Journal of the Neurological Sciences 322 (2012) 2–10

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Vascular dementia

Amos D. Korczyn [a], Veronika Vakhapova [b], Lea T. Grinberg [c,d,*]

[a] Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel
[b] Maccabi Health Foundation, Israel
[c] Department of Neurology, University of California San Francisco, 305 Parnassus Avenue, San Francisco, CA, 94143, USA
[d] Aging Brain Study Group, Department of Pathology, University of Sao Paulo Medical School, Brazil

ARTICLE INFO

Article history:
Received 7 March 2012
Received in revised form 19 March 2012
Accepted 20 March 2012
Available online 8 May 2012

Keywords:
Vascular
Dementia
Stroke
Diagnosis
Neuropathology
Biomarkers
Cognitive impairment

ABSTRACT

The epidemic growth 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 the vascular component, even in patients with presumed mixed pathology. Symptomatic treatment of VaD and AD is similar, although the former is less effective. For prevention of dementia it is important to treat all factors aggressively, 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.

1. 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 developing preventative and curative treatments are top priorities.

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 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.

2. 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

* Corresponding author at: Memory and Aging Center, Department of Neurology, University of California San Francisco, 350 Parnassus Avenue, San Francisco suite 905, CA, 94143, USA. Tel.: +1 415 3750418.
E-mail address: lea.grinberg@ucsf.edu (L.T. Grinberg).

0022-510X/$ – see front matter
doi:10.1016/j.jns.2012.03.027

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 1960s [12]. These investigators concluded that a stroke of considerable volume (>100 ml) was accompanied by a great risk of dementia development. In the 1970s, 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 case 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].

3. 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 a 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 is 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].

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	

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 ε4 (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).

4. 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].

5. 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

Table 2
Genetic causes of VaD.

Disease	Affected protein	Gene	Chromosome	Genetic trasmission	Comments
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)	Transmembrane receptor vascular smooth muscle cell	NOTCH3	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	E693G of APP D694N of APP cystatin C	APP gene	21	Dominant	Codon 693 mutation
Hereditary cerebral hemorrhage with amyloidosis Dutch type (HCHWA-D)	BRI2 gene		21		Alzheimer's disease like dementia, cortical calcifications, leukoencephalopathy
Arctic variant Iowa variant			21		
HCHWA-I (Icelandic type)			20	12	
			Familia British dementi (FBD) Familia Danish dementi	12	
			13		
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	9		
		ALK-1	12		
		SMAD4	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
Moya-moya		Different loci	Linked to several chromosomes 3, 6, 8, 12, and 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.

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 the reliance on several imaging methods, (and different criteria of abnormalities), impose imprecise diagnosis [58].

6. 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 increases 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].

7. 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 the 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.

8. 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 Aβ 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

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
Visuosaptial and graphomotor impairment	Clock drawing, Rey complex figure test	
Attention deficit	Digit symbol substitution test, 7 serias, 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

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 stroke. 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 was 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].

9. 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 (Fig. 1).

Vascular associated lesions commonly associated with cognitive decline (Fig. 2).

9.1. 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.

9.2. 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].

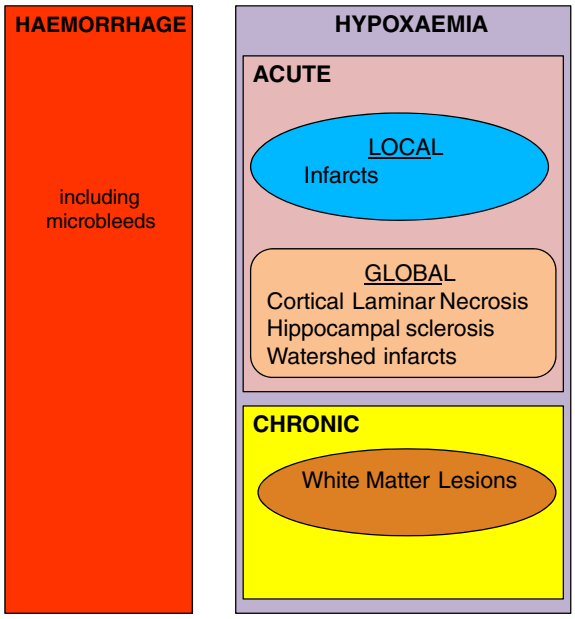

Fig. 1. Major pathological findings underlying vascular dementia.

