abstract

Cerebrovascular disease is a potential cause of vascular dementia. Vascular dementia is not an univocal entity; it encompasses at least four types of dementia: multi-infarct, subcortical, strategic infarct, and posthemorrhage dementia. Vascular dementia does not contain cognitive problems only. There are also noncognitive behavioural alterations. The major noncognitive behavioural situations are depression, anxiety, agitation, delusions, and insomnia. Disorders such as depression, anxiety, and psychosis not only affect the quality of life of a patient but also that of the caregiver. Behavioural disturbances may also contribute to morbidity and are a major cause of institutionalization since they result in inadequate nutrition and sleep and enhance cognitive disruption. Diagnosing depression in the context of vascular dementia is challenging given the overlap of signs and symptoms between depression and dementia. Both disorders can be characterized by apathy and loss of interest, an impaired ability to think, psychomotor agitation, and psychomotor retardation.

Key words: *behaviour, subcortical vascular dementia,, vascular dementia, small-vessel dementia*

Behavioural Disorders in Vascular Dementia

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Introduction

The mechanisms by which cerebrovascular risk factors lead to cognitive impairment remain unclear, but a number of studies have suggested that these risk factors are associated with accelerated brain atrophy, abnormalities of cerebral white matter, and silent stroke, which could impact on cognitive performance.[1–4] Multiple studies have consistently showed significant associations between the extent of brain atrophy or white matter hyperintensity (WMH) volumes and diminished cognitive performance,[5–10] including deficits in tests of attention and mental processing,[1–4,11] and impairments in memory and general intelligence.[11,12] Other studies have also found significant associations between cognitive impairment, including incident dementia, and clinically silent cerebral infarcts.[4,5,13] In a study of older male veteran twins, individuals with memory impairments sufficient for mild cognitive impairment (MCI) were found to have significantly greater WMH volumes and higher blood pressure than those with normal memory.[14] This has been confirmed by a second, larger epidemiological study.[15] A third study examined individuals over a wide range of cognitive performance from normal to dementia, and found increased volumes of WMH were associated with cognitive impairment, including memory loss.[16] Moreover, this study also showed a strong interaction between evidence of cerebrovascular brain injury and hippocampal atrophy, suggesting that these two processes may work synergistically to increase the likelihood of clinical dementia.[16] The notion that cerebrovascular insult and Alzheimer's disease (AD) may work synergistically to produce clinical dementia is given further support by preliminary evidence showing that extensive WMH increases the likelihood of conversion from MCI to AD.[17] Taken together, studies of older individuals with and without MCI suggest that cerebrovascular disease, even in the absence of clinical symptoms, may place an older person at substantial risk for cognitive impairment, particularly substantial memory impairment. Very early evidence also suggests that cerebrovascular disease might accelerate the process by which individuals transition from MCI to dementia.

Numerous epidemiological studies have shown a high prevalence of vascular brain injury among older adults,[16,18] and recent evidence supports a strong association between vascular risk factors and dementia.[4,19] Therefore, vascular dementia (VaD) is defined simply as the syndrome of dementia due to brain vascular disease.[20] In the Western world, vascular disease is the second most common cause of dementia,[21] and in the very old (85 years and older), there is a high risk of both stroke and AD, and the prevalence of VaD is reported to be slightly higher than that of AD (46.9% and 43.5%, respec-

Table 1: NINDS-AIREN Criteria for Diagnosis of Vascular Dementia

Dementia caused by strategic infarct	Dementia caused by few or single, often restricted infarcts but with a strategic location in functionally important regions (e.g., bilateral anterior thalamic infarct, angular gyrus, caudate nucleus).
Multi-infarct dementia	Derived by the sum of multiple infarcts, in different regions
Posthemorrhage dementia	Determined by the hemorrhage and by the vasospam, consequent to the bleeding
Subcortical VaD (SVaD)	Mainly due to a lacunar infarct, usually <2 cm, usually in the white matter, basal ganglia, thalamus, and pons. Incomplete infarct may also be present, due to a selective loss of neurons, myelin, and oligodendrocytes, without cystic necrosis, occurring in the periphery of major artery distribution infarcts (e.g., penumbra) or in deep white matter.

