Vascular Dementia

6

Contents

Synonyms

Vascular dementia (VaD), post-stroke dementia, multi-infarct dementia, strategic infarct dementia, arteriosclerotic dementia, Binswanger's disease, 'état lacunaire', subcortical ischaemic vascular dementia (SIVD)

6.1 Introduction

Vascular dementia (VaD) is the second most common type of dementia after AD, especially in the elderly. Recently, the scope of VaD has been broadened to include also more subtle cognitive dysfunction that can be caused by vascular damage to the brain, designated as 'vascular cognitive impairment'. The term VaD implies the existence of dementia, which is assumed to be secondary to cerebrovascular disease. Not only is the latter difficult to prove, VaD is also a heterogeneous entity. It encompasses a group of conditions related to a variety of pathophysiological vascular mechanisms. The neuropathological changes associated with VaD include multifocal and/or diffuse disease, and also single focal lesions. The range of pathology includes:

- Diffuse confluent age-related white matter changes (ARWMC)
  - Also referred to as subcortical arteriosclerotic encephalopathy (SAE)
- Multi-lacunar state ('état lacunaire')
- Multiple (territorial) infarcts
- Strategic cortical–subcortical or watershed lesions
- Cortical laminar necrosis (granular cortical atrophy)
- Delayed post-ischaemic demyelination (see Sect. 7.5.5)
- Hippocampal sclerosis

F. Barkhof et al., *Neuroimaging in Dementia*,
DOI: 10.1007/978-3-642-00818-4_6, © Springer-Verlag Berlin Heidelberg 2011

Reflecting this heterogeneity, the underlying vascular pathology may involve either the grey or the white matter, the small or the large vessels and have a local or systemic cause. In any case, brain imaging is essential for the diagnosis, as it reveals most of the (macroscopic) cerebrovascular pathology.

Given that VaD has many expressions and even more causes, we attempt to classify it in this chapter by the main underlying pathophysiological mechanism (i.e. large vessel, small vessel, systemic). Within the group of small vessel disease, several homogenous disorders can be discerned from the garden variety; these will be discussed in Sect. 6.4.3. Likewise, within the group of systemic disorders, several specific diseases can be singled out (e.g. vasculitis). Deep venous thrombosis and dural arteriovenous fistulae are also vascular abnormalities that may rarely cause venous hypertensive encephalopathy or bilateral thalamic congestion, and lead to dementia. Since the latter are associated with brain swelling, they will be discussed in Chap. 8.

The relevance of many vascular lesions in patients with dementia is often unclear, given the frequent coexistence of vascular and degenerative pathology, especially in the very old. In addition, cerebrovascular disease and late-onset Alzheimer disease (AD) share common risk factors. The concept of VaD is changing but – regardless of what it may be – it is fair to say that there is a considerable proportion of patients with dementia and substantial cerebrovascular disease. The pathophysiological interplay and overlap between AD and VaD is discussed in Sect. 6.7 in more detail.

6.2 History and Nosology

6.2.1 *Binswanger's Disease, 'État lacunaire', Multi-infarct Dementia, Strategic Infarct Dementia – Current Concepts*

In 1672, Thomas Willis provided the first accurate clinical observations of patients with post-stroke dementia. In 1894, Otto Ludwig Binswanger described the so-called *encephalitis subcorticalis chronica progressiva* and 'arteriosclerotic cerebral degeneration'. The following year, Aloïs Alzheimer wrote about 'arteriosclerotic atrophy of the brain'. Both of them were probably referring to a clinical condition characterised by slowly progressive dementia and subcortical white matter atrophy. It was assumed that the white matter atrophy was secondary to vascular insufficiency and could result in dementia. In 1896, the term 'arteriosclerotic dementia' was included in the text book *Psychiatrie* by Emil Kraepelin. It became clear that 'arteriosclerotic dementia' was a clinical condition that should be differentiated from the neurosyphilitic general paresis of the insane (dementia *paralytica*), a major cause of dementia and insanity at that time. In 1902, Alzheimer named the clinical condition believed to be secondary to vascular insufficiency (not to focal cerebrovascular lesions) as Binswanger's disease. Currently, Binswanger's disease is considered a synonym for subcortical ischaemic VaD due to diffuse confluent microvascular white matter damage.