Sporadic *cerebral amyloid angiopathy* (CAA) is characterized by amyloid-β protein (Aβ) 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.

9.3. Infarcts

Large infarcts, exceeding 10 mm in diameter, are most frequently ischemic as a 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 [59,60,97,98]. 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 are 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 *etat lacunaire* or *status lacunaris* (when seen in the gray matter) and *etat crible* or *status*

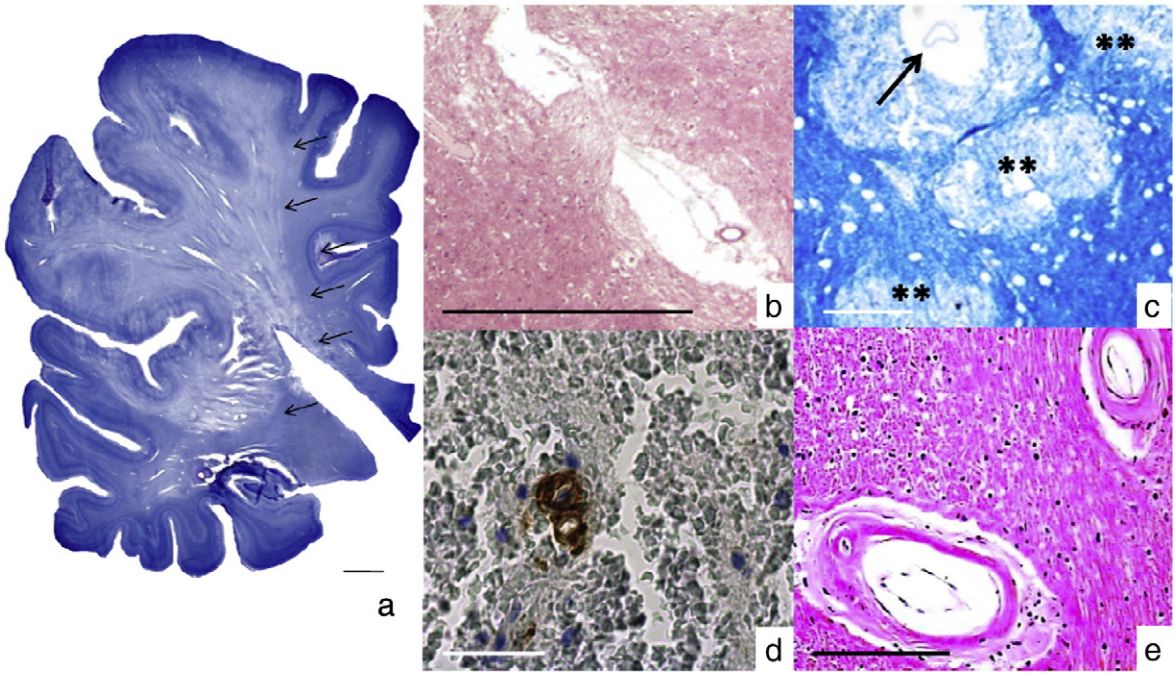

Fig. 2. Some of the major pathological changes underlying vascular dementia. a) Ischemic infarct. Note the wedge-shape border of the infarct (arrows). Both white and gray matter are involved. Nissl staining. b) Lacunar infarct characterized by an irregular cavity and a central blood vessel surrounded 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 Aβ-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 μm.

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].

10. Biomarkers

Since its inception, brain imaging methods particularly CT and MRI, are being used as important tools 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 Aβ, 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.

11. Therapy

11.1. Primary prevention

Prevention of VaD, will, in principle, depend on the 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.

11.2. Secondary prevention

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

11.3. 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 (ChEIs) [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).

12. 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 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.

