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Vascular dementia

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Abstract

The epidemic grow of dementia causes great concern for the society. It is customary to consider Alzheimer's disease (AD) as the most common cause of dementia, followed by vascular dementia (VaD). This dichotomous view of a neurodegenerative disease as opposed to brain damage caused by extrinsic factors led to separate lines of research in these two entities. Indeed, accumulated data suggest that the two disorders have additive effects and probably interact; however it is still unknown to what degree. Furthermore, epidemiological studies have shown "vascular" risk factors to be associated with AD. Therefore, a clear distinction between AD and VaD cannot be made in most cases, and is furthermore unhelpful. In the absence of efficacious treatment for the neurodegenerative process, special attention must be given to vascular component, even in patients with presumed mixed pathology. Symptomatic treatment of VaD and AD are similar, although the former is less effective. For prevention of dementia it is important to treat aggressively all factors, even in stroke survivors who do not show evidence of cognitive decline. In this review, we will give a clinical and pathological picture of the processes leading to VaD and discuss its interaction with AD.

Keywords

vascular; dementia; stroke; diagnosis; neuropathology; bio markers; cognitive impairment

Introduction

The dramatic increase in the proportion of elderly people worldwide has brought attention to ageing-related impairments. Dementia has a prominent presence among the chronic diseases in the elderly [1], and has emerged as a major health problem worldwide [2–3], with great impact on families and national economies [4–5]. Due to the continuous population aging, this problem is expected to grow dramatically in the future. Therefore understanding dementia pathogenesis, and development of preventative and curative treatments are top priorities.

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Dementia is a syndrome, encompassing a large number of distinctive brain disorders. Although memory dysfunction is the basis of most formal definitions of dementia, cognitive impairment can be devastating even when memory is relatively preserved, such as when speech and executive functions are affected.

Damage to the central nervous system, from whatever cause, can lead to cognitive impairment. However an important issue is of specificity. The clinical phenotype resulting from brain insults is the result of a combination of factors, including the site and size of the lesions, amount and location of neuronal loss, as well as the particulars of the brain in which this lesion occurred. For many years, Alzheimer's disease (AD) was considered to be the most common form of dementia, followed by vascular dementia (VaD). Recently however, this concept has been challenged by the recognition that vascular-associated cognitive decline was found to be more common than previously thought either in isolation or associated with a neurodegenerative condition [6–7]. Vascular changes typically occur in elderly people, whose brains may be affected by age-related degenerative changes and additional diseases. Thus in many cases, the pathogenesis of the dementia is complex, with vascular lesions interacting with primary neurodegenerative processes [8–10].

Due to the fact that the brain is already considerably damaged by the time full-blown dementia is detected, attempts to capture patients with minimal cognitive impairment, have led to the introduction of a broader terms, including mild cognitive impairment.

In this review we shall use VaD as an umbrella term, describing dementia resulting from arterial brain lesions (Venous thrombosis may also cause cognitive impairment, but this topic will not be detailed here). It became evident that VaD is heterogeneous in terms of pathogenesis, pathology, and clinical phenotype.

History

Early views in the beginning of the twentieth century considered senile dementia to result from cerebral arteriosclerosis [11]. Alois Alzheimer's description of microscopic dementia caused by neuritic plaques and neurofibrillary changes as oppose to the vascular changes created the concept that although cerebral arteriosclerosis was associated with dementia in older subjects, in younger ones, plaques and tangles were the culprit. This concept prevailed for several decades until it was challenged by pathological findings showing plaques and neurofibrillary deposits in the brains of most demented elderly individuals, regardless of age.

Therefore, dementia of vascular origin was progressively dismissed in dementia differential diagnosis, and only started to come back in focus after the careful analysis by Tomlinson et al. in the 1960's [12]. These investigators concluded that a stroke of considerable volume (>100 ml) was accompanied by a great risk of dementia development. In the 1970's, Hachinski et al went further and coined the term multi-infarct dementia (MID) implying that a cumulative result of multiple strokes, not necessarily symptomatic or occurring at the same time, could cause dementia [13]. This major advance was soon supported by neuroimaging, especially after the introduction of computed tomography (CT) and magnetic resonance imaging (MRI). Modern neuroimaging subsequently helped to introduced non-infarct vascular changes, such as white matter lesions (WML), small subcortical lacunes and microbleeds, as contributors to cognitive decline [14].

