Vascular dementia: past, present and future

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Summary

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Knowledge and understanding of vascular dementia has greatly evolved since its first descriptions in the 19th century. The term now refers to a broad concept that encompasses many different pathophysiological mechanisms that include single strategic infarcts, multiple infarcts, small vessel disease, hypoperfusion and haemorrhage. This evolution has prompted the development of new clinical criteria. These include the ICD-10, DSM-IV and those developed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) and by the National Institute for Neurological Disorders and Stroke with support from the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN). Most are relatively specific but suffer from low sensitivity and, most importantly, they are not interchangeable. Clinicopathological correlation studies have shown that the ICD-10 research criteria and the probable vascular dementia category of the ADDTC and NINDS-AIREN were unable to detect the vast majority of vascular dementia cases. The best compromise appears to be the possible vascular dementia category of the ADDTC that has a sensitivity of 0.70 and a specificity of 0.78 for multi-infarct dementia. The important differences among the various diagnostic systems currently in use partly explain the marked variations in prevalence (5 to 31 per 1000) among vascular dementia epidemiological studies. Specific epidemiological data for vascular dementia is not available in Switzerland, however, the prevalence of dementia in general parallels that of other countries and increases sharply with age from 2.7% in individuals aged 65 to 69 to 24.8% in people who are 90 years old or older.

Vascular dementia should be suspected when dementia occurs abruptly, is associated with focal neurological signs and symptoms and follows a stepwise deteriorating course. However, over half of the cases may present with a more variable course. The proposed neuropsychological pattern for vascular dementia includes marked deficits in attention, concentration and executive function and less pronounced memory impairment compared to Alzheimer's disease. Improved information retrieval with cueing is highly unusual in Alzheimer's disease and common in vascular dementia. It is important to note that cognitive and behavioural consequences of vascular brain damage depend upon type, number, size and location of lesions. Mental slowing is suggestive of subcortical vascular dementia. Behavioural deficits consistent with a frontal lobe dysfunction have also been described.

Treatment options remain essentially preventive through interventions aimed at controlling vascular risk factors. Treatment of hypertension is particularly important. It can reduce stroke risk by approximately 40% and cut dementia risk in half. Once dementia is present, the objective is to slow down its progress, prevent new cerebral lesions, maximise cognition and function and control behaviour. In this situation, pharmacological options are limited. However, recent reports of acetylcholinesterase use in mixed and vascular dementia have shown encouraging results on cognition, function and behaviour and further studies of these compounds are ongoing. Future prospects include the development of diagnostic markers that can help discriminate vascular dementia from Alzheimer's disease and the continued search for prognostic indicators that could help identify which individuals with mild cognitive changes will develop a true dementia. Further clinicopathological correlation studies are also necessary to better identify the respective contributions of

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vascular and degenerative lesions in mixed dementia cases.

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Historical perspective

Apoplexy has already been described in ancient times and was known to have effects on behaviour and mental function beyond its effects on consciousness and motor activity. Clinicopathologic correlations in the early 19th century closely linked dementia to arteriosclerosis and cerebral softening [1]. In the late 19th century, Ball and Chambard recognised the role of vascular occlusions in apoplectic dementia [2] and several forms of vascular dementia were described by Alzheimer and Binswanger [3, 4]. Binswanger recognised three major types of dementia of vascular origin: (1) encephalitis subcorticalis chronica progressiva associated with severe white matter atrophy and ventricular enlargement without any evidence of focal disease, (2) arteriosclerotic brain degeneration which presented with widespread large artery arteriosclerosis and cortical and white matter discoloration, and (3) dementia post apoplexiam which was characterised by acute onset and focal deficits [4, 5]. Alzheimer provided some microscopic descriptions of encephalitis subcorticalis chronica progressiva and arteriosclerotic brain degeneration which included enlargement of the perivascular spaces, glial proliferation and scarring. He also described senile cortical atrophy associated with wedge-shaped cortical infarcts and softened and atrophic convolutions with numerous punctate indentations [6]. This clinicopathological spectrum has been understood to include multiple lacunar strokes, granular atrophy and what is currently called Binswanger's disease [5–7]. Chronic brain syndrome associated with cerebral arteriosclerosis was recognised in the first edition of the American Psychiatric Association's Diagnostic and Statistical Manual [DSM-1]. In 1968 the landmark studies of Tomlinson emphasised the role of cerebral infarction. Tomlinson believed that loss of brain tissue secondary to stroke was the pathophysiological mechanism behind dementia of vascular origin and suggested that cognitive symptoms were related to the volume of affected cerebral matter. In his experience, cerebral softening of 50 ml or more occurred in one third of demented individuals but only rarely in nondemented individuals and cerebral softening larger than 100 ml was only encountered in demented individuals [8, 9]. However, more recent clinicopathological studies have shown a significant overlap between affected volumes in demented and nondemented elderly [10]. Hachinski et al. proposed the term multi-infarct dementia to describe a dementia resulting from multiple strokes of thromboembolic origin [11]. The number and location of strokes was felt to be more important than the actual volume of damaged tissue. At the end of the 20th century, the concept evolved further to include multiple physiopathological mechanisms related to deficiencies in cerebral blood supply and the various types of brain pathology encountered in cases of vascular dementia. These include multiple infarcts, a single strategic infarct, small vessel disease, hypoperfusion and haemorrhage [12]. This expanded concept has prompted the use of the broader term *vascular dementia.* However, there is still no consensus regarding type, location and extent of lesions required for vascular dementia.