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

References

[1] Sousa RM, Ferri CP, Acosta D, Albanese E, Guerra M, Huang Y, et al. Contribution of chronic diseases to disability in elderly people in countries with low and middle incomes: a 10/66 Dementia Research Group population-based survey. Lancet 2009;374:1821–30.
[2] Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol 2008;7:812–26.
[3] Llibre Rodriguez JJ, Ferri CP, Acosta D, Guerra M, Huang Y, Jacob KS, et al. Prevalence of dementia in Latin America, India, and China: a population-based cross-sectional survey. Lancet 2008;372:464–74.
[4] Wimo A, Winblad B, Jonsson L. The worldwide societal costs of dementia: estimates for 2009. Alzheimers Dement 2010;6:98–103.
[5] Brodaty H, Donkin M. Family caregivers of people with dementia. Dialogues Clin Neurosci 2009;11:217–28.
[6] Grinberg LT, Heinsen H. Toward a pathological definition of vascular dementia. J Neurol Sci 2010;299:136–8.
[7] Korczyn AD, Vakhapova V. The prevention of the dementia epidemic. J Neurol Sci 2007;257:2–4.
[8] Korczyn AD. Mixed dementia—the most common cause of dementia. Ann N Y Acad Sci 2002;977:129–34.
[9] Korczyn AD. The complex nosological concept of vascular dementia. J Neurol Sci 2002;203–204:3–6.
[10] Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. JAMA 2004;292:2901–8.
[11] Roman GC, Sachdev P, Royall DR, Bullock RA, Orgogozo JM, Lopez-Pousa S, et al. Vascular cognitive disorder: a new diagnostic category updating vascular cognitive impairment and vascular dementia. J Neurol Sci 2004;226:81–7.
[12] Tomlinson BE, Blessed G, Roth M. Observations on the brains of non-demented old people. J Neurol Sci 1968;7:331–56.
[13] Hachinski VC, Lassen NA, Marshall J. Multi-infarct dementia. A cause of mental deterioration in the elderly. Lancet 1974;2:207–10.
[14] Hachinski V. Vascular dementia: a radical redefinition. Dementia 1994;5:130–2.
[15] Chui HC, Mack W, Jackson JE, Mungas D, Reed BR, Tinklenberg J, et al. Clinical criteria for the diagnosis of vascular dementia—a multicenter study of comparability and interrater reliability. Arch Neurol 2000;57:191–6.
[16] Knopman DS, Parisi JE, Boeve BF, Cha RH, Apaydin H, Salviati A, et al. Vascular dementia in a population-based autopsy study. Arch Neurol 2003;60:569–75.
[17] Gold G, Giannakopoulos P, Montes-Paixao Junior C, Herrmann FR, Mulligan R, Michel JP, et al. Sensitivity and specificity of newly proposed clinical criteria for possible vascular dementia. Neurology 1997;49:690–4.
[18] Zaccai J, Ince P, Brayne C. Population-based neuropathological studies of dementia: design, methods and areas of investigation—a systematic review. BMC Neurol 2006;6:2.
[19] Leys D, Henon H, Mackowiak-Cordoliani MA, Pasquier F. Poststroke dementia. Lancet Neurol 2005;4:752–9.
[20] Leys D, Pasquier F, Parnetti L. Epidemiology of vascular dementia. Haemostasis 1998;28:134–50.
[21] Middleton LE, Grinberg LT, Miller B, Kawas C, Yaffe K. Neuropathologic features associated with Alzheimer disease diagnosis: age matters. Neurology 2011;77:1737–44.
[22] Ikeda M, Hokoishi K, Maki N, Nebu A, Tachibana N, Komori K, et al. Increased prevalence of vascular dementia in Japan: a community-based epidemiological study. Neurology 2001;57:839–44.
[23] Yamada M, Mimori Y, Kasagi F, Miyachi T, Ohshita T, Sudoh S, et al. Incidence of dementia, Alzheimer disease, and vascular dementia in a Japanese population: Radiation Effects Research Foundation adult health study. Neuroepidemiology 2008;30:152–60.
[24] Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:2672–713.
[25] Beeri MS, Ravona-Springer R, Silverman JM, Haroutunian V. The effects of cardiovascular risk factors on cognitive compromise. Dialogues Clin Neurosci 2009;11:201–12.
[26] Mielke MM, Rosenberg PB, Tschanz J, Cook L, Corcoran C, Hayden KM, et al. Vascular factors predict rate of progression in Alzheimer disease. Neurology 2007;69:1850–8.
[27] Strozyk D, Dickson DW, Lipton RB, Katz M, Derby CA, Lee S, et al. Contribution of vascular pathology to the clinical expression of dementia. Neurobiol Aging 2010;31:1710–20.
[28] Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69:2197–204.