Epidemiology and risk factors

While it is universally accepted that the prevalence of dementia is increasing, reflecting the population aging, exact figures may not be reliable, particularly in developing countries [3].

Data on the epidemiology of VaD are probably even less reliable, since different studies looked at VaD using various methods and particularly, different diagnostic criteria in several geographic areas and ethnic groups. The different clinical sets of criteria used are not interchangeable and lead to significantly discrepant results [15]. It is believed that in general, epidemiological studies are likely to underestimate the number of VaD cases because of restrictive clinical criteria [16–17]. Over the years, imaging has been added as an important contributing diagnosis tool, but imaging is expensive and not readily available, limiting the population which could be studied. In addition, imaging, whenever used, usually did not consider white matter lesions (WMLs) as an indicator of vascular contribution.

Few epidemiological studies on VaD meet criteria for real population-based studies [18]. Data from memory clinics may underestimate VaD because of referral bias, since patients with vascular brain disease are more likely to be followed-up in stroke units. The lack of criteria differentiating VaD from mixed dementia resulted in mixed cases being variably included in epidemiological studies [15]. Finally few data are available for different subtypes of VaD [19].

Nevertheless, it is clear that VaD prevalence, as of dementia in general, increases steeply with age at least until age 90, after which data are unclear [20–21]. Apparently higher prevalence of VaD (as compared to AD) occurs in east-Asia [22], although this difference may have diminished lately [23], and men are affected more frequently than women [19]. The mortality of VaD patients exceeds that of AD patients, probably because of the added coronary morbidity [2].

There are almost no data on secular trends of VaD. However, considering that stroke incidence seems to have dropped, VaD incidence may have decreased [20]. In the same line, the widespread decrease in smoking and common use of antihypertensive and antidyslipidaemic drugs may have contributed to a decrease in VaD prevalence. On the other hand, the increased prevalence of obesity may all affect future VaD prevalence and incidence rates [24].

Atherosclerotic disease in general is, as expected, a risk factor for stroke and for VaD (Table 1). The realization that AD and VaD share several risk factors, one of the most important discoveries in the past two decades regarding dementia [25–26]. This overlap may indicate that brain ischemia is an important factor contributing to AD pathogenesis. Indeed, most cases of dementia in the elderly actually do not result from a single pathogenic mechanism but represent mixed dementia [8, 27–28]. In addition, abdominal obesity, insulin resistance, hypertension and dyslipidemia, components of the metabolic syndrome, are well known risk factors for vascular diseases in general and therefore presumably for VaD [29–32]. It appears that midlife, rather than late life exposure significantly increases the risks [33].

Microbleeds are now easily identified in the MRI and seen more frequently among people with dementia [34–35]. It is yet unknown whether microbleeds are risk indicators for dementia or whether the hemorrhages are causally related to cognitive decline. Depression is observed frequently among people with vascular disease [36], and is commonly seen following strokes [37]. Depression may be a significant risk factor for future development of dementia [38], but the relationship of depression to vascular disease on the one hand and to dementia on the other is complex [39].

Genetic factors for stroke and VaD have not been studied widely [40]. Apolipoprotein E ϵ 4 (APOE4) is a known risk factor for atherosclerotic disease in general [40] as well as for AD [41]. Surprisingly, it has a negligible effect on stroke [42] and on VaD [43–44]. However, APOE4 may increase the risk for cognitive decline after stroke [45]. Rare monogenic vascular diseases can all result in stroke as well as in VaD (Table 2).