tively, with some patients possibly having mixed forms of dementia).[21] There is widespread literature concerning the development of dementia after stroke,[22–26] but it is unclear why some individuals with cerebrovascular injury, in the absence of clinical stroke, develop dementia, whereas others do not. Currently, the impact of this asymptomatic cerebrovascular brain injury remains unclear, but accumulating evidence suggests that clinically silent cerebrovascular disease may significantly increase the likelihood to develop dementia.[27,28]

Importantly, Fein *et al.*[29] noted significant correlations between the extent of WMH and grey matter volume across dementia groups. It is therefore possible that diffuse brain atrophy in association with extensive WMH may be an index of neuronal and synaptic loss and increase the risk for dementia. It has also been hypothesized that WMH may lead to cognitive impairment through the disruption of white matter tracts carrying cholinergic neurons.[30]

It is currently accepted that VaD is not a disease unto itself but, rather, a dementia that results from any number of cerebrovascular diseases affecting the brain. Current concepts of VaD have therefore focused on the notion of clinical and neuroimaging phenotypes that establish the presence of cerebrovascular brain injury that is believed sufficiently severe to contribute to, if not fully explain, the dementia.[31]

A certain portion of the pathology of cerebrovascular disease is relatively obvious. This is macrovascular pathology—that is, infarcts that can be seen with the naked eye at postmortem and on magnetic resonance imaging. Large cortical or deep infarcts involving all or part of a major vascular distribution and lacunar infarcts are macrovascular lesions. One difficulty that has plagued the field since the pioneering work in quantitating dementia pathology by Blessed *et al.*[32] is deciding how much infarct is enough to make the diagnosis. Should the pathology be bilateral, or can unilateral pathology suffice? Should there be a certain volume of tissue infarcted, or is the location of the infarct the determinant in the development of dementia?

The other type of vascular pathology that is relevant to dementia, but is less obvious, is microvascular.[33] One other critical issue in understanding dementia with cerebrovascular disease is the contribution of Alzheimer pathology. Ironically, it is the inability to define sufficient AD either clinically or pathologically that makes the definition of VaD much more difficult. Current understanding of cerebrovascular disease as a cause for dementia is further confounded by the facts that both AD and cerebrovascular disease are common to older adults and coincidental cerebrovascular disease is often found in older individuals with dementia, even though they may have a slowly progressive dementing illness most consistent with AD. As expected, the potential impact of cerebrovascular disease on the AD process is even less well understood than its impact on VaD, and the presence of concurrent cerebrovascular disease causes diagnostic confusion for the treating physician, potentially limiting effective care for these individuals.

With all these points taken in account, it is clear that the definition of VaD is a major point of controversy and disagreement. Indeed, some influential thinkers in the field have even questioned the term *vascular dementia* itself, preferring *vascular cognitive impairment* as a more general term.[34]

A better definition of dementia that would capture VaD is one that requires cognitive impairment in more than one domain, but does not specify that memory must be one of them. The National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN)[35] have developed diagnostic criteria for VaD outlined in Table 1.

Subcortical Vascular Dementia

Vascular lesions cause dementia on their own, as shown by the many proven pathology cases with various types of pure vascular disease with dementia. The clinical profile of these cases varies, for example, with or without neurological deficits, and with or without obvious stepwise progression. Hence, it is difficult to justify the clinical term *dementia of the cerebrovascular type*. This term also fails to cover noncerebral causes such as cardiac and hypotensive or hypoperfusive forms. *Multi-infarct dementia*, a term introduced by Hachinski *et al.*,[36] was original-

Table 2: Qualitative Analysis of the Behavioural Disturbances in the Two Groups at Baseline*

	SVaD Group	MID Group	p Value
Depression	72 (63%)	60 (52%)	<.05
Somatic symptoms	60 (52%)	14 (12%)	<.01
Anxiety	56 (49%)	54 (47%)	NS
Agitation	55 (48%)	48 (41%)	NS
Apathy	29 (25%)	74 (64%)	<.01
Cognitive abulia	28 (24%)	13 (11%)	<.05
Social withdrawal	30 (26%)	16 (14%)	<.05
Loss of insight or awareness	25 (22%)	7 (6%)	<.01
Suicide ideations	7 (6%)	14 (11%)	<.05

*As measured with the Behavioral Pathology in Alzheimer's Disease Rating Scale, and according to a Wilcoxon signed rank test.