[29] Hayden KM, Zandi PP, Lyketsos CG, Khachaturian AS, Bastian LA, Charoonruk G, et al. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. Alzheimer Dis Assoc Disord 2006;20:93–100.
[30] Raffaitin C, Gin H, Empana JP, Helmer C, Berr C, Tzourio C, et al. Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: the Three-City Study. Diabetes Care 2009;32:169–74.
[31] Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, Frisardi V, et al. Metabolic syndrome and the risk of vascular dementia: the Italian Longitudinal Study on Ageing. J Neurol Neurosurg Psychiatry 2010;81:433–40.
[32] Albers GW, Goldstein LB, Hess DC, Wechsler LR, Furie KL, Gorelick PB, et al. Stroke Treatment Academic Industry Roundtable (STAIR) recommendations for maximizing the use of intravenous thrombolytics and expanding treatment options with intra-arterial and neuroprotective therapies. Stroke 2011;42:2645–50.
[33] Xu W, Qiu C, Gatz M, Pedersen NL, Johansson B, Fratiglioni L. Mid- and late-life diabetes in relation to the risk of dementia: a population-based twin study. Diabetes 2009;58:71–7.
[34] Werring DJ, Frazer DW, Coward LJ, Losseff NA, Watt H, Cipolotti L, et al. Cognitive dysfunction in patients with cerebral microbleeds on T2*-weighted gradient-echo MRI. Brain 2004;127:2265–75.
[35] De Reuck J, Auger F, Cordonnier C, Deramecourt V, Durieux N, Pasquier F, et al. Comparison of 7.0-T T*-magnetic resonance imaging of cerebral bleeds in post-mortem brain sections of Alzheimer patients with their neuropathological correlates. Cerebrovasc Dis 2011;31:511–7.
[36] Kent LK, Shapiro PA. Depression and related psychological factors in heart disease. Harv Rev Psychiatry 2009;17:377–88.
[37] Kumar S, Selim MH, Caplan LR. Medical complications after stroke. Lancet Neurol 2010;9:105–18.
[38] Pohjasvaara T, Erkinjuntti T, Ylikoski R, Hietanen M, Vataja R, Kaste M. Clinical determinants of poststroke dementia. Stroke 1998;29:75–81.
[39] Korczyn AD, Halperin I. Depression and dementia. J Neurol Sci 2009;283:139–42.
[40] Leblanc GG, Meschia JF, Stuss DT, Hachinski V. Genetics of vascular cognitive impairment: the opportunity and the challenges. Stroke 2006;37:248–55.
[41] Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med 2002;137:149–55.
[42] Abboud S, Viiri LE, Lutjohann D, Goebeler S, Luoto T, Friedrichs S, et al. Associations of apolipoprotein E gene with ischemic stroke and intracranial atherosclerosis. Eur J Hum Genet 2008;16:955–60.
[43] Rowan E, Morris CM, Stephens S, Ballard C, Dickinson H, Rao H, et al. Impact of hypertension and apolipoprotein E4 on poststroke cognition in subjects >75 years of age. Stroke 2005;36:1864–8.
[44] Treves TA, Bornstein NM, Chapman J, Klimovitzki S, Verchovsky R, Asherov A, et al. APOE-epsilon 4 in patients with Alzheimer disease and vascular dementia. Alzheimer Dis Assoc Disord 1996;10:189–91.
[45] Chapman J, Wang N, Treves TA, Korczyn AD, Bornstein NM. ACE, MTHFR, factor V Leiden, and APOE polymorphisms in patients with vascular and Alzheimer's dementia. Stroke 1998;29:1401–4.
[46] Koga H, Takashima Y, Murakawa R, Uchino A, Yuzuriha T, Yao H. Cognitive consequences of multiple lacunes and leukoaraiosis as vascular cognitive impairment in community-dwelling elderly individuals. J Stroke Cerebrovasc Dis 2009;18:32–7.
[47] Handley A, Medcalf P, Hellier K, Dutta D. Movement disorders after stroke. Age Ageing 2009;38:260–6.
[48] Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 2006;37:2220–41.