The term lacune (derived from the Latin word *lacuna*, plural: *lacunae* – meaning 'depth' or 'loss') was first described by Amédée Dechambre in 1838. Although lacunes are usually considered to result from ischaemic infarcts of the deep perforating small vessels, the term is sometimes (confusingly) also used to encompass microhaemorrhages and enlarged perivascular (Virchow–Robin) spaces, according to a classification proposed by Poirier and Derouesné in 1984. Durand-Fardel described the so-called 'état criblé' in 1842, a denomination that now refers to the occurrence of multiple enlarged Virchow–Robin spaces in the basal ganglia (see Fig. 3.14). In 1901, Pierre Marie introduced the term 'état lacunaire' (lacunar state), still used to describe subcortical ischaemic VaD secondary to multiple lacunar infarcts.

In 1974, the term multi-infarct dementia (MID) was coined by Vladimir Hachinski and colleagues as a cause of mental deterioration in the elderly due to multiple strokes, giving the clinicians a new perspective that (multi) focal cerebrovascular lesions could lead to dementia. The rationale underlying the concept of MID was that multiple infarcts would have a synergistic effect on mental functions, resulting in dementia independently of the specific location (topography) or severity of lesions.

In 1975, Hachinski et al. also proposed a clinical scale to aid in the differentiation between what was then called MID and AD. The scale represents a set of clinical features thought to be characteristic of dementia caused by vascular disease, and characteristics of

vascular disease in itself: abrupt onset, stepwise deterioration and fluctuating course, history of strokes and focal neurological signs. However, the scale does not take into account imaging criteria; neither does it provide any evidence for a causal relationship between dementia and vascular disease. Although the corresponding score is still useful as a 'bedside' clinical tool to distinguish between AD and VaD, the scale ignores the fact that both neurodegenerative and vascular pathology frequently coexist, a notion increasingly supported by neuroimaging and pathological findings. Currently, this perhaps represents the major limitation of the Hachinski ischaemic score.

The advent of modern neuroimaging with computed tomography (CT) and magnetic resonance imaging (MRI) allowed for a better diagnosis and reclassification of MID and VaD. In 1993, the National Institute of Neurological Disorders and Stroke (NINDS)–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) formulated criteria that recognised structural neuroimaging as a crucial element for the diagnosis of VaD, providing indications on the topography and severity of cerebrovascular lesions thought to be causative of dementia. In 1995, the term strategic infarct dementia was proposed by Tatemichi and colleagues for patients with an abrupt change in behaviour after acute (single) infarcts occurring in functionally critical areas of the brain, as documented by CT or MRI. Currently, both MID and strategic infarct dementia are not very widely used terms anymore, but both can be considered as synonyms of large vessel VaD – the subgroup of VaD secondary to multiple or single strategic large vessel cortical–subcortical or subcortical (e.g. watershed) cerebrovascular lesions.

Neuroimaging also provided added value for the detection of cerebrovascular lesions, as small vessel disease, and so-called silent strokes may occur without noticeable clinical symptoms. Finally, neuroimaging has shown that an overlap may exist between different expressions of cerebrovascular disease in patients with VaD, such as coexistence of large vessel and small vessel disease. Actually, a patient with VaD may either have diffuse confluent ARWMC and/or multiple lacunes (isolated small vessel disease), infarcts located in strategic regions of the brain (isolated large vessel disease) or a combination of both. Furthermore, and as previously mentioned, neuroimaging is increasingly providing evidence (supported by pathological findings) that cerebrovascular and neurodegenerative pathology frequently coexist.

6.2.2 Current Diagnostic Criteria and Limitations

Vascular pathologies like atherosclerosis and arteriolosclerosis are extremely common in the general (ageing) population. They are a necessary, but not sufficient prerequisite for the diagnosis of VaD. Ideally, criteria for VaD should include criteria for dementia, vascular disease and some sort of evidence for a relation between the two. In practice, the latter may be rather difficult to establish and even falsely assumed, for example. AD may develop in elderly subjects with concomitant atherosclerosis. By contrast, in some clearly vascular cases (e.g. extensive white matter disease), it may be difficult to proof the vascular nature of the lesions, especially when the usual risk factors (e.g. hypertension, diabetes, smoking or hypercholesterolaemia) are absent. The issue is further complicated by the fact that VaD is quite a heterogeneous group of disorders and by the fact that agreement among neuropathologists on the exact criteria and their interpretation is limited – there is not a true gold standard. Therefore, it is important to use strict diagnostic criteria for VaD that will be discussed in the following sections, and not over-interpret the finding of vascular changes in the elderly presenting with cognitive decline, since such abnormalities are ubiquitous.