Clinical phenotypes

Vascular related brain lesions are heterogeneous, leading to a variety of cognitive deficits. Likewise in other brain conditions, clinical manifestation is a product of the brain region involved by the pathological process. Thus, cortical lesions can cause aphasia, apraxia, and epileptic seizures, while subcortical lesions, including WMLs, are associated with bradyphrenia, executive dysfunctions, gait abnormalities, urinary incontinence and parkinsonism [46–47]. Recently, the term vascular cognitive impairment (VCI) was coined, to denote the spectrum of cognitive changes resulting from, or contributed to vascular lesions of the brain [11, 48]. This term expands the previously used term VaD, incorporating also more minor deficits, such as vascular MCI. MCI was first introduced to state a transitional stage between normal cognition aging and AD [49]. It is unfortunately not easy to predict the outcome of a individual MCI patient. The risk of progression of vascular MCI to dementia was estimated at 50% over five years [50].

Clinical diagnosis

The diagnosis of VaD is rarely straightforward. The clinical severity is variable ranging from mild cognitive impairment (MCI) through severe dysfunction. Clinical evolution is frequently unpredictable, with acute or insidious onset, possible improvement, stabilization or subsequent decline, either step-wise or slow deterioration. In addition, the neuropsychological profile of VaD is also variable. All these factors complicate the clinical definition of cognitive impairment related to vascular-related brain lesions.

Several clinical criteria of VaD have been proposed and used extensively (NINDS-AIREN, ICD 10, ADDTC, DSM IV, Mayo clinic) [51–55]. These definitions focus on dementia, and thus exclude cases with milder cognitive impairment. All of them have been composed by experts, yet validation was incomplete, partly due to lack of autopsy verification, but also because it is not clear what should be the gold standard.

The Hachinski ischemic scale (HIS) developed on the basis of the MID concept [56], has been borrowed to be used in other VaD entities in which it may be even less useful than in MID. The score is an arbitrary one, with equal weight given to individual items, and without attention to possible redundancy [57].

Although neuropathological assessment is frequently assumed to be the gold standard for diagnosis, no consensus criteria are available for the pathological definition of VaD [6]. Brain imaging is very sensitive in demonstrating vascular changes of the brain, but is unable to differentiate on an individual level, between people with and without cognitive impairment.

In summary, the occurrence of co-morbid changes in the brain, the availability of multiple diagnostic criteria, and reliance on several imaging methods, (and different criteria of abnormalities), impose imprecise diagnosis [58].

Natural history

Several studies have confirmed reduced survival of VaD patients, due to concomitant vascular disease (myocardial infarctions and recurrent strokes) [59–60]. On the other hand, the cognitive deterioration may be slower in VaD than in AD [61]. This slower progression is also seen in placebo arms of drug studies in VaD patients [62–64], although the measures used may not be equally sensitive to measure decrease in VaD and in AD. VaD natural history is type-specific and depends on brain preconditions. For instance, the occurrence of an ischemic stroke increases the risk of developing dementia significantly [65–66]. Pre-

stroke cognitive impairment increases this risk of a more severe cognitive impairment immediately after the stroke [66]. Whether the existence of vascular risk factors and metabolic stress increase the risk of poor cognitive outcome after stroke is still debated [66–67]. Cognitive impairment is determined partly by the occurrence of recurrent strokes [65–66, 68–69], but other factors, possibly related to accelerated AD-like processes, may also be involved [70]

Corroborating the latter, medial temporal lobe atrophy, suggestive of preclinical AD is associated with a poorer outcome [71]. Epileptic seizures after stroke were also associated with increased risk of dementia [72].

Neuropsychological profile

The first cortical neuropathological changes in AD occur in the medial temporal lobes, and this correlates nicely with the memory impairment in early AD. Interestingly, medial temporal atrophy also occurs in VaD [71]. Nevertheless, the neuropsychological profile of VCI is heterogeneous (Table 3). The so-called typical expression of VaD is executive dysfunction, manifested as impaired attention, planning, difficulties in complex activities, and disorganized thought, behaviour, or emotion [73–74]. However, this applies mainly to patients with subcortical white matter disease and patients with frontal lobe lesions. As mentioned above, changes following cortical strokes depend on their location. Slower reactions are the expected result of lesions in the frontal lobes or subcortical damage affecting the cortico-basal ganglionic-thalamic circuits. Unfortunately, reaction time is not measured routinely in cognitive testing of dementing individuals. Attempts to compare the neuropsychological profile of VaD and AD showed some differences, which were, however, not consistent from one study to another [75].