[49] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Kokmen E, Tangelos EG. Aging, memory, and mild cognitive impairment. Int Psychogeriatr 1997;9(Suppl. 1):65–9.
[50] Wentzel C, Rockwood K, MacKnight C, Hachinski V, Hogan DB, Feldman H, et al. Progression of impairment in patients with vascular cognitive impairment without dementia. Neurology 2001;57:714–6.
[51] Knopman DS, Rocca WA, Cha RH, Edland SD, Kokmen E. Incidence of vascular dementia in Rochester, Minn, 1985–1989. Arch Neurol 2002;59:1605–10.
[52] Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 1992;42:473–80.
[53] Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia—diagnostic criteria for research studies—report of the NINDS-AIREN international workshop. Neurology 1993;43:250–60.
[54] World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva, Switzerland; 1993. p. 36–40.
[55] American Psychiatric Association. Diagnostic and Statistical Manual of Mental DisordersFourth Edition. ; 1994. p. 143–7. (DSM-IV). Washington, DC.
[56] Hachinski V, Lee TY. Commentary on "Alzheimer's disease drug development and the problem of the blood–brain barrier." The blood–brain barrier: a physical and conceptual challenge. Alzheimers Dement 2009;5:435–6.
[57] Moroney JT, Bagiella E, Desmond DW, Hachinski VC, Molsa PK, Gustafson L, et al. Meta-analysis of the Hachinski ischemic score in pathologically verified dementias. Neurology 1997;49:1096–105.
[58] Garrett KD, Paul RH, Libon DJ, Cohen RA. Defining the diagnosis of vascular dementia. Appl Neuropsychol 2004;11:204–9.
[59] Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol 2009;8:1006–18.
[60] Hoffmann M, Schmitt F, Bromley E. Vascular cognitive syndromes: relation to stroke etiology and topography. Acta Neurol Scand 2009;120:161–9.
[61] Bruandet A, Richard F, Bombois S, Maurage CA, Deramecourt V, Lebert F, et al. Alzheimer disease with cerebrovascular disease and vascular dementia: clinical features and course compared with Alzheimer disease. J Neurol Neurosurg Psychiatry 2009;80:133–9.
[62] Orgogozo JM, Rigaud AS, Stoffler A, Mobius HJ, Forette F. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). Stroke 2002;33:1834–9.
[63] Meyer JS, Chowdhury MH, Xu G, Li YS, Quach M. Donepezil treatment of vascular dementia. Ann N Y Acad Sci 2002;977:482–6.
[64] Auchus AP, Brashear HR, Salloway S, Korczyn AD, De Deyn PP, Gassmann-Mayer C. Galantamine treatment of vascular dementia: a randomized trial. Neurology 2007;69:448–58.
[65] Aharon-Peretz J, Daskovski E, Mashiach T, Tomer R. Natural history of dementia associated with lacunar infarctions. J Neurol Sci 2002;203:53–5.
[66] Savva GM, Stephan BC. Epidemiological studies of the effect of stroke on incident dementia: a systematic review. Stroke 2010;41:e41–6.
[67] Newman GC, Bang H, Hussain SI, Toole JF. Association of diabetes, homocysteine, and HDL with cognition and disability after stroke. Neurology 2007;69:2054–62.
[68] van der Linde R, Stephan BC, Matthews FE, Brayne C, Savva GM. Behavioural and psychological symptoms in the older population without dementia—relationship with socio-demographics, health and cognition. BMC Geriatr 2010;10:87.
[69] Srikanth VK, Quinn SJ, Donnan GA, Saling MM, Thrift AG. Long-term cognitive transitions, rates of cognitive change, and predictors of incident dementia in a population-based first-ever stroke cohort. Stroke 2006;37:2479–83.
[70] Li L, Zhang X, Yang D, Luo G, Chen S, Le W. Hypoxia increases Abeta generation by altering beta- and gamma-cleavage of APP. Neurobiol Aging 2009;30:1091–8.