Vascular dementia today: diagnostic challenges and preventive strategies

Prevalence and incidence

The prevalence of vascular dementia ranges from 5 to 31 per 1000 and to a large extent depends upon the population studied. There are marked geographical differences including regional variations within countries [13–18]. A large European study, EURODEM, reported a prevalence of 24 per 1000 [14]. Vascular dementia prevalence increases steeply with age reaching 30 to 110 per 1000 in 85-year-old individuals and, contrary to Alzheimer's disease, most studies report higher rates in men although a gender effect is not always present [19].

Little is known regarding vascular dementia incidence. In one rare study, the average annual rate per thousand of vascular dementia ranged from 11 to 16 in individuals aged 65 or more, 19 to 43 in those aged 75 or more and 84 or higher in the eldest aged 85 or more [20].

Specific epidemiological data for vascular dementia is not available in Switzerland, however, the prevalence of dementia in general parallels that of other countries and increases sharply with age from 2.7% in individuals aged 65 to 69 to 24.8% in people who are 90 years old or more [21]. A review of pooled studies from various countries found that the proportion of dementia cases diagnosed as vascular dementia ranged from 10 to 38% making it the second most common cause of dementia after Alzheimer's disease [22].

Several methodological issues may explain the large range of values encountered in the epidemiological literature of dementia. In particular, the use of different diagnostic systems may markedly influence the results of incidence and prevalence studies [23, 24].

Clinical aspects and diagnostic criteria

Vascular dementia is traditionally suspected when dementia occurs abruptly, is associated with focal neurological signs and symptoms and follows a stepwise deteriorating course. However, over half of vascular dementia patients may present with an insidious onset and follow a slowly progressive course [25]. Several studies have suggested that certain neuropsychological patterns are typical of vascular dementia. It has been proposed that, as opposed to Alzheimer's disease, vascular dementia is associated with more marked deficits in attention, concentration and executive function and less pronounced memory impairment [26–28]. Information retrieval tends to improve with cueing in vascular dementia, contrary to Alzheimer's disease [29]. Individuals with vascular dementia may perform more poorly on verbal fluency tests compared to Alzheimer's disease cases and also exhibit more perseverations particularly during tasks that assess frontal lobe functions [30, 31]. In an analysis of 27 neuropsychological studies, vascular dementia patients tended to have greater preservation of long-term memory and greater deficits in executive functioning compared to Alzheimer's disease patients but language, constructional abilities, memory registration, conceptual function, and attention and tracking were similar in both types of dementia [32]. However, in the absence of clinicopathological correlations, these proposed neuropsychological profiles suffer from the limitations of current clinical diagnostic criteria for vascular dementia. It is important to note that vascular dementia can result from different pathophysiological processes and that a single neuropsychological pattern is unlikely. Furthermore, findings also depend on size, location and number of lesions. Behavioural deficits consistent with a frontal lobe dysfunction and mental slowing suggesting subcortical involvement have been described in vascular dementia [33].