The widespread bedside instrument used to evaluate cognitive dysfunction, the mini-mental state examination (MMSE) [76] is frequently employed in the evaluation of VaD. However it contains few items related to executive functions and thus, may underestimate the cognitive decline. The Montreal Cognitive Assessment (MoCA) may be better suited for this purpose [77]. These tests are both aimed to evaluate the severity of cognitive impairment, rather than to diagnose dementia, and they are more sensitive to left hemisphere than to right hemisphere dysfunction. Importantly, a given score on each of these tests may have a different significance in AD than in VaD patients. The clock-drawing test [78] and the trail making test [79] are both short bedside tests, useful in measurement of executive function. However, no neuropsychological test has been proven to reliably differentiate VCI from other dementia syndromes, and particularly none can distinguish mixed dementia from either VaD or pure AD. The distinction between VCI and FTD or DLB is not assisted by neuropsychological testing, since executive functions are impaired at an early stage in FTD and DLB as well.

Differential diagnosis

In many cases, dementia is clearly of vascular origin. This is particularly the case in younger individuals, where there is an abrupt cognitive decline associated with focal signs such as hemiparesis. Since mental changes are something recovered after a vascular brain injury, the term dementia should be used only when proved that the condition is permanent. The NINDS-AIREN [53] acknowledges cognitive deterioration up to three months after a stroke as consistent with VaD.

As mentioned before, cognitive deterioration can develop belatedly over months following an acute stroke [80–81]. In many patients the decline occurs without new ischemic lesions,

possibly due to enhanced deposition of A β in the brain following the stroke [70, 82–83], clouding the border between VaD and AD [84].

White matter changes are very frequent in the elderly, including in AD patients [85], may be manifested as depression [86], gait impairment or parkinsonism [47], or cognitive decline, although many elderly patients with WML are symptom-free. In cases of WMLs, the cognitive decline is usually insidious and may mimic the clinical deterioration in AD. Subcortical VaD patients may have slow mentation, as opposed to the memory decline which is typical for AD. However, slow mentation can also occur in AD patients who have leukoaraiosis.

Another important distinction is between VaD from DLB and FTD. Fluctuating alertness is frequent in both DLB and vascular brain disease. Parkinsonian signs, slowness, and particularly gait impairment, may be of vascular, rather than neurodegenerative origin [87]. Although language problems or behavioral changes characterize FTD they usually progress insidiously, as oppose to the abrupt deficits seen after a strokes. In this cases, brain imaging can help to discriminate vascular from neurodegenerative changes.

A formal division of dementia cases using the dichotomy, vascular versus neurodegenerative may be inappropriate. While logical and conceptually valid, most elderly subjects have multiple brain pathologies. In an excellent series of autopsy cases studied by Schneider et al. [28, 88], most brains with pure AD pathology belonged to people who had not been demented, and the number of demented people who had pure AD changes were considerably fewer than those who had both AD and vascular brain pathology. An analogous picture emerged when vascular changes were looked at: most people with pure vascular brain pathology at death had not been demented, while dementia was much more common in people with dual pathology (AD and vascular) than vascular alone. Mixed dementia may even be more common than these results suggest since the investigators disregarded WMLs in the criteria for VaD [88].

Neuropathology

To date there are no accepted neuropathological criteria for diagnosing VaD or VCI, as agreed for AD, DLB or FTD. Vascular lesions are rather classified based on their morphological characteristics than by their pathogenesis. A drastic change in the way these changes are defined is critical for the creation of a new set of pathological diagnostic criteria [6].