Source: Data from Moretti R et al.[56]

ly meant to cover the whole field of VaD but is now mostly used to designate dementia due to multiple large infarcts. A similar definition also limits the usefulness of the term *post-stroke dementia*. *Vascular cognitive impairment,* suggested by Bowler and Hachinski,[37] does not explicitly imply dementia but, rather, may denote a stage that may or may not evolve into dementia.

One of the most common confounding factors in VaD is the aging process, which can be described as a combination of milder degenerative and cerebrovascular changes among which the latter may be difficult to single out from a superimposed vascular dementing disease. The importance of aging in this context is emphasized by the finding that VaD is the most common form of organic dementia after the age of 85 years.[38] Normal aging, with its grey and especially white matter loss, degenerative changes, and small, silent vascular lesions, can be viewed as predisposing to dementia due to a reduction of brain reserve capacity. This brings an aged individual closer to the level of insufficiency where only minor additional lesions may be required to precipitate dementia. The degenerative aging changes, though milder, repeat much of the pathology of AD. Senile plaques and neurofibrillary tangles are the most obvious of these. The latter are particularly pronounced in the entorhinal area of the hippocampus, an area vital to memory processing.

Small-vessel dementia (SVaD) is due to infarcts caused by obstruction of mainly intracerebral vessels of arteriolar size, subcortically represented by the long penetrants. The cause may be micro emboli from heart valves or atheromatous large-vessel lesions, particularly carotid stenosis, or special-vessel diseases such as collagen or inflammatory diseases,[39] amyloid angiopathy (particularly the hemorrhagic familial forms), and other hereditary angiopathies.

The major cause of small-vessel dementia, however, is hypertensive angiopathy, which may assume two forms: cortical plus subcortical, and purely subcortical, referred to as Binswanger's disease or progressive subcortical vascular encephalopathy; the lacunar state may be regarded as a milder form of the latter. The two varieties are basically similar, showing mostly small infarcts of lacunar size up to 15 mm in diameter.[40] Esiri *et al.*[41] referred to small-vessel dementia as "microvascular disease" and found it to be the most common variety in their neuropathological study. Small-vessel dementia was also reported by Akiguchi *et al.*[42] to be the leading cause of VaD in Japan. This is in agreement with our finding that small-vessel dementia accounts for 33% of cases of both pure and mixed AD/VaD. [42]

The vascular alterations also cover a number of vessel pathologies beyond the white matter, from atherosclerosis and hypertensive alterations of large, medium, and small vessels, to amyloidosis of small and medium-sized vessels, to fibrohyalinosis or lipohyalinosis of the smallest arteries.[35,43–46] The complete and incomplete white matter infarct, frequently coexisting, would, by virtue of their high prevalence, be the underlying substrate in the recognition of white matter disease.[47–49] The model is that of peri-infarct tissue in the white matter, namely, the transitional zone between the glial scar or cavity of a complete infarct and the better-preserved periphery at some distance from the infarct midpoint. The tissue within the incomplete infarct is partly attenuated, exhibiting all grades except total devitalization. The diffuse changes generally cover a region many times larger than the central focal lesion and may dominate over the latter by 200 times the volume.[45,46] The periphery merges with the surrounding normal white matter at a distance from the infarct centre that varies due to localization and specific preconditions in each situation. In between, the gradient shows increasing numbers of viable axons and myelin sheaths toward the periphery. The tissue gradient toward fully normal tissue was described by qualitative and quantitative neurochemical analyses of the white matter components.[45,46,50]

In these studies, the relative preservation of gangliosides versus decreased myelin lipids suggested a particular vulnerability of the myelin sheath, which is corroborated by correlative magnetic resonance and neuropathological studies of the very early stages of ischemia.[46] The

diffuse damage may be functionally silent in an initial ischemic stage with an edema that later subsides, but may in a stabilized phase regain at least partial functioning. The vessels show a degeneration of the smooth muscle layer, which is replaced by collagen in a hyaline fibrosis, leading to a subtotal luminal occlusion. These arterioles share traits with nonhypertensive lipohyalinosis[51] as well as with hypertensive arteriolosclerosis and may concur with hypertensive changes. There are, however, no microaneurysms or fibrinoid vessel wall necroses; there also is no marked association with large-vessel arteriosclerosis.