6.2.2.1 DSM-IV Criteria for Vascular Dementia

In 1994, the DSM-IV criteria for VaD were proposed by the American Psychiatric Association on the basis of a general definition of dementia (Table 6.1). Vascular disease is clinically defined (physical examination) or inferred from laboratory evidence. No criteria are mentioned to establish a causal relationship between dementia and vascular disease ('judged to be aetiologically related').

Note that the DSM-IV criteria for VaD do not really require neuroimaging evidence of cerebrovascular damage. More specific criteria including neuroimaging features for VaD will be discussed in the following sections.

Table 6.1 DSM-IV criteria for vascular dementia

(**a**) Multiple cognitive deficits manifested by both memory impairment and one or more of the following cognitive disturbances: aphasia, apraxia, agnosia, disturbance in executive functioning
(**b**) The cognitive deficits cause significant impairment in social or occupational activities and represent a significant decline from a previous level of functioning
(**c**) Focal neurological signs and symptoms (e.g. exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g. multiple infarcts involving the cortex and the underlying white matter) that are judged to be aetiologically related to the disturbance
(**d**) The deficits do not exclusively occur during the course of a delirium

6.2.2.2 NINDS-AIREN Criteria for Vascular Dementia

In comparison to histopathological examination, the most specific diagnostic criteria for VaD are those formulated by NINDS-AIREN. These criteria were developed for research purposes and emphasise the heterogeneity of both clinical syndromes and pathological subtypes of VaD, the need to establish a temporal relation between stroke and the onset of dementia as well as the crucial importance of brain imaging to support clinical findings. The clinical and radiological parts of the NINDS-AIREN criteria were proposed in 1993 – operational definitions for their radiological part were subsequently specified in 2003 and will be discussed in the following section.

6.2.2.3 Operational MRI Definitions for the NINDS-AIREN Criteria

The NINDS-AIREN criteria provide a list of possible vascular lesions considered relevant for the pathogenesis; however, without clearly defining their imaging criteria in terms of topography and severity of lesions. To enhance their clinical implementation, operational definitions for the radiological part of the NINDS-AIREN criteria were subsequently defined (Table 6.2).

6.2.3 *Towards More Homogeneous Criteria*

By far, most patients with VaD have small vessel rather than large vessel disease. Therefore, research criteria were specifically formulated for subcortical ischaemic VaD, now recognised as the most broad and homogeneous subtype. Recognising that the NINDS-AIREN criteria do not cover the subgroup of patients with small vessel VaD in too much detail, Erkinjuntti and colleagues proposed separate criteria for subcortical ischaemic vascular dementia (SIVD) in 2000. The brain imaging criteria are described in Table 6.3 – these encompass Binswanger's disease and 'état lacunaire'.

6.3 Large Vessel Vascular Dementia

Synonyms

Large vessel vascular dementia (VaD), post-stroke dementia, multi-infarct dementia, strategic infarct dementia

Large vessel VaD results from multiple or single cortical–subcortical or subcortical (e.g. watershed) cerebrovascular lesions involving strategic regions of the brain, such as the hippocampus, paramedian thalamus and the thalamocortical networks.

6.3.1 *Aetiology, Pathology and Genetics*

The risk factors for VaD are believed to be the same as those for stroke in general. The aetiology and pathology of large vessel VaD may be described considering either the type of brain lesion or the underlying type of vessel abnormality. Brain lesions mostly include: large vessel cortical–subcortical or subcortical infarcts (e.g. watershed infarcts) and haemorrhages. Vessel abnormalities encompass atherosclerosis and embolic sources. Vasculitis is another cause of large vessel disease (see Sects. 6.5 and 7.2).