Multiple vessel disorders occur in the aging human brain, frequently in combination and with other non-vascular changes. These vessel disorders can induce various types of cerebral tissue lesions like haemorrhage, infarction, hippocampal sclerosis, and white matter lesions [89], any of which can result in cognitive decline. Vascular changes are found frequently in brains of cognitively normal elderly [28], making it difficult to establish a causal relationship between brain lesions and cognitive decline. Therefore, a pathological diagnosis of VaD is very frequently granted when non-vascular findings are ruled out. Classifications currently in use distinguish disorders of large-sized vessels from those of small brain vessels, and also lesions due to impaired perfusion (Figure 1).

Vascular associated lesions commonly associated with cognitive decline (Figure 2)

Large- and medium-sized vessel disorders—*Atherosclerosis* is a degenerative vessel disorder that affects large- to medium-sized arteries. The vessels of the circle of Willis are most frequently affected and the occurrence of those changes increases as a function of age and risk factors such as hypertension and dyslipidemia. Evidence shows a significant

coexistence of atherosclerosis of the circle of Willis and dementia, but it is unclear if a relationship exist or if it is a coincidental finding [90]. Atherosclerotic plaques are prone to rupture and the resulting thrombus can lead to vessel occlusion or it can obstruct smaller arteries.

Small sized vessel disorders—The term *small vessel disease (SVD)* describes a distinct group of small vessel changes also known as: small vessel arteriosclerosis, atherosclerosis, arteriolosclerosis, arteriohyalinosis, and lipohyalinosis [89, 91–92]. White matter arteries often show loss of smooth muscle cells, fibrosis, and thickening of the basement membrane, and enlarged perivascular spaces, with leakage of plasma proteins [93]. These changes can lead to vessel occlusion, microaneurysms, and fibrinoid necrosis of the vessel wall. SVD is an important cause of white matter destruction, but WMLs may have other origins, such as inflammatory processes [94–95] and Wallerian degeneration [96].

Sporadic *cerebral amyloid angiopathy (CAA)* is characterized by amyloid- β protein (A β) deposition in cerebral and leptomeningeal arteries, veins and capillaries. CAA is strongly associated with the development of AD-related pathology in the brain, and therefore, it will not be further discussed in this review.

Infarcts—*Large infarcts*, exceeding 10 mm in diameter, are most frequently ischemic as consequence of artery occlusion. Approximately 10% of all brain infarcts are located between the territories of two major arteries, and are called *watershed or borderzone infarct*.

Single large strokes or strokes at strategic locations are the most clinically obvious and easy to diagnose. Indeed, acute hemispheric strokes, whether cortical or thalamic, ischemic or hemorrhagic, result in cognitive deterioration in a significant proportion of patients [60]. A recent meta-analysis showed that 10% of patients had dementia before their first stroke while another 10% developed it soon after the first stroke, and more than a third developed dementia after recurrent strokes [59]. The cognitive decline may appear insidiously within several months after the stroke [60] [59, 97–98]. The term Multi-infarct dementia (MID) describes the cumulative effect of multiple strokes [13]. This implies that small, even clinically unrecognized lesions can culminate in cognitive decline, although large strokes are important contributors.

Lacunar infarcts are cavitating anemic infarcts, measuring up to 10 mm in diameter, visible radiologically and upon gross examination. They are largely confined to the cerebral white matter and subcortical structures. Subcortical nuclei are most vulnerable given they are irrigated by end arteries, which are almost devoid of anastomoses. Lacunar infarcts are associated to hypertension [89] and were shown to be associated with cognitive decline [46, 99]. Although special terms are used to denote a large number of lacunes in the same region, such as *état lacunaire* or *status lacunaris* (when seen in the gray matter) and *état crible* or *status cribrosus* (when seen in the white matter), these terms are merely descriptive terms and do not reflect the pathogenesis [100].