The pathophysiology of acute cerebral ischemia has been described, but the mechanisms leading to the selective vulnerability of some brain regions and the heterogeneity of injury are not yet fully understood. The most vulnerable areas to acute cerebral ischemia include the cerebral cortex, Purkinje cells of the cerebellum, and the CA1 sector of the hippocampus. Selective injury is also noted in different layers of the cortex, with layer three being the most sensitive, followed by layers five and six. The cortex is more susceptible to injury compared with the deeper structures, such as the brainstem. With cortical injury, seizures and impairment in cognition and memory may be observed. The thalamus and basal ganglia are other structures that are susceptible to injury. Among the myriad functions of the thalamus, it is probably the role in arousal and consciousness that is most critical during the recovery phase from global ischemia. The reestablishment of functional thalamocortical processing is vital in coma emergence after cardiac arrest. Injury to the basal ganglia and cerebellum account for subsequent problems with movement and coordination.

SVaD relates to small-vessel disease and hypoperfusion resulting in focal and diffuse ischemic white matter lesions and incomplete ischemic injury.[52] In patients with SVaD, ischemic lesions are particularly apparent in the prefrontal subcortical circuit, including the prefrontal cortex.[53] This deterioration of the frontal lobe is reflected in the fact that the so-called dysexecutive syndrome seems to be the core feature of SVaD.[54,55] Memory impairment and attentional deficits are also apparent, and patients often experience mood changes such as depression, personality changes, and emotional lability. In particular, these behavioural symptoms can be a major cause of stress, anxiety, and concern for caregivers and frequently lead to the institutionalization of patients.

As reported in a recent study,[55] the most frequently involved alteration in the cognitive profile of SVaD is dysexecutive syndrome. This concept seems even more evident when the scores obtained by patients with SVaD are compared with those obtained by patients with AD. Executive function refers to cognitive abilities involved in volition, planning, purposive action, and effective performance. While these abilities are critical to the daily functioning and maintenance of independence in a complex society, many executive abilities are not adequately assessed by the traditional standardized neuropsychological examinations as the testing environment and the examiner provide the patient with motivation, goals, planning, and structure. In particular, planning involves the capacity to conceptualize change from present circumstances, deal objectively with the environment and with the self in relationship to the environment, and weigh and evolve a framework for carrying on a plan.[56]

Behavioural Alterations

Problems of behaviour are commonly manifested by persons with dementia, and their presence may be devastating. In the spectrum of behavioural symptoms in VaD,[57] depression, often mistaken as apathy, occurs almost frequently

Table 3: A Qualitative Synopsis of the Results Obtained by the Two Groups at 24 Months*

	SVaD Group	MID Group	p Value
Depression	39 (34%)	55 (51%)	<.01
Somatic pain	60 (52%)	17 (15%)	<.01
Anxiety	60 (52%)	51 (44%)	<.05
Agitation	11 (10%)	52 (45%)	<.01
Apathy	77 (67%)	44 (38%)	<.01
Cognitive abulia	61 (53%)	13 (11%)	<.01
Social withdrawal	49 (43%)	16 (14%)	<.01
Delusions	49 (23%)	55 (47%)	<.01
Hallucinations	15 (13%)	51 (44%)	<.01
Craving for food	25 (22%)	45 (39%)	<.05
Sundowning	29 (25%)	35 (30%)	NS
Loss of insight or awareness	37 (32%)	17 (23%)	<.01
Suicide ideations	2 (2%)	14 (12%)	<.01

*As measured with the Behavioral Pathology in Alzheimer's Disease Rating Scale, and according to a Wilcoxon signed rank test.

Source: Data from Moretti R et al., 2006.[56]

and is often cited as an important factor for initiating drug therapy. Apathy, depression, and loss of awareness are, in our experience, the characteristics that caregivers mostly underline as behaviour changes among individuals with VaD, and these complaints are referred constantly with somatic pain and discomfort (even more evident than when they refer with memory loss or verbal defect).