Table 6.2 Operational imaging definitions for the NINDS–AIREN criteria

(**a**) Topography criteria Large vessel stroke – arterial territorial infarct involving the cortical grey matter • Anterior cerebral artery (ACA) infarcts – only bilateral ACA infarcts suffice • Posterior cerebral artery (PCA) infarct – involving one of the following regions: 1. Paramedian thalamus (in contact with the third ventricle) 2. Inferior medial temporal lobe
• Association areas – a middle cerebral artery (MCA) infarct involving: 1. Parieto-temporal cortex (e.g. angular gyrus) 2. Temporo-occipital cortex
• Watershed territories – infarcts between MCA and ACA or between MCA and PCA involving: 1. Superior frontal region 2. Parietal region
Small vessel disease • Ischaemic pathology resulting from occlusion of small perforating arteries: 1. Extensive white matter lesions (leukoaraïosis), or 2. Multiple basal ganglia, thalamic and frontal white matter lacunar infarcts: i. ≥2 lacunar infarcts in the basal ganglia, thalamus or internal capsule, AND ii. ≥2 lacunar infarcts in the frontal white matter, or 3. Bilateral thalamic lesions
(**b**) Severity criteria • Large vessel disease of the dominant hemisphere – in the absence of clinical information, the left hemisphere is considered to be the dominant one • Bilateral large vessel hemispheric strokes – only the infarct located in the non-dominant hemisphere should involve an area listed under topography • Extensive leukoencephalopathy involving at least ¼ of the total white matter: – Confluent lesions – grade 3 on the ARWMC scale – in at least two regions, AND – Beginning confluent – grade 2 on the ARWMC scale – in two other regions
(**c**) Fulfilment of radiological criteria for probable VaD • Large vessel disease – a lesion must be scored in at least one subsection of both topography and severity (both the topography and severity criteria should be met) • Small vessel disease – for white matter lesions, both the topography and severity criteria should be met; for multiple lacunar infarcts and bilateral thalamic lesions, only the topography criterion is sufficient

Source: Modified from Stroke 2003;34:1907–1912.

Table 6.3 Neuroimaging criteria for subcortical ischaemic vascular dementia (SIVD)

(**a**) Computed tomography: Extensive periventricular and deep WM lesions: patchy or diffuse symmetrical low attenuation AND Absence of cortical or cortical–subcortical (non-lacunar) territorial infarcts, watershed infarcts, or haemorrhages indicating large vessel disease. No other cause of WM lesions
(**b**) Magnetic resonance imaging: 1. Extensive periventricular and deep WM lesions, and lacune(s) in the deep grey matter OR 2. Multiple lacunes (e.g. >5) in the deep grey matter, and at least moderate WM lesions AND Absence of cortical and/or cortical–subcortical (non-lacunar) territorial infarcts, watershed infarcts, haemorrhages, and other specific causes of white matter lesions

Source: Adapted from J Neural Transm Suppl 2000;59:23–30

Infarcts may either be complete or incomplete. Complete infarcts correspond to areas of tissue destruction/liquefaction and are the most frequent pathological findings in large vessel VaD. Incomplete infarcts may only represent demyelination and oedema and are mostly due to small vessel pathology. Therefore, they will be more extensively discussed in Sect. 6.4.

Genetic factors play a role in VaD. Genes conferring susceptibility to vascular cognitive impairment may be grouped into two different classes: genes that confer susceptibility to cerebrovascular disease and genes that determine the brain tissue response to cerebrovascular insults. As to the former, some progress has been made in identifying genes that confer susceptibility to hypertension and stroke during the past few years. In addition, several monogenic forms of cerebrovascular disease have been identified. The best defined examples relate to small vessel VaD (Sect. 6.4.3). Even less is known about genes that determine brain tissue vulnerability to cerebrovascular disease, but they include the ones related with AD, such as the apolipoprotein E genes, which play a role in subjects with ARWMC (see also Sect. 6.7).

6.3.2 Clinical Presentation, Epidemiology and Treatment

A diagnosis of vascular cognitive impairment or dementia is made by demonstrating the presence of cognitive change from medical history and examination, and by showing that the patient had vascular events sufficient to produce the cognitive change; the latter requirement can be difficult, even in large vessel VaD. From the clinical point of view, findings that increase the likelihood of large vessel VaD are a history of transient ischaemic attack (TIA) and/or cerebrovascular accident, 'stepwise decline' in mental status, and the presence of abnormal neurologic signs. In general, executive dysfunction is commonly seen in VaD and memory impairment is usually less severe than in AD.

The reported frequency of large vessel VaD in demented populations is very variable among studies. Up to one third of stroke survivors exhibit dementia within 3 months after their stroke. As with cerebrovascular disease in general, treatment options include control of vascular risk factors.