In contrast to gross infarction and lacunar infarcts, *microinfarcts* not visible on gross or in imaging examinations. They are most commonly seen in the watershed areas of cortex and apparently do contribute to cognitive decline [101]

Cortical laminar necrosis or pseudolaminar necrosis is characterized by neuronal loss and gliosis in the neocortex caused by global hypotension or hypoxaemia [102]. It appears more commonly at arterial borderzones and is often associated with WML.

Hippocampal sclerosis (HS) is a pathological term used to describe severe loss of neurons and reactive gliosis without pseudocystic cavitation in the CA1 sector of the hippocampus and the subiculum. It is commonly seen after global hypoxemia because the pyramidal neurons of CA1 sector are particularly vulnerable to ischemia. However, HS is also seen in epilepsy, frontotemporal lobar degeneration [103], and even in normal people [104].

White matter lesions are found in up to 65% of subjects over 65 years of age, and their frequency increases in patients with cerebrovascular disease or with cardiovascular risk. WMLs have been recognized since the work of Binswanger, as causing dementia [105]. It is of course not surprising that extensive destruction of the connectivity between neurons will result in cognitive impairment. WMLs usually comprise, in variable degrees, demyelination, axonal loss, mild reactive astrocytosis, oedema, macrophage reaction, and microangiopathy of the penetrating arteries [95]. As a rule, the subcortical U-fibers are spared. The underlying pathology of WML includes a wide range of lesions, including microangiopathy, venous collagenosis [106], global chronic ischemia [95] and Wallerian degeneration [96].

Microbleed is the term used to describe blood extravasation into perivascular or Virchow-Robin spaces, or small intracerebral haemorrhages, less than 10 mm in diameter. Their prevalence increases with age. Usually, microbleeds are associated with CAA and hypertension. Their exact pathogenesis and cognitive effects remain to be clarified, as these may be surrogate for microvascular disease. [35, 107].

Biomarkers

Since its inception, brain imaging methods particularly CT and MRI, is being used as important tool for supporting the diagnosis of VaD [108]. Imaging changes frequently seen in patients diagnosed with VaD include infarcts of variable size, white matter changes, hippocampal sclerosis, and hemosiderin deposits indicative of hemorrhages. However, caution must be exercised in the interpretation of vascular related brain lesions found in imaging, since lacunes and WMLs are commonly seen in non-demented elderly individuals. Moreover, imaging lack specificity of other causes of dementia, such as AD, and thus relying on imaging alone will result in excessive diagnosis of VaD, and underestimation of mixed dementia cases [8, 109]. Lately, the advent of amyloid imaging is helping to identify mixed dementia cases, although this is expensive and not widely available. Cerebrospinal fluid changes on A β , tau and phosphorylated tau levels indicate AD in a group level [110]. On the other hand, to date, no reliable CSF biomarkers for VaD exist.

Therapy

Primary prevention

Prevention of VaD, will, in principle, depend on prevention of strokes through risk factor modification. Positive results have so far been demonstrated with the calcium channel blocker nitrendipine [111], ACE inhibitors, and diuretics [112]. It is still unclear whether all antihypertensive drugs have the same effect. Angiotensin II receptor blockers may be particularly effective because of their direct effects on the brain [113]. Because of the proven efficacy of antihypertensive drugs against cardiovascular diseases, placebo-controlled trials with these drugs are unethical. Any differences between drugs could be shown only by head-to-head comparisons.

Blood hypertension is considered to be an important cardiovascular risk. However, As opposed of previously believed, lowering blood pressure in older people may have a deleterious effect on the cognition, by causing ischemic damage to these brains, usually affected by impaired cerebral autoregulation [114–115].

On the other hand, epidemiological data suggest a benefit in controlling vascular risk factors, including hypertension in midlife [116]. Yet, if protective actions need to extend for several decades, it may be impossible to prove its efficacy.

Secondary prevention

In the event of cognitive decline following a stroke, aggressive protective measures against further strokes should be initiated. Indeed, such protective measures may also benefit AD patients [117–118].