[71] Firbank MJ, Burton EJ, Barber R, Stephens S, Kenny RA, Ballard C, et al. Medial temporal atrophy rather than white matter hyperintensities predict cognitive decline in stroke survivors. Neurobiol Aging 2007;28:1664–9.
[72] Cordonnier C, Henon H, Derambure P, Pasquier F, Leys D. Early epileptic seizures after stroke are associated with increased risk of new-onset dementia. J Neurol Neurosurg Psychiatry 2007;78:514–6.
[73] Sachdev PS, Brodaty H, Valenzuela MJ, Lorentz L, Looi JC, Wen W, et al. The neuropsychological profile of vascular cognitive impairment in stroke and TIA patients. Neurology 2004;62:912–9.
[74] Nordlund A, Rolstad S, Klang O, Lind K, Hansen S, Wallin A. Cognitive profiles of mild cognitive impairment with and without vascular disease. Neuropsychology 2007;21:706–12.
[75] Laukka EJ, Jones S, Small BJ, Fratiglioni L, Backman L. Similar patterns of cognitive deficits in the preclinical phases of vascular dementia and Alzheimer's disease. J Int Neuropsychol Soc 2004;10:382–91.
[76] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
[77] Smith T, Gildeh N, Holmes C. The Montreal Cognitive Assessment: validity and utility in a memory clinic setting. Can J Psychiatry 2007;52:329–32.
[78] Sunderland T, Hill JL, Mellow AM, Lawlor BA, Gundersheimer J, Newhouse PA, et al. Clock drawing in Alzheimer's disease. A novel measure of dementia severity. J Am Geriatr Soc 1989;37:725–9.
[79] Brown EC, Casey A, Fisch RI, Neuringer C. Trial making test as a screening device for the detection of brain damage. J Consult Psychol 1958;22:469–74.
[80] Pendlebury ST, Rothwell PM. Risk of recurrent stroke, other vascular events and dementia after transient ischaemic attack and stroke. Cerebrovasc Dis 2009;27(Suppl. 3):1–11.
[81] Tatemichi TK, Paik M, Bagiella E, Desmond DW, Stern Y, Sano M, et al. Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study. Neurology 1994;44:1885–91.
[82] Bell RD, Zlokovic BV. Neurovascular mechanisms and blood–brain barrier disorder in Alzheimer's disease. Acta Neuropathol 2009;118:103–13.
[83] Iadecola C. Cerebrovascular effects of amyloid-beta peptides: mechanisms and implications for Alzheimer's dementia. Cell Mol Neurobiol 2003;23:681–9.
[84] Korczyn AD. The clinical differential diagnosis of dementia: concept and methodology. Psychiatr Clin North Am 1991;14:237–49.
[85] Henry-Feugeas MC. MRI of the 'Alzheimer syndrome'. J Neuroradiol 2007;34:220–7.
[86] Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. Arch Gen Psychiatry 1997;54:915–22.
[87] Balash Y, Korczyn AD. Vascular parkinsonism. Handb Clin Neurol 2007;84:417–25.
[88] Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. Ann Neurol 2009;66:200–8.
[89] Grinberg LT, Thal DR. Vascular pathology in the aged human brain. Acta Neuropathol 2010;119:277–90.
[90] Suemoto CK, Nitrini R, Grinberg LT, Ferretti RE, Farfel JM, Leite RE, et al. Atherosclerosis and dementia: a cross-sectional study with pathological analysis of the carotid arteries. Stroke 2011;42:3614–5.
[91] Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010;9:689–701.
[92] Jellinger KA. The enigma of vascular cognitive disorder and vascular dementia. Acta Neuropathol 2007;113:349–88.
[93] Simpson JE, Wharton SB, Cooper J, Gelsthorpe C, Baxter L, Forster G, et al. Alterations of the blood–brain barrier in cerebral white matter lesions in the ageing brain. Neurosci Lett 2010;486:246–51.
[94] Takao M, Koto A, Tanahashi N, Fukuuchi Y, Takagi M, Morinaga S. Pathologic findings of silent, small hyperintense foci in the basal ganglia and thalamus on MRI. Neurology 1999;52:666–8.

