Cognitive impairment after stroke
Hans-Peter Haring

The concept of vascular dementia is undergoing revision. The multi-infarct model and the Alzheimer’s model of dementia, usually referred to as ‘multi-infarct dementia’, are gradually being replaced by a much broader concept of vascular cognitive impairment. This conceptual evolution reflects a more profound understanding of the pathogenic mechanisms that underlie this complex syndrome. As a consequence of this revision new diagnostic criteria have been established during the past 25 years, resulting in new problems with regard to precise disease definition and limited inter-rater reliability. The particular criteria chosen by a clinician or investigator to diagnose vascular dementia have a major impact on epidemiology, disease management and health economic estimates. Curr Opin Neurol 15:79–84. © 2002 Lippincott Williams & Wilkins.

Introduction
Cerebrovascular disease is a risk factor for impaired cognitive functioning. Approximately one-quarter of patients remain demented 3 months after a stroke. If selected impaired cognitive functions are considered, 50–75% of stroke patients are found to be affected, depending on age [1**,2,3]. Even among patients who remain cognitively intact after their index stroke, hospital-based and population-based studies [4,5] have revealed a significant risk for developing delayed dementia. However, physical handicaps rather than cognitive deficits attract most attention after stroke, and sufferers of strokes that merely affect cognition frequently do not receive medical treatment at all.

Irrespective of the type of dementia, population-based studies yield extremely diverse data when different criteria for dementia are applied. According to the criteria of the International Classification of Disease, 10th edition, 3.1% of the population older than 65 years is demented; according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-III criteria, however, the proportion is almost 10 times greater (29.1%) [6]. The criteria of the International Classification of Disease, 10th edition, refer to the essential features of dementia, which comprise acquired, chronic and irreversible impairment of thinking and memory [7]. In contrast, DSM-IV is based on a much less refined concept [8]. This presents particular difficulties when those criteria are applied to cognitive inabilities of vascular origin. Location-specific cognitive deficits, such as aphasia, apraxia or agnosia, do not represent global intellectual dysfunction, even when they exist in various combinations. Clearly, such focal neurological dysfunctions should not be classified as dementia, and are not addressed in the present review.

The pathogenic concept of vascular dementia
The classic concept implies that dementia of vascular origin is the result of a critical volume of infarcted brain tissue, irrespective of its topography [9]. However, isolated but strategically positioned lesions may also lead to significant cognitive decline, even when they are of small volume [10]. In addition, poststroke dementia is well documented in patients with extensive subcortical white matter lesions [11]. On the basis of the current pathological and functional imaging data, three pathogenic concepts of vascular dementias (VaDs) have been described [12,13*]: accumulated cortical infarcts; strategic subcortical infarcts; and functional cortical disconnection.
Accumulated cortical infarcts

Certain cortical lesions may generate defined cognitive signs and symptoms (amnesia, aphasia, apraxia, alexia, agraphia). In combination with noncognitive abnormalities, such as emotional instability or loss of initiative, these lesions in various combinations and extensions may constitute a cortical dementia syndrome [14**,15–18].

Strategic subcortical infarcts

Disruption of subcorticofrontal and thalamocortical projections through even small and isolated lesions can result in dementia. Critical locations comprise the thalamus, the caudate nucleus, and the genu and anterior limb of the internal capsule [19–22]. These strategic infarcts disrupt important prefrontal, orbito-frontal, dorsolateral, or anterior cingulate circuits, thereby interfering with essential connections between the prefrontal cortex and the basal ganglia or the thalamus [23–25].

Functional cortical disconnection

Extensive white matter lesions (WMLs) reflect a diffuse loss of axons, with consequent widespread functional disconnection of the cortex. Functional brain imaging studies revealed reduced cerebral blood flow and metabolism not only in the morphologically altered white matter but also in structurally intact frontal, temporal and parietal cortices [26,27**]. In patients with cerebral microangiopathy, neuropsychological impairment correlates with cortical hypoperfusion and hypometabolism but not with the extent of WMLs [28]. The relationship between WMLs and cognitive dysfunction is more complex, however. It is clinically well known that even those patients with extensive WMLs may present with intact memory, indicating that additional factors may play a role. Corpus callosum atrophy was shown in a magnetic resonance imaging (MRI) study [29**] to be an important predictor of global cognitive impairment in patients with WMLs. Interestingly, however, these impairments were clearly more restricted to those of frontal lobe functioning.