Symptomatic therapy

No drug has so far been approved for the treatment of VaD. However, all approved anti-AD drugs have been investigated in VaD, including the cholinesterase inhibitors (ChEI's) [63–64, 119–120], and memantine [62]. While all were found to be useful in some (but not all) measures, the effect size was rather small and marked heterogeneity among studies was observed [120–121]. Actually, the observed benefit could result from an effect on co-existing AD [120], although it is recognized that vascular lesions involved the cholinergic pathways from the nucleus basalis of Meynert or the nucleus itself [121]. Donepezil has been tested in CADASIL [117], a rare genetic disorder causing VaD, with no benefits. In clinical practice, ChEI and memantine are usually given empirically to VaD patients and continued when symptomatic improvement is observed.

Several other studies reported beneficial effects of cerebrolysin [122], citicoline [123] and ginkgo biloba [124], but these results need confirmation. Other drugs such as anxiolytics, antidepressant drugs, sleeping pills, anticonvulsants can be prescribed to modulate for non-cognitive manifestations. Special care needs to be employed when using neuroleptic drugs because of their unfavourable effect on cardiovascular disease [125–126]. Non-medicamental therapies have been suggested for improving VaD symptoms and recurrence of vascular lesions, including social interaction and intellectual stimulation, treatment of aphasia and emotional changes, and acupuncture (Table 4).

Conclusions

Vascular brain disease can take several forms, most commonly associated with stroke. However, multiple vascular disorders occur in the aging human brain, which may induce various types of cerebral tissue lesions like hemorrhage, infarction, hippocampal sclerosis, and white matter lesions. Any of these changes can result in cognitive decline and dementia is also. Recent studies suggest that parkinsonism and depression can also present a presumably vascular etiology. Pure VaD appears to be rare, but strong evidence point that vascular changes do worsen the cognition and even other brain functions when associated with other neurodegenerative changes. Considering that among the common etiologies of dementia, vascular changes are the only ones which can at present be prevented, special attention to vascular risk factors must be employed in patients with either dementia or incipient cognitive decline.

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Figure 1.
Major pathological findings underlying vascular dementia

Figure 2.

Some of the major pathological changes underlying vascular dementia.

A) Ischemic infarct. Note the wedge-shape border of the infarct (arrows). Both white and gray matter are involved. Nissl staining.

B) Lacunar infarct characterized by an irregular cavity and a central blood vessel surrounded by a rim of gliotic, rarefied brain tissue (arrow). Hematoxylin and Eosin stain (H&E).

C) Histopathological counterpart of a white matter lesion detected by MRI in a 62 years-old male. Note the regions of myelin pallor (**) and an enlarged perivascular space (arrow). Kluever-Barrera stain.

D) Cerebral amyloid angiopathy (CAA). The A β -deposition in the wall of a cortical artery is colored in brown (arrow). In this case, there is a microbleed around this artery (note the anuclear red blood cells). Immunostain with an antibody against Ab17-24 (4G8; Covance).
E) Small vessel disease. Two white matter arteries exhibit fibrosis and hyalinization of wall (arrows). These lesions are also referred to as arteriolosclerosis, arteriohyalinosis or lipohyalinosis (arrow). H&E.

The calibration bars correspond to: 100 μ m.

Table 1

Risk factors for dementia

Risk factors for both VaD and AD	Risk factors for AD
Age	Female gender
Coronary artery disease	
Midlife hypercholesterolaemia	Apolipoprotein E status
High dietary saturated fat and cholesterol	Head trauma
Hyperhomocysteinaemia	
Midlife diabetes mellitus	
Midlife hypertension	
Obesity	
Metabolic syndrome	
Arteriosclerosis	
Smoking	
Poor education	