[95] Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology 1993;43:1683–9.
[96] Leys D, Pruvo JP, Parent M, Vermersch P, Soetaert G, Steinling M, et al. Could Wallerian degeneration contribute to "leuko-araiosis" in subjects free of any vascular disorder? J Neurol Neurosurg Psychiatry 1991;54:46–50.
[97] Sachdev PS, Brodaty H, Valenzuela MJ, Lorentz LM, Koschera A. Progression of cognitive impairment in stroke patients. Neurology 2004;63:1618–23.
[98] Tatemichi TK, Paik M, Bagiella E, Desmond DW, Pirro M, Hanzawa LK. Dementia after stroke is a predictor of long-term survival. Stroke 1994;25:1915–9.
[99] Jellinger KA. A critical evaluation of current staging of alpha-synuclein pathology in Lewy body disorders. Biochim Biophys Acta 2009;1792:730–40.
[100] Kalaria RN, Kenny RA, Ballard CG, Perry R, Ince P, Polvikoski T. Towards defining the neuropathological substrates of vascular dementia. J Neurol Sci 2004;226: 75–80.
[101] Kovari E, Gold G, Herrmann FR, Canuto A, Hof PR, Bouras C, et al. Cortical microinfarcts and demyelination affect cognition in cases at high risk for dementia. Neurology 2007;68:927–31.
[102] Jellinger KA. Understanding the pathology of vascular cognitive impairment. J Neurol Sci 2005;229–230:57–63.
[103] Probst A, Taylor KI, Tolnay M. Hippocampal sclerosis dementia: a reappraisal. Acta Neuropathol 2007;114:335–45.
[104] Labate A, Gambardella A, Aguglia U, Condino F, Ventura P, Lanza P, et al. Temporal lobe abnormalities on brain MRI in healthy volunteers: a prospective case-control study. Neurology 2010;74:553–7.
[105] Binswanger O. Die Abgrenzung der allgemeinen progressiven Paralyse. Berl Klin Wochenschr 1894;31:1102–5.
[106] Brown WR, Moody DM, Thore CR, Anstrom JA, Challa VR. Microvascular changes in the white mater in dementia. J Neurol Sci 2009;283:28–31.
[107] Tsushima Y, Aoki J, Endo K. Brain microhemorrhages detected on T2*-weighted gradient-echo MR images. Am J Neuroradiol 2003;24:88–96.
[108] O'Brien JT. Role of imaging techniques in the diagnosis of dementia. Br J Radiol 2007:80 Spec No 2:S71-.
[109] Nagga K, Radberg C, Marcusson J. CT brain findings in clinical dementia investigation—underestimation of mixed dementia. Dement Geriatr Cogn Disord 2004;18:59–66.
[110] Halperin I, Morelli M, Korczyn AD, Youdim MB, Mandel SA. Biomarkers for evaluation of clinical efficacy of multipotential neuroprotective drugs for Alzheimer's and Parkinson's diseases. Neurotherapeutics 2009;6:128–40.
[111] Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med 2002;162:2046–52.
[112] Shah K, Qureshi SU, Johnson M, Parikh N, Schulz PE, Kunik ME. Does use of antihypertensive drugs affect the incidence or progression of dementia? A systematic review. Am J Geriatr Pharmacother 2009;7:250–61.
[113] Mogi M, Horiuchi M. Effects of angiotensin II receptor blockers on dementia. Hypertens Res 2009;32:738–40.
[114] McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. Cochrane Database Syst Rev 2009:CD004034.
[115] Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ. Low blood pressure and the risk of dementia in very old individuals. Neurology 2003;61:1667–72.
[116] Monsuez JJ, Gesquiere-Dando A, Rivera S. Cardiovascular prevention of cognitive decline. Cardiol Res Pract 2011;2011:250970.
[117] Deschaintre Y, Richard F, Leys D, Pasquier F. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. Neurology 2009;73:674–80.
[118] Richard E, Gouw AA, Scheltens P, van Gool WA. Vascular care in patients with Alzheimer disease with cerebrovascular lesions slows progression of white matter lesions on MRI: the evaluation of vascular care in Alzheimer's disease (EVA) study. Stroke 2010;41:554–6.
[119] Moretti R, Torre P, Antonello RM, Cazzato G. Rivastigmine in subcortical vascular dementia: a comparison trial on efficacy and tolerability for 12 months follow-up. Eur J Neurol 2001;8:361–2.
[120] Dichgans M, Markus HS, Salloway S, Verkkoniemi A, Moline M, Wang Q, et al. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. Lancet Neurol 2008;7:310–8.
[121] Kavirajan H, Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. Lancet Neurol 2007;6:782–92.
[122] Muresanu DF, Alvarez XA, Moessler H, Buia M, Stan A, Pintea D, et al. A pilot study to evaluate the effects of cerebrolysin on cognition and qEEG in vascular dementia: cognitive improvement correlates with qEEG acceleration. J Neurol Sci 2008;267:112–9.
[123] Secades JJ, Lorenzo JL. Citicoline: pharmacological and clinical review, 2006 update. Methods Find Exp Clin Pharmacol 2006;28:1–56 Suppl. B.
[124] Napryeyenko O, Sonnik G, Tartakovsky I. Efficacy and tolerability of Ginkgo biloba extract EGb 761 by type of dementia: analyses of a randomised controlled trial. J Neurol Sci 2009;283:224–9.
[125] Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med 2009;360:225–35.
[126] Trifiro G, Spina E, Gambassi G. Use of antipsychotics in elderly patients with dementia: do atypical and conventional agents have a similar safety profile? Pharmacol Res 2009;59:1–12.