Table 1 Hachinski ischaemic score.

item	score
abrupt onset	2
stepwise progression	1
fluctuating course	2
nocturnal confusion	1
relative preservation of personality	1
depression	1
somatic complaints	1
emotional incontinence	1
history of hypertension	1
history of strokes	2
evidence of associated atherosclerosis	1
focal neurologic symptoms	2
focal neurologic signs	2

Alzheimer's disease: ≤4; mixed dementia = 5 or 6; vascular dementia: ≥7.

The Hachinski ischaemic score (HIS), introduced in 1974, does not contain criteria for the diagnosis of dementia per se and can be applied without any imaging (table 1) [11]. It is largely based on the multi-infarct concept of vascular dementia and may not perform as well in detecting other subtypes of vascular dementia. It has been modified several times to remove items of questionable diagnostic value and include head CT findings [34, 35]. None of these modified versions have been conclusively shown to be superior to the initial HIS.

Table 2 Summary of ICD-10 research criteria for vascular dementia.

dementia as defined by
a decline in memory and other cognitive abilities that has been present for at least 6 months
intact consciousness
a decline in emotional control or motivation, or a change in social behaviour manifest as at least one of the following: emotional lability, irritability, apathy, coarsening of social behaviour
uneven distribution of deficits in higher cognitive functions
Focal brain damage, manifest as at least one of the following: unilateral spastic weakness of the limbs, unilaterally increased tendon reflexes, an extensor plantar response, pseudobulbar palsy.
Evidence from the history, examination or tests of significant cerebrovascular disease, which may reasonably be judged to be aetiologically related to the dementia.

The ICD-10 research criteria and the DSM-IV include items related to the general diagnosis of dementia and additionally require the presence of significant cerebrovascular disease which may reasonably be judged to be aetiologically related to the dementia (tables 2 and 3) [36, 37]. However, it remains unclear how focal neurological findings or neuroimaging data should be interpreted with regard to a potential vascular aetiology. Each investigator is left to make this judgment on his or her own. The DSM-IV tends to follow the general

Table 3 Summary of DSM-IV criteria for vascular dementia.

multiple cognitive deficits manifested by both
impaired memory
at least one of apraxia, agnosia, aphasia or disturbance in executive functions
Significant impairment in social or occupational functioning as a result of the above cognitive deficits, representing a decline from a previous level of functioning.
Focal neurological signs and symptoms or laboratory evidence of cerebrovascular disease that are judged to be aetiologically related to the disturbance.
The deficits do not occur exclusively during the course of a delirium.

pattern of its Alzheimer's disease criteria and stresses memory deficits, a symptom that is not always at the forefront of vascular dementia. The ICD-10 has unusually restrictive requirements that may not reflect the pathophysiological heterogeneity of the vascular dementia concept.

Other criteria were proposed in 1992 by the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) [38] (table 4) and in 1993 by the National Institute for Neurological Disorders and Stroke (NINDS) with support from the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) [39] (table 5). They both require the presence of dementia, evidence for cerebrovascular disease and, in most cases, a clear relationship between the two such as a close temporal association. They include a probable category which is relatively restrictive and a possible category that takes into account variable clinical presentations of vascular dementia. Neuroimaging is required for the probable category.

The above criteria are not interchangeable and often identify different clusters of patients [23]. In most clinicopathological studies, all of the vascular dementia clinical criteria demonstrate a moderate to very low sensitivity suggesting that they may not be suitable for the detection of vascular dementia from an epidemiological point of view [40–42]. In one recent study reported sensitivities for the ICD-10, and probable categories of the NINDS-AIREN and ADDTC were 25% or less; the sensitivity of the DSM-IV and the possible categories of the ADDTC and NINDS-AIREN was 50, 70 and 55% respectively and the specificity 84, 78 and 84% [41]. The latter three criteria thus remain specific enough to rule out pure Alzheimer's disease and can be used in therapeutic clinical trials. The ADDTC criteria for possible vascular dementia achieved a reasonable balance between an acceptable level of sensitivity and relatively high specificity and may represent the best alternative for use in clinical settings.