Table 2

Genetic causes of VaD

Disease	Affected protein	Gene	Chromosome	Genetic transmission	Comments
CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy)	Transmembrane receptor Vascular smooth muscle cell	NOTCH 3	19q12	Dominant	Non-hypertensive young and middle-aged adults affected
CARASIL (cerebral autosomal-recessive arteriopathy with subcortical infarcts and leukoencephalopathy, Maeda syndrome)	HtrA serine protease 1	HTRA1	10q	Recessive	May be late onset. Accompanied by alopecia and disco-vertebral degeneration. In Japanese and Chinese populations
Cerebral amyloid angiopathies Hereditary cerebral hemorrhage with amyloidosis Dutch type (HCHWA-D) Arctic variant Iowa variant HCHWA-I (Icelandic type)	E693G of APP D694N of APP Cystatin C BR12 gene	APP gene	21 21 21 20 Familia British dementi (FBD) Familia Danish dementi 13	Dominant 12 12 12 12	Codon 693 mutation Alzheimer's disease like dementia, cortical calcifications, leukoencephalopathy
HERNS (hereditary endotheliopathy, retinopathy, nephropathy, and stroke)	3'-5' exonuclease	TREX1 suspected	3p21	Dominant	One of retinal vasculopathy and cerebral leukodystrophies, encompassing three conditions with a common etiology-Cerebroretinal Vasculopathy, Hereditary Vascular Retinopathy and HERNS, all mapped to chr 3p21
Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu)	Type 1 - ENG (endoglin) Type 2 - ALK-1 (actin-like kinase receptor 1) Type 3 - SMAD4	ACVRL1 ALK-1 SMAD4	9 12 5	Dominant	Affected proteins modulate transforming growth factor (TGF)- β signalling in vascular endothelial cells and lead to the development of fragile telangiectatic vessels and arteriovenous malformations. Cerebral occurrence in 10% stroke may be ischemic or hemorrhagic
Hyperhomocysteinaemia	Methyltetrahydro-folate reductase (MTHFR)	MTHFR	1p	Recessive	Simply modified by folate supplement C677T genotype
Fabry Disease	α -galactosidase A	GLA	X	X-linked	Lysosomal storage disease. Accumulation of globotriaosylceramide Gb3. Enzyme replacement therapy exists
MELAS (mitochondrial encephalopathy with lactic acidosis and seizures)	A-to-G transition mutation	at position 3243 (most common), or 3271	mitochondrial genome	Maternal inheritance	Multiple systems affected. May be overlapping with other mitochondrial diseases

Disease	Affected protein	Gene	Chromosome	Genetic trasmission	Comments
Moya-moya		Different loci	Linked to several chromosomes 3,6,8,12,17	Different transmission modes	Asian population susceptibility
Sickle-cell disease	foetal haemoglobin	substitution of glutamic acid by lysine at codon 26 of the β -globin gene	6q	Recessive	Common mutation

AD – autosomal dominant, AR – autosomal recessive

Table 3

Neuropsychological findings of vascular lesion

Neuropsychological changes	Assessment tool	Brain lesion suspected location
“Patchy” cognitive profile: better oriented to time, better recall (compared to AD), poor working memory, graphomotor impairment	Mattis dementia rating scale, MMSE, MoCA	Cortical-subcortical or interhemispheric disconnection, frontal lobes, striatum diencephalon, basal forebrain, limbic paralimbic area
Slow motor and information processing	Word-list generation task, spelling backward, Rey complex figure test	White matter, particularly affecting basal-ganglionic-frontal connections
Visuospatial and graphomotor impairment	Clock drawing, Rey complex figure test	
Attention deficit	Digit symbol substitution test, 7 series, Trail making test B	
Executive dysfunction	Trail making, maze test, clock drawing, spelling backward	White matter, particularly affecting basal-ganglionic-frontal connections
Language difficulties	Wechsler Adult Intelligence Scale (similarities subtest), Boston naming test	Dominant hemisphere lesions
Abrupt behavioural changes		Thalamus, angular gyrus, caudate nucleus or inferior genu of internal capsule

Table 4

Targets of non-pharmacological interventions to modify vascular risk factors

Heart failure
Blood hyperviscosity
Polycythaemia
Carotid artery and intracranial arteries stenosis
Overweight
Physical inactivity
Smoking
Diet