In a recent study,[56] 240 men and women outpatients who were not bedridden and were 62–85 years old were examined and followed up for 24 months. The aim of the study was to define the eventual differences of behavioural alterations in the two distinct types of VaD, subcortical and multi-infarct, and to consider whether these points seem to influence cognitive aspects, global daily living performances, and caregiver stress. Patients were divided into two homogeneous groups, matched for age and education levels. One hundred twenty patients with SVaD comprised group A; 120 individuals with multi-infarct dementia comprised group B. All were followed up for 24 months, with periodic neurological and neuropsychological examinations. Main outcome measures were global performance, assessed using the Clinical Dementia Rating[58] at every visit; global behavioural symptoms, assessed using the Neuropsychiatric Inventory[59]; and caregiver stress, assessed by the Relative Stress Scale.[60] In addition to these main outcome measures, three further scales were used. The Cornell Scale for Depression in Dementia[61] was performed at every visit, and the Behavioral Pathology in Alzheimer's Disease Rating Scale[62] was performed at baseline and at 24 months (Tables 2 and 3). The Clinical Insight Rating Scale[63] was performed at every visit to provide a measure of its four comprising items—awareness, cognitive deficit, disease progression, and functional deficit.[56]

Quite interesting is the demonstration that, even from a behavioural perspective, multi-infarct dementia does not have the same effects as SVaD.[56] This must be taken into account in order to find more suitable and tailored therapies to specific pathologies and not to a single, generic entity. This means that studies involving individuals with VaD should focus on particular subtypes of the condition because the heterogeneity seen across the different subtypes may mask beneficial treatment effects. What emerged from the study report[56] was that more patients with SVaD experienced depression, somatic pains, cognitive abulia, social withdrawal, and loss of insight at baseline; more patients with multi-infarct dementia manifested apathy and expressed suicide ideations. Two months later, more patients with SVaD presented with somatic pain, anxiety, cognitive abulia, social withdrawal, and loss of insight; more patients with multi-infarct dementia presented with depression, agitation, delusions, hallucinations, craving for food, and suicidal ideation.

A fascinating, rather debated, and not fully understood is the behavioural alteration due to strategic infarct lesions. A superb work of categorizing the different alterations of behaviour derived from thalamus infarct has been conducted by Bogousslavsky *et al.*[64] Considering the anterior nuclei group, relayed to the tract of Vicq d'Azyr, and reciprocally connected to the anterior limbic system including cingulated gyrus, hippocampus, and parahippocampal formation, including the entorhinal, retrosplenium, and orbitofrontal cortices, patients with an infarct in the anterior territory frequently show a perseverative pattern in thinking and speech with inappropriate maintenance of category but also in all memory and executive tasks, with increased sensitivity to interferences. In addition, many patients show a superimposition and "telescoping" of unrelated information, with parallel expression of mental activities that we have called "palipsychism."

Paramedian nuclei consist mainly of dorsomedial and intralaminar nuclei, mainly connected with the anterior and medial prefrontal cortices but also with the mediobasal nucleus, the ventral pallidum, and the entorhinal cortex. The intralaminar nuclei have reciprocal connections to the substantia nigra pars reticulate, internal globus pallidus, and orbitofrontal and prefrontal cortices. The most frequent behavioural changes after paramedian infarcts are loss of self activation or akinetic mutism, amnesia-aphasia (in the case of a left or bilateral lesion), and disinhibition syndrome.

After paramedian infarcts involving the intralaminar nuclei (including the paracentral, centrolateral, centromedian, and parafascicular) and also the dorsomedian nucleus, patients who were physically and emotionally active before stroke may become severely apathetic, aspontaneous, and indifferent, as if they have lost motor and affective drive, especially after bilateral lesions.[64] These patients need constant external programming, which makes them appear as robots. The term *loss of psychic self-activation* has been proposed to describe this peculiar behaviour pattern.[65]

A disinhibition syndrome may occur after paramedian infarcts, although apathy and loss of psychic self-activation are most frequently encountered. When present, the disinhibition syndrome, resulting from a thalamofrontal disconnection, is often difficult to distinguish from psychiatric pathologies.