6.3.3 Neuroimaging Strategy and Key Findings in Large Vessel VaD

In general, T2-weighted MRI sequences (including FLAIR) are far more sensitive to depict cerebrovascular disease than CT, although CT was found to be more specific than MRI in predicting subsequent symptomatic cerebrovascular disease. However, both modalities perform relatively well in depicting the large vessel infarcts that may cause VaD. Marked hypointensity on T1-weighted images usually represents tissue destruction, and is a marker for complete infarcts (Fig. 6.1).

The key neuroimaging features to identify patients with large vessel VaD rely on the assessment of the topography and severity of large vessel disease, according to the NINDS-AIREN criteria (Table 6.2 and Fig. 6.2).

More advanced neuroimaging modalities, such as diffusion-weighted imaging (DWI) and perfusion MR or CT techniques like CT angiography and perfusion may be of use in VaD. In particular, the value of DWI is already well established in clinical practise for the diagnosis of recent onset ischaemia

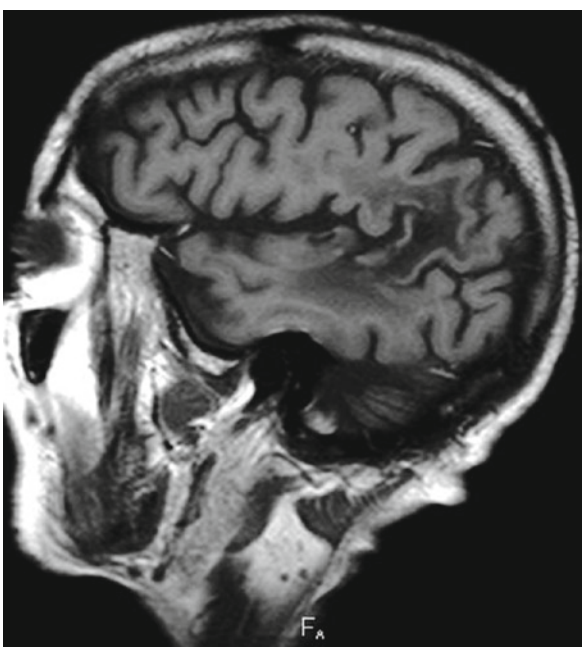

Fig. 6.1 Parasagittal left T1-weighted image showing a cortical–subcortical hypointensity in the parietal-temporal region involving the left angular gyrus, which is part of a critical association area of the brain. The hypointensity on T1 represents tissue destruction – complete infarct

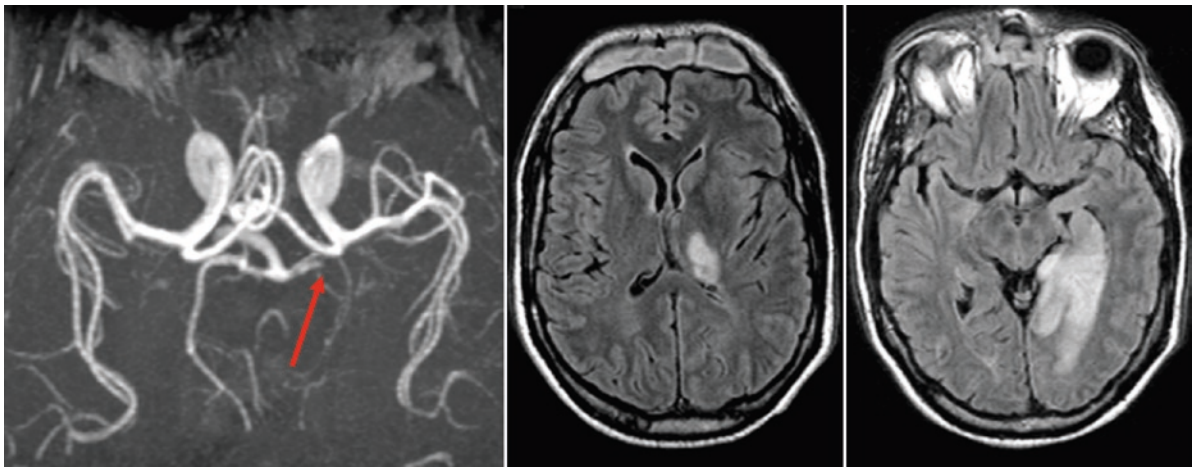

Fig. 6.2 Medial temporal lobe infarct of dominant hemisphere. MRA (*left*) shows an occlusion in the left posterior cerebral artery (*arrow*), and FLAIR (*middle* and *right*) depicts an infarction involving both the left thalamus and the left medial temporal lobe (including the hippocampal body)

(Fig. 3.7). DWI may detect recent infarcts causing the so-called stepwise decline in patients with large vessel VaD.