Clinical diagnosis and differential diagnosis

The clinical diagnosis of VaD in a demented person is usually based on factors that are characteristic for a vascular aetiology. The presence of cerebrovascular disease, however, does not necessarily imply that stroke caused the dementia, or even contributed to it, in particular because concomitant Alzheimer’s disease (AD) is frequently present [30*]. The duration of the dementia, the signs of cerebrovascular disease and the results of brain imaging should be considered.

During the past decade a panel of new criteria for the clinical diagnosis of VaD has been introduced (Table 1) [7,8,31–35]. All sets of criteria have one weakness in common – the lack of evidence to relate pathological (i.e. ischaemic) findings or clinical events with the unspecific dementia syndrome [36**]. In an attempt to address this limitation, certain criteria (i.e. those of the Alzheimer Disease Diagnostic and Treatment Center [34], and National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l’Enseignement en Neurosciences [35]) seek causal temporal relations between ischaemic lesions or events and the development of dementia. Another major limitation of this diverse set of diagnostic criteria is the fact that they are not interchangeable. Applying, for example, both the most restrictive (i.e. National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l’Enseignement en Neurosciences [35]) and the most liberal (i.e. DSM-IV) criteria to the same population, the diagnosis of VaD may differ up to fivefold [37**,38,39]. This poses the question of accuracy and relevance of the respective diagnostic criteria [40**].

In evidence-based medicine, a reliable test is required to identify a particular disease with sufficient sensitivity and specificity. This requires a ‘gold standard’, and to date none is available for the diagnosis of VaD [36**]. In contrast to AD, a blinded pathologist is unable to determine reliably whether a vascular lesion was causal, contributory, or simply coincidental to a dementia syndrome. In the absence of such a gold standard in the diagnosis of VaD, data on the differential accuracies of the referred clinical criteria remain controversial and of limited value for the clinician [41–45].

Despite differences in the profile of cognitive decline between patients with VaD and those with AD, it is still uncertain whether patients may be reliably discriminated on the basis of those differences alone. Because motor symptoms are absent in AD until the late stages and are

Table 1. Diagnostic criteria for vascular dementia reported during the past 25 years

<table>
<thead>
<tr>
<th>Acronym (definition and reference)</th>
<th>Neuroimaging required</th>
<th>Established</th>
</tr>
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<tbody>
<tr>
<td>HIS (Hachinski Ischemic Score) [34]</td>
<td>No</td>
<td>1974</td>
</tr>
<tr>
<td>DSM-III (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition) [32]</td>
<td>No</td>
<td>1980</td>
</tr>
<tr>
<td>DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition [33]</td>
<td>No</td>
<td>1987</td>
</tr>
<tr>
<td>ADDTC (Alzheimer Disease Diagnostic and Treatment Center) [34]</td>
<td>Yes</td>
<td>1992</td>
</tr>
<tr>
<td>NINDS/AIREN (National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l’Enseignement en Neurosciences) [35]</td>
<td>Yes</td>
<td>1993</td>
</tr>
<tr>
<td>ICD-10 (International Classification of Diseases, 10th revision) [7]</td>
<td>No</td>
<td>1993</td>
</tr>
<tr>
<td>DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) [8]</td>
<td>No</td>
<td>1994</td>
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common in patients with VaD, these may represent a more accurate discriminating criterion. When infarcts or WMLs are present on computed tomography (CT) or MRI, they may only be incidental findings or may explain the dementia. Such considerations are also of importance in patients with possible diffuse Lewy body disease, in whom a fluctuating course may suggest VaD, and in patients with possible subcortical arteriolar sclerotic encephalopathy (SAE), who may present with a similar clinical course.

Because of the heterogeneous pathophysiology and pathology of VaD, diagnostic criteria for VaD might never be simple. The primary degenerative and vascular diseases in the elderly are often combined, however, and therefore the diagnosis of VaD will probably become more valid when specific diagnostic tests for the different degenerative diseases become available.

**Neuroimaging**

Diagnostic accuracy can be enhanced by the additional use of brain imaging techniques, and they are an integral part of some of the more recent diagnostic criteria of VaD (Table 1). Whereas both CT and MRI are equally reliable in detecting large artery ischaemic brain lesions, MRI is clearly superior with respect to small vessel disease and deep WMLs.

The frequency of WMLs (also known as leukoaraiosis) increases with age and increased blood pressure [46,47]. Also, among patients with small vessel strokes the presence of leukoaraiosis indicates a poor prognosis with an increased risk for stroke recurrence and dementia [48,49]. Several studies have tried to establish a semiquantitative relation between the extension of WMLs and cognitive impairment. Various threshold volumes (e.g. >10 cm² in area or >0.5–4% of intracranial volume) beyond which cognitive impairment might become clinically apparent have been reported [36,50,51]. If such a relation holds true is questionable, however.

The periventricular and deep white matter receive their blood supply through narrow penetrating endarterioles that are subject to small vessel disease. Thus, WMLs may primarily reflect chronic hypoperfusion and are regarded as major markers of brain tissue at risk rather than of cognitive impairment [36]. This is supported by the fact that there are patients with even widespread and confluent WMLs who do not have cognitive dysfunction. This requires a discrimination of the clinical syndrome SAE (Binswanger’s disease) from the radiological diagnosis leukoaraiosis. The following criteria have been suggested for the diagnosis of SAE [45]: dementia; leukoaraiosis on CT or MRI; and two of the following three characteristics – presence of a vascular risk factor or evidence of systemic vascular disease, evidence of focal cerebrovascular disease, and evidence of subcortical cerebral dysfunction (gait disorder, urinary incontinence).

**Stroke, depression and cognitive impairment**

Irrespective of cerebrovascular disease, affective disorders and cognitive functioning are known to be interrelated [52–54]. Depression is also a common sequelae in stroke, with a reported frequency of up to 65% of all patients [55–58]. This raises the critical question of whether depression and cognitive impairment after stroke evolve independently, or simply cause each other. Prior trials failed to find a positive correlation between successful treatment of poststroke depression and improved cognitive functioning [59–61]. This resulted in the hypothesis that cognitive deficits are the cause rather than the consequence of poststroke depression [59,62]. In contrast, one recent, double-blind, controlled nortriptyline trial [63] revealed that depressive stroke patients gained improved cognitive functions after successful treatment of their mood disorder. Another intriguing detail of that study is that those patients whose depression responded to placebo also improved in cognitive tasks. This might imply that the mechanism of depression, and not that of nortriptyline itself, was responsible for the observed cognitive improvements. That trial thus refutes the hypothesis that cognitive deficits cause poststroke depression, but supports the reverse contention that depression (among other mechanisms) adds to cognitive impairment in stroke patients.

Another issue is how the lesion site influences poststroke depression and cognition. A number of studies reported a significantly stronger relation in left as compared with right hemisphere strokes [59,64,65]. This has also been addressed in a recent prospective study [66] that evaluated the relations between aphasia, depression and nonverbal cognitive functioning in a large series of stroke patients. The major finding of that study was a high susceptibility of aphasic patients to major depression; this continued to increase over the 1-year study period. Moreover, the data also revealed a significant association between aphasia and nonverbal cognitive deficits. Those findings suggest that cognitive deficits in aphasic patients do not simply reflect the linguistic disorder, but rather reflect a more complex impairment of the memory process [67].

**Therapeutic approach**

Drug therapy for cognitive impairment following cerebrovascular disease must focus on at least two diverse targets, namely stroke prevention and specific interventions to improve cognitive functioning.
Preventive measures
Preventive measures comprise risk factor modification and both primary and secondary stroke prevention. Although the majority of vascular risk factors are not modifiable, hypertension and hyperlipidaemia are. Several controlled trials [68,69] confirmed a significant reduction in both initial and recurrent strokes with sufficient antihypertensive therapy. Cholesterol (i.e. low-density lipoprotein)-lowering drugs are also successful in preventing stroke [70]. Furthermore, several lines of evidence have confirmed that antiaggregant and antithrombotic drugs are effective in primary and/or secondary stroke prevention, as is surgical carotid artery management in selected patients [71–73].

Only very few data are available regarding the direct impact of controlling vascular risk factors on cognitive improvement itself. A single small observational study [74] suggested that maintaining systolic blood pressure within the range 135–150 mmHg results in stabilization of cognitive functioning, whereas lowering the blood pressure to below this range would be associated with decline. Those data received support from the larger and much more recent Baltimore Longitudinal Study on Aging [75].

Specific measures
Specific measures are primarily based on vasoactive, haemorheological and neuronal metabolic mechanisms. The most promising compounds available thus far are a set of cholinesterase inhibitors. Some of those drugs have already been licensed for treatment of AD, and a multicentre trial for the use of donepezil in VaD is currently underway [36**]. Another ongoing trial [76] is evaluating the agent memantine – a reversible γ-aminobutyric acid antagonist. The vast majority of compounds studied (i.e. hydrgine, pentoxyfylline, propentofylline, piracetam, nimodipine, ginkgo biloba, etc.) have shown only modest and clinically irrelevant effects [36**]. The magnitude of the therapeutic effects is usually very similar in patients with AD and VaD, suggesting that the modes of action in these patients share a common pharmacodynamic basis.

Conclusion
Stroke-related cognitive dysfunction is surrounded by many problems with respect to heterogeneity, relevance, prevalence and uniqueness. There is no consistent phenotype because strokes can strike any region of the brain. Moreover, it is difficult to establish a causal link between stroke and dementia, or to exclude the possibility that AD is responsible for the cognitive dysfunction. Defining the term ‘vascular dementia’ is a challenge that presents problems in establishing an appropriate medical definition, in conducting epidemiological and interventional studies, and in providing best care. The conceptual change in the approach to cognitive impairment of vascular origin was intended to recognize that several vascular mechanisms and many vascular diseases may lead to dementia. Patients with small-vessel disease are not the same as those with cardioembolic strokes or large vessel occlusive disease. White matter changes are more likely to occur in patients with chronic hypertension. Thus, from a nosological point of view, VaD is a highly heterogeneous issue that, in most cases, does not yet find adequate reflection in clinical practice.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
** of outstanding interest


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28 This is a well-designed study of the clinically crucial issue of reliability and validity of various diagnostic concepts of VaD.


36 This study in 62 patients presents clinical and MRI data indicating that callosal atrophy and WMHs have different consequences with respect to cognitive dysfunction.


38 This clinically oriented review focuses on the problem of mixed dementia.


41 This study in 62 patients presents clinical and MRI data indicating that callosal atrophy and WMHs have different consequences with respect to cognitive dysfunction.


43 This clinically oriented review focuses on the problem of mixed dementia.


50 This superb review discusses the entire field of the topic, ranging from definition problems through therapeutic aspects.


52 This important study was conducted to assess the inter-rater reliability of the four most recent diagnostic criteria of VaD.

Cerebrovascular disease

62 Murata Y, Kimura M, Robinson RG. Does cognitive impairment cause poststroke depression? Am J Geriatr Psychiatry 2000; 8:310–317. This consecutive series compared patients with and without poststroke depression; the report includes an interesting discussion on the causal relation between the two entities.

63 Kimura M, Robinson RG, Kosier JT. Treatment of cognitive impairment after poststroke depression, a double-blind treatment trial. Stroke 2000; 31:1482–1486. This is a placebo-controlled trial on the response of cognitive function to treatment with nortriptyline. An interesting discussion is provided on the discriminating impacts of drug therapy versus the mechanism of the mood disorder itself on the cognitive improvement.