Table 4 Summary of the ADDTC clinical criteria.

dementia definition	Deterioration in intellectual function sufficient to interfere with customary affairs of life, which is not isolated to a single category of intellectual performance and is independent of the level of consciousness.	
probable vascular dementia	requires all the following:	
	1	dementia
	2	evidence of two or more strokes by history, neurological signs, and/or neuroimaging; or a single stroke with a clear temporal relationship to the onset of dementia
	3	evidence of at least one infarct outside the cerebellum by CT or T_1-weighted MRI
	The diagnosis of *probable vascular dementia* is supported by	
	1	evidence of multiple infarcts in brain regions known to affect cognition
	2	a history of multiple transient ischaemic attacks
	3	history of vascular risk factors (e.g. hypertension, heart disease, diabetes mellitus)
	4	elevated Hachinski ischaemic score
possible vascular dementia	1	Dementia and one or more of the following:
	2a	history or evidence of a single stroke without a clear temporal relationship with dementia onset, or
	2b	Binswanger's disease that includes all the following:
		early onset of urinary incontinence or gait disturbance
		vascular risk factors
		extensive white matter changes on neuroimaging

Table 5 Summary of the NINDS-AIREN clinical criteria.

dementia definition	Decline in intellectual function affecting memory plus at least two other cognitive domains, sufficient to interfere with activities of daily living and not due to physical effects of stroke alone. Cases with disturbed consciousness and delirium are excluded.
probable vascular dementia	requires all the following:
	1 dementia
	2 cerebrovascular disease defined by
	focal signs on neurologic examination (such as hemiparesis, lower facial weakness, Babinski's sign, sensory deficit, hemianopia and dysarthria)
	evidence of relevant cerebrovascular disease by CT or MRI
	– multiple large-vessel infarcts or
	– a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories) or
	– multiple basal ganglia and white matter lacunes or extensive periventricular white matter lesions, or combinations thereof
	3 a relationship between dementia and cerebrovascular disease, manifested by
	a dementia onset within 3 months of a stroke or
	b abrupt deterioration in cognitive functions or fluctuating stepwise course
	Clinical features consistent with the diagnosis of *probable vascular dementia* include the following:
	early presence of a gait disturbance
	history of unsteadiness or frequent unprovoked falls
	early urinary symptoms not explained by urologic disease
	pseudobulbar palsy
	personality and mood changes, abulia, depression, emotional incontinence, psychomotor retardation and abnormal executive function
possible vascular dementia	may be made in the presence of dementia and focal neurological signs when
	1 no neuroimaging studies exist, or
	2 in the absence of clear temporal relationship between stroke and dementia, or
	3 there is subtle onset and variable course of cognitive deficit and evidence of cerebrovascular disease

Preventive strategies

Vascular dementia is felt to be a preventable senility [43]. Preventive therapy is directed at vascular risk factors that may lead to vascular dementia [44]. This includes the treatment of hypertension, smoking cessation, control of diabetes, anticoagulation when atrial fibrillation is present, carotid endarterectomy for symptomatic patients with 70–99% carotid stenosis and aspirin for patients at high primary vascular risk. Treatment of isolated systolic hypertension in individuals over the age of 60 led to a reduction in the incidence of stroke of 36% in the SHEP study [45] and 42% in the SYST-EUR trial [46]. In the latter trial, treatment with the calcium channel blocker nitrendipine and, in a second step, the ACE inhibitor enalapril reduced the incidence of dementia by 50% from 7.7 to 3.8 cases per 1000 patient-years when compared to placebo [47]. The investigators estimated that 19 cases of dementia might be prevented if 1000 patients with isolated systolic hypertension were treated for 5 years. Interestingly, this reduction applied to both Alzheimer's disease and vascular dementia.

Future prospects

Recent efforts have focused on providing more precise definitions for the various subtypes of vascular dementia, in particular subcortical ischaemic vascular dementia [48]. Criteria for subcortical vascular dementia will need to be evaluated through clinicopathological correlations. The high prevalence of mixed dementia and the synergy between vascular and Alzheimer's disease lesions have increasingly been recognised and need to be better defined [49, 50].

Identifying individuals at risk for vascular dementia and particularly those with very mild cognitive deficits that do not warrant a diagnosis

of dementia may be of particular interest for preventive interventions. Such cases are described as vascular mild cognitive impairment (vascular MCI) or cognitive impairment no dementia (CIND). The predictive value of such diagnostic categories remains to be determined. The search for biological markers that can differentiate between different types of dementia or predict which patients with mild cognitive changes will eventually develop a dementia has intensified. However, reliable markers have yet to be found.

From a therapeutic point of view, recent studies regarding the use of acetylcholinesterase inhibitors in mixed dementia and vascular dementia have shown encouraging results leading to improved cognition, function and behaviour [51].

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