MR/CT and catheter angiography (DSA) may also be useful to identify occluded vessels (Fig. 6.2), arterial stenoses and extracranial arterial dissections. Doppler sonography may complement the assessment of arterial stenoses and dissections. Angiographic techniques are crucial for the diagnosis of less frequent pathologies that may rarely cause dementia and involve large vessels, such as deep venous thrombosis (Fig. 6.3) and dural arteriovenous fistulae (Chap. 8). Catheter angiography (DSA) can be useful for the interventional therapy of these abnormalities.

6.3.4 Differential Diagnosis

The differential diagnosis of large vessel VaD mostly corresponds to the one applied to cerebrovascular disease involving large vessels in general and includes, for example:

- Cerebral amyloid angiopathies (Sect. 6.4.3.2)
- Vasculitis (Sect. 6.5)
- Sickle cell disease (Sect. 6.6.1)
- Infections; for example syphilis (Sect. 7.2.4)
- Mitochondrial diseases (Sect. 7.4.3)
- Venous thrombosis and dural arteriovenous fistulae (Chap. 8)

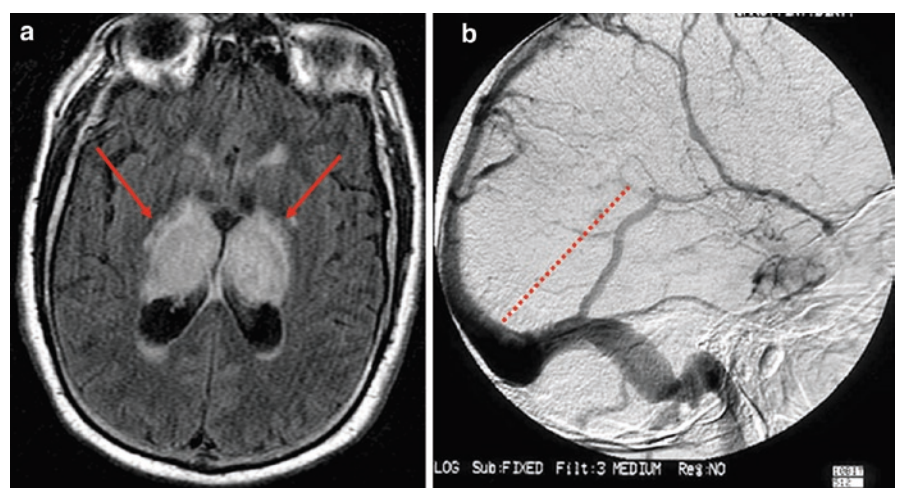

Fig. 6.3 Deep venous thrombosis with thalamic congestion. Axial FLAIR (**a**) showing bilateral thalamic hyperintensity (*red arrows*) due to venous congestion caused by a straight sinus thrombosis, confirmed by digital subtraction angiography (**b**), which fails to opacify the deep veins including straight sinus (*dotted line* represents expected course)

- Moyamoya disease
- Fibromuscular dysplasia
- Cardiac or other source of emboli

6.4 Small Vessel Vascular Dementia

Synonyms

Small vessel vascular dementia (VaD), arteriosclerotic dementia, Binswanger's disease, 'état lacunaire', subcortical ischaemic vascular dementia

6.4.1 Age-Related White Matter Changes, Lacunes, 'État criblé' – What Is Abnormal for Age?

Small vessel VaD may either result from diffuse confluent white matter lesions (Binswanger's disease) or from multiple subcortical lacunar infarcts ('état lacunaire'). According to the NINDS-AIREN criteria, it may result from bilateral thalamic lesions (Fig. 6.4) as well. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is also an example of a clinical condition representing small vessel VaD (see Sect. 6.4.3.3). Cerebral amyloid angiopathies (CAA) are additional subtypes of small vessel VaD (see Sect. 6.4.3.2), but they may have associated large vessel pathology, such as deposition of amyloid in the wall of medium-to-large vessels leading to cortical–subcortical (lobar) haemorrhages. Both CADASIL and some forms of CAA have a genetic basis.

Ischaemic pathology resulting from occlusion of small perforating arteries (Fig. 6.5) may become apparent as white matter lesions or as focal infarcts of the deep small vessels