antiplatelet drugs based on these new clinical and MRI markers of vascular disorders remains to be investigated in future large trials.

References


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