After a bilateral paramedian infarct involving the anterior part of intralaminar nuclei and the contiguous part of the dorsalis medialis nucleus, an individual[66] presented an acute-onset cyclical behaviour change that showed similarities with a patient of Bogousslavsky *et al.*[67] The individual, cheerful and lucid before the stroke, became apathetic and was "like a zombie," sleeping and eating excessively. However, every 3 months, he became alert, played with his children, and slept little during the night. During these episodes, his behaviour was frankly manic: the patient prayed, cried, and had a labile affect with flight of ideas. After 36 hours, he relapsed to his former apathetic state. A role of the thalamus in Kleine-Levin syndrome was suggested in this report.[66] A single-photon emission computed tomography (SPECT) scan showed severe hypoperfusion of both frontal lobes (left more marked than right) and of both thalami, suggesting a thalamocortical disconnection.

Utilization behaviour is defined by disinhibited, exaggerated responses to objects and environmental cues, with excessive utilization of objects. This peculiar behaviour has been described in a patient after a right thalamic infarct involving anterior parts of intralaminar and dorsomedial nuclei bilaterally;[68] it has also been seen in a patient after a lesion of the same nuclei but only on the right side.[69]

In humans, Klüver-Bucy syndrome consists mainly of hyperorality, with oral exploration of objects, uncontrolled food intake, affective dyscontrol (e.g., inappropriate social behaviour, aggression, and lack of shame), severe amnesia, and overattention to external stimuli. A patient with persistent Klüver-Bucy syndrome was reported after bilateral lesions of the dorsomedian nucleus and part of the intralaminar nuclei.[70] The patient, who had had an active social and intellectual life prior to the stroke, developed severe behavioural abnormalities. Two days after the stroke, when consciousness disturbances resolved, she started to eat and smoke compulsively. The patient stopped only when food and cigarettes were out of sight. The patient also expressed a lack of inhibition: she walked about her room undressed, flirted, and joked spontaneously. She was highly distractible and reacted to every auditory, visual, olfactory, and tactile cue.

Conclusion

A high index of suspicion of cerebrovascular disease as a cause for cognitive impairment is likely to result in better detection and treatment, leading to improved cognitive health for our aging population. VaD does not contain cognitive problems only. There are also noncognitive, behavioural alterations. The major noncognitive, behavioural situations are depression, anxiety, agitation, delusions, and insomnia. Disorders such as depression, anxiety, and psychosis clearly affect the quality of life of the patient and also commonly affect the quality of life of the caregiver.[71]

Behavioural disturbances may contribute to the overall morbidity of the disease and are the major cause of institutionalization[72,73] since they result in inadequate nutrition, sleep, and enhanced cognitive disruption. Diagnosing depression in the context of VaD is challenging given the overlap of signs and symptoms between depression and dementia.[74] Both disorders can be characterized by apathy and loss of interest, an impaired ability to think, psychomotor agitation, and psychomotor retardation. How to diagnose depression in the context of a chronic neurological illness that involves cognitive decline and prominent behavioural change is under debate.

The following aspects merit some consideration:

- The successful management of troublesome behaviours associated with VaD can significantly improve the overall quality of life for patients and their caregivers, as reflected by a significant reduction in scores on the Relative Stress Scale, a reduction of agitation and of wandering, and thereby, a drastic reduction in falls and dangerous fractures. [60]
- Negative signs such as apathy, abulia, opposition, and agnosia are badly tolerated and dramatically experienced by caregivers—more so than the other signs of cognitive decline.

Key Points

Vascular dementia is not a disease unto itself but, rather, a dementia that results from any number of cerebrovascular diseases affecting the brain.

Vascular dementia involves both cognitive and noncognitive problems.

The major noncognitive behavioural symptoms of vascular dementia are depression, anxiety, agitation, delusions, and insomnia.

Negative signs such as apathy, abulia, opposition, and agnosia are badly tolerated and dramatically experienced not only by the individual but also by caregivers.

Finding effective therapies to reduce mood and behavioural symptoms is likely to have an important impact on patient care, caregiver distress, and institutionalization.

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