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INTRODUCTION

Vascular dementia is one of the most frequent causes of dementia in the elderly and therefore a major burden on health care systems in ageing societies. Cognitive dysfunction frequently occurs after a clinically obvious ischaemic or haemorrhagic stroke, and even a subclinical or 'silent' stroke, and ranges from subjective memory complaints that cannot be detected even by detailed neuropsychological examination, to full-blown dementia (Tatemichi *et al.* 1992; Van Zandvoort *et al.* 1998). The diagnosis of vascular dementia may be difficult because the temporal relation between a stroke first and then the occurrence of cognitive decline is not always obvious at first sight. This may be because the stroke was silent, or it may be difficult to relate the location of the stroke lesion to the cognitive consequences. In addition, in Alzheimer's disease vascular events in the brain may worsen its course and confuse any diagnostic classification (Pasquier *et al.* 1998). Treatment of vascular dementia can be approached from two different angles: the control of classical vascular risk factors that obviously contribute to the development of vascular disease and so dementia and the use of drugs such as acetylcholine esterase inhibitors (Erkinjuntti *et al.* 2002).

In this review we will first discuss the clinical picture and diagnostic criteria for vascular dementia, followed by a brief epidemiological perspective on frequency and risk factors. Last, but not least, we will consider treatment.

CLINICAL FEATURES

By definition, a dementia syndrome requires decline in memory as well as decline in at least two other intellectual domains – orientation, attention, verbal skills, visuospatial abilities, calculations, executive function, motor control, praxis, abstraction and judgement. According to the international criteria for a dementia syndrome, the sum of these symptoms must also cause impairment of independent functioning in daily life (World Health Organization 1991).

In vascular dementia the decline is not necessarily progressive, as cognitive function can remain relatively stable for a long period of time after an initial reduction caused by an acute vascular event, either clinically obvious or 'silent'.

A sign of a vascular cause for a dementia syndrome is a sudden onset after stroke with a fluctuating or stepwise course. On the other hand, dementia associated with severe white matter lesions (still widely known as Binswanger's disease) has a gradual onset and be slowly progressive (Bennet *et al.* 1994). An additional history of gait disturbance, frequent falls and urinary incontinence is evidence for this diagnosis .

Typical symptoms of vascular dementia are focal neurological signs such as hemiparesis, hemianopia and pseudobulbar symptoms

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(swallowing disturbance, spastic dysarthria, uncontrollable laughing or crying).

Depending on the site and extent of the lesions, a variety of clinical presentations of vascular dementia may emerge. These range from a predominantly cortical to a typically subcortical vascular dementia syndrome (Erkinjuntti *et al.* 2000; Tatemichi 1990). For example, large anterior cerebral artery infarcts (or haemorrhage in the same area) may present with abulia, transcortical motor aphasia, memory impairment and dyspraxia. Severe amnesia, apathy and other behavioural changes are frequently encountered with infarction in the territory of the anterior cerebral artery, especially if the lesions are bilateral, as occurs after rupture of an anterior communicating artery aneurysm. Right middle cerebral artery occlusion may present with behavioural abnormalities (psychosis) and cognitive decline. Patients with a left middle cerebral artery infarct cannot be diagnosed with definite vascular dementia if aphasia precludes adequate assessment of mental function. A posterior cerebral artery infarct may present with an amnestic syndrome through involvement of the thalamoperforating artery territory with damage of the intralaminar nuclei of the thalamus. Posterior cerebral artery infarcts are frequently associated with psychomotor agitation, visual hallucinations and other visual disturbances.

Chronic and insidious ischaemia of the white matter caused by diffuse small vessel disease is characterized by a mostly mild degree of subcortical cognitive impairment and is extremely common in the general population (de Groot *et al.* 2000a). Ultimately and exceptionally this may lead to a complete dementia syndrome characterized by memory deficits, and in particular slowing of executive function (de Groot *et al.* 2000b; van Gijn, 2000). Common in this type of vascular dementia are extrapyramidal features, gait disturbances (lower body parkinsonism), and mood changes (de Groot *et al.* 2000a; Hennerici *et al.* 1994; Tarvonen-Schroder *et al.* 1996).

DIAGNOSTIC CRITERIA

Diagnostic criteria are essential for such a heterogeneous clinical entity as vascular dementia. A proper and uniform diagnosis facilitates the identification of risk factors for the disease and allows evaluation of treatment strategies, but this is really more for research studies than diagnosis and management of the individual patient. Criteria for the diagnosis of vascular dementia were put forward in 1993 by the US National Institute of Neurological Disorders and Stroke, and the French Association Internationale pour la Recherche et l'Enseignement en Neurosciences – these are now known as the NINDS-AIREN criteria for vascular dementia (Roman *et al.* 1993) (Table 1).

Table 1 The NINDS-AIREN criteria for the diagnosis of vascular dementia*

Clinical
(a) Dementia
(b) Cerebrovascular disease†
(c) Temporal relation between (a) and (b), i.e. evidence of cerebrovascular disease first
Radiological
Topography
Large vessel stroke in
bilateral anterior cerebral artery territory
or posterior cerebral artery territory
or association areas‡
or border zone carotid territories
Small vessel disease
extensive periventricular white matter lesions
or lacunes in basal ganglia or frontal white matter
or bilateral thalamic lesions
Severity
Large vessel stroke
Large vessel territory lesions of the dominant hemisphere, or bilateral large vessel hemispheric strokes
Small vessel disease
White matter lesions involving at least 25% of the total cerebral white matter

*Both clinical as well as radiological criteria (topography and severity) should be fulfilled to diagnose vascular dementia.
†See text for definition.
‡Parieto-temporal, temporo-occipital territories (including angular gyrus).

For a diagnosis of vascular dementia, both clinical and radiological criteria must be fulfilled, as follows.

Clinical criteria

- The patient must be demented (decline in memory and in at least two other intellectual domains, severe enough to interfere with daily life).
- There must be evidence of cerebrovascular disease based on a history and examination consistent with stroke, in combination with relevant lesions on brain imaging (CT or MRI; see below). If there is no definite history, then subtle focal signs may indicate a 'silent' stroke (reflex asymmetry, upgoing plantar response etc).
- The dementia syndrome should develop within 3 months of the stroke. This time span is arbitrary but helps avoid misclassification in patients who develop a dementia syndrome years after a stroke. However, the time criterion is difficult because the stroke may have been 'silent', or there may only be progressive dementia and widespread white matter lesions on brain imaging. The diagnosis of vascular dementia can then only really be 'possible'.

Radiological criteria

- **Topography**. Brain imaging should reveal large vessel strokes, or a single strategically located infarct (or old haemorrhage), or multiple lacunar infarcts in the basal ganglia or frontal lobes, or extensive white matter lesions in the periventricular regions.
- **Severity**. Large vessel lesions should be present in the dominant hemisphere, or in both hemispheres. It is believed, but certainly not proven, that cognitive deficits in dementia should be attributed mostly to the dominant hemisphere. White matter lesions should involve at least 25% of the white matter.

The radiological criteria consist of topography and severity sections, both of which must be fulfilled to diagnose vascular dementia according to the NINDS-AIREN criteria. This combination of topography and severity is required to exclude, for example, individuals with relatively mild white matter lesions.

Therefore, it is essential to have adequate information both about the clinical and radiological aspects of the patient. This is illustrated by fig. 1, which shows MR scans of two different patients with an identical white matter lesion load: one was a healthy independently living

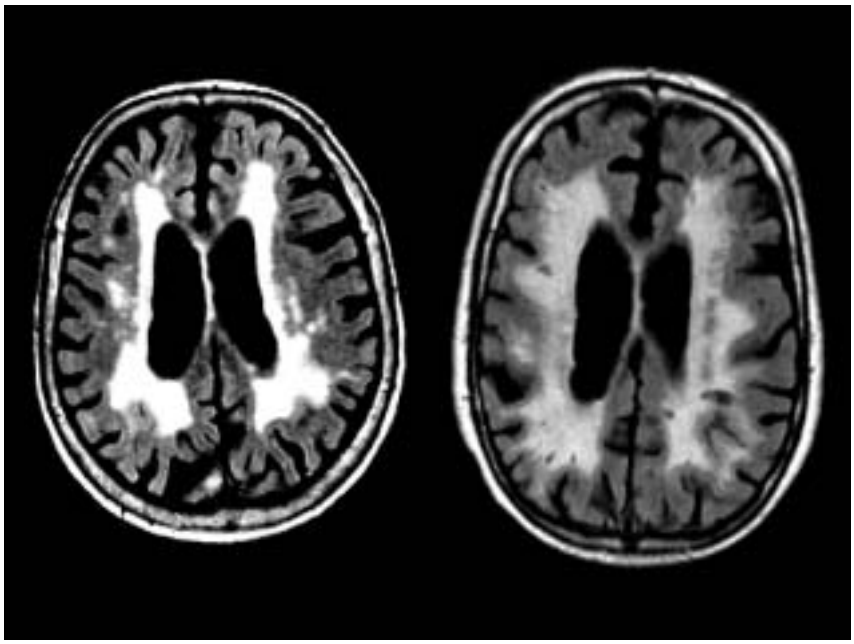

Figure 1 Fluid-attenuated inversion recovery (FLAIR) image showing identical extensive white matter lesions in a healthy, non-demented non-institutionalised elderly person (left) and in a patient with vascular dementia (right). Kindly provided by Prof. Ph. Scheltens.

non-demented individual, whereas the other had dementia.

Regrettably we have no practical definition of what exactly 25% of the white matter is. Also there are no precise radiological criteria for lacunar infarcts in the basal ganglia and frontal lobes, or for bilateral thalamic lesions, because there is no defined severity dimension. For this reason any patient with a dementia syndrome with multiple lacunar infarcts in the basal ganglia on MRI but without hemispheric lesions cannot be diagnosed as having vascular dementia according to the NINDS-AIREN criteria (fig. 2).

On the basis of the clinical and radiological criteria, probable and possible vascular dementia can be defined (Roman *et al.* 1993). Definite vascular dementia can only be diagnosed with additional neuropathological evidence.

Definite vascular dementia

- Dementia as defined previously.
- Radiological evidence of cerebrovascular disease as defined previously.
- No more than 3 months between the occurrence of the stroke (which therefore must have been clinically obvious) and the diagnosis of dementia.
- Histopathological evidence of cerebrovascular disease (old infacts or haemorrhages) from brain biopsy or autopsy and no more neurofibrillary tangles and neuritic plaques than expected for the patient's age, and no other factor that could explain the dementia.

Probable vascular dementia

All the above-mentioned criteria should be fulfilled except for the pathological evidence.

Possible vascular dementia

This diagnosis can be made in the presence of dementia with focal neurological signs in patients for whom there are no brain imaging studies, or when a clear temporal relationship with stroke cannot be documented.

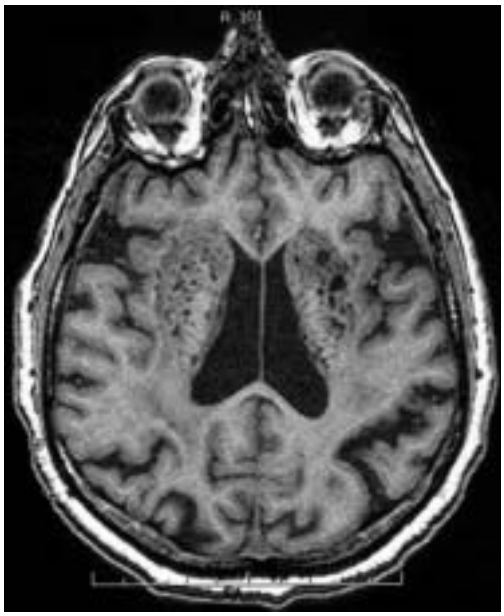

Figure 2 Three lacunar infarcts in the left hemisphere in a demented patient and enlarged perivascular spaces in the basal ganglia region on both sides. (T1-weighted image). This cannot be strictly diagnosed as vascular dementia according to the NINDS-AIREN criteria because there is no defined severity criterion for lacunar infarcts. (Kindly provided by Dr I. van Straaten.)

EPIDEMIOLOGY OF VASCULAR DEMENTIA

Vascular dementia is the second most frequent cause of dementia after Alzheimer's disease. Approximately one-third of individuals above 85 years of age has a dementia syndrome and about one-sixth of them suffer from vascular dementia, resulting in a prevalence of about 4–5% (Ott *et al.* 1995). The absolute numbers continue to rise, as people get older.

In a population-based study of over 7000 participants who were followed for about 6 years, the incidence of vascular dementia was 0.1 per 1000 person years in those aged 60–64 years, rapidly increasing to 7.0 per 1000 person years in those aged 90–94 years (Ruitenberg *et al.* 2001). The incidence of vascular dementia is significantly lower in women than men (overall rate ratio 0.6, 95% CI 0.3 to 1.0). This gender difference is most marked above 80 years of age (Ruitenberg *et al.* 2001).

RISK FACTORS

Not surprisingly for a vascular disorder, the most important risk factors are the usual classical vascular risk factors. In a population-based study it was found that each 10 mmHg increase in both systolic and diastolic blood pressure was associated with a 40% increase in the risk of vascular dementia (Ruitenberg 2000). A persistently elevated blood pressure is also associated with carotid atherosclerosis, identified by ultrasonography, and there is a significant relationship between the severity of atherosclerosis (based on carotid ultrasonography and peripheral arterial disease) and the prevalence of vascular dementia, especially in the presence of the ApoE 4 allele (Hofman *et al.* 1997). In a small hospital-based series of recent stroke patients, diabetes and atrial fibrillation were identified as risk factors for the occurrence of vascular dementia (Censori *et al.* 1996).

Because cholesterol is a key factor in the development of atherosclerosis, it is likely that vascular dementia occurs as a consequence of elevated blood levels of cholesterol. To date no studies have clarified this subject, but the recently completed PROSPER study did not find any effect of lowering cholesterol with pravastatin on cognitive decline, although there was no information on the incidence of dementia (Shephard *et al.* 2002).

PRIMARY PREVENTION

If increasing blood pressure leads to an increased risk of vascular dementia, it seems plausible that any decrease in blood pressure should reduce that risk. In the large population-based Rotterdam study, participants who were already using blood pressure lowering agents had a relative risk of 0.3 (95% CI 0.1 to 0.9) for the development of vascular dementia compared with those not on blood pressure lowering agents, irrespective of possible confounding factors such as diastolic and systolic blood pressure, diabetes, previous stroke, body-mass-index, smoking and atherosclerosis (int'l Veld *et al.* 2001). Light to moderate alcohol consumption is associated with relatively low risks of vascular disease (Berger *et al.* 1999). Hence blood pressure lowering and moderate alcohol intake *may* lead to a reduction in the risk of vascular dementia.

TREATMENT OF VASCULAR DEMENTIA

Daily aspirin (325 mg), in addition to control of the classical vascular risk factors, has been reported to stabilize or even improve cognitive function in patients with vascular dementia in a small randomised controlled trial (Meyer *et al.* 1989). But there are still no large randomised trials being conducted.

A common feature of most dementias is lack of acetylcholine in the brain, and evidence is accumulating that such a deficit may also play a role in the cognitive symptoms in vascular dementia (Grantham & Geerts 2002). One possible way of increasing the level of cerebral acetylcholine is by inhibiting its degradation by acetylcholine esterase. This therapeutic strategy has some effect in Alzheimer's disease but to date no data are available in vascular dementia.

Galantamine is a novel cholinergic drug that both inhibits acetylcholine esterase activity and stimulates the acetylcholine receptor. In a recently completed, large, randomised trial, there were beneficial effects of 24 mg daily on cognition, global function, functional abilities and behavioural symptoms in patients with probable vascular dementia (Erkinjuntti *et al.* 2002). The beneficial effects appeared to last for at least 6 months and may even be sustained for 12 months. However, these findings are derived from a post-hoc subgroup analysis and must be confirmed in further trials.

Other, still experimental, therapeutic strategies aim to improve cerebral blood flow in patients with vascular dementia by removing low-density lipoproteins and fibrinogen from the blood by means of heparin-induced extra corporeal low density lipoprotein precipitation,

which is a form of plasmaphoresis. In small, non-randomised studies with short follow-up of only two months, the cognitive function modestly improved (Walzl *et al.* 1995).

CONCLUSIONS

No neurologist will have any difficulty recognizing a patient with full-blown dementia after a stroke. But far more often the patients present with less obvious symptoms of subjective memory dysfunction or 'just being different than before the stroke'. It is important to recognize these cognitive symptoms so they can be explained to the patient and his or her family, and so that further cognitive decline can be ameliorated. Of course, it is also worth considering depression as an explanation for the cognitive symptoms. There is some evidence that adequate control of vascular risk factors may reduce the incidence of cognitive decline in stroke patients.

REFERENCES

Bennet DA, Gilley DW, Lee S, Cochran EJ (1994) White matter changes: neurobehavioral manifestations of Binswanger´s disease and clinical correlates in Alzheimer´s disease, *Dementia*, **5**, 148–52.

Berger K, Ajani UA, Kase CS *et al.* (1999) Light-to-moderate alcohol consumption and risk of stroke among US male physicians. *New England Journal of Medicine*, **341**, 1557–64.

Censori B, Manara O, Agostinis C *et al.* (1996) Dementia after first stroke. *Stroke*, **27**, 1205–10.

de Groot JC, de Leeuw FE, *et al.* (2000a) Cerebral white matter lesions and cognitive function, the Rotterdam Scan Study. *Annals of Neurology*, **47**, 145–51.

de Groot JC, de Leeuw FE, Oudkerk M *et al.* (2000b) Cerebral white matter lesions and depressive symptoms in elderly adults. *Arch Gen Psychiatry*, **57**,1071–76.

Erkinjuntti T, Inzitari D, Pantoni L *et al.* (2000) Limitations of clinical criteria for the diagnosis of vascular dementia in clinical trials. Is a focus on subcortical vascular dementia a solution? *Ann N Y Acad Sci*, **903**, 262–72.

Erkinjuntti T, Kurz A, Gauthier S *et al.* (2002) Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease, a randomised trial. *Lancet*, **359**, 1283–90.

Grantham C & Geerts H (2002) The rationale behind cholinergic drug treatment for dementia related to cerebrovascular disease. *J Neurol Sci*, **203–204**, 131–6.

Hennerici MG, Oster M, Cohen S, Schwartz A *et al.* (1994) Are gait disturbances and white matter degeneration early indicators of vascular dementia? *Dementia*, **5**, 197–202.

Hofman A, Ott A, Breteler MMB *et al.* (1997) Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet*, 349, 151–4.

in't Veld BA, Ruitenberg A, Hofman A, Stricker BH, Breteler MMB (2001) Antihypertensive drugs and incidence of dementia, the Rotterdam Study. *Neurobiological Aging*, **22**, 407–12.

Meyer JS, Rogers RL, McClintic K, Mortel KF, Lotfi J (1989) Randomized clinical trial of daily aspirin therapy in multi-infarct dementia. A pilot study. *Journal of the American Geriatric Society*, **37**, 549–55.

Orgogozo JM, Dartigues JF, Lafont S *et al.* (1997) Wine consumption and dementia in the elderly, a prospective community study in the Bordeaux area. *Rev Neurol (Paris)*, **153**, 185–92.

Ott A, Breteler MMB, van *et al.* (1995) Prevalence of Alzheimer's disease and vascular dementia, association with education. The Rotterdam study. *BMJ*, **310**, 970–3.

Pasquier F, Leys D, Scheltens P (1998) The influence of coincidental vascular pathology on symptomatology and course of Alzheimer's disease. *J Neural Transm*, **54** (Suppl), 117–27.

Roman GC, Tatemichi TK, Erkinjuntti T *et al.* (1993) Vascular dementia, diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*, **43**, 250–60.

Ruitenberg A (2000) *Vascular factors in dementia.* Thesis, Erasmus Medical Centre Rotterdam, The Netherlands.

Ruitenberg A, Ott A, van Swieten JC, Hofman A, Breteler MMB (2001) Incidence of dementia, does gender make a difference? *Neurobiolical Aging*, **22**, 575–80.

Ruitenberg A, van Swieten JC, Witteman JC *et al.* (2002) Alcohol consumption and risk of dementia, the Rotterdam Study. *Lancet*, **359**, 281–6.

Shephard J, Blauw GJ, Murphy MB *et al.* (2002) Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised clinical trial. L*ancet*, 360, 1623–30.

Tarvonen-Schroder S, Roytta M, Raiha I *et al.* (1996) Clinical features of leuko-araiosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **60**, 431–6.

Tatemichi TK (1990) How acute brain failure becomes chronic, a view of the mechanisms of dementia related to stroke. *Neurology*, **40**, 1652–9.

Tatemichi TK, Desmond DW, Mayeux R *et al.* (1992) Dementia after stroke, baseline frequency, risks, and clinical features in a hospitalized cohort. *Neurology*, **42**, 1185–93.

van Gijn J (200) White matters, small vessels and slow thinking in old age. *Lancet*, **356**, 612–3.

Van Zandvoort MJ, Kappelle LJ, Algra A, De Haan EH (1998) Decreased capacity for mental effort after single supratentorial lacunar infarct may affect performance in everyday life. *Journal of Neurology, Neurosurgery and Psychiatry*, **65**, 697–702.

Walzl M, Walzl B, Lechner H (1994) Results of a two-month follow-up after single heparin induced extracorporeal LDL precipitation in vascular dementia. *Stroke Cerebrovasc Dis*, **4**,179–182.

World Health Organization (1991) The Neurological adaptation of the International Classification of Diseases (ICD 10). Geneva, World Health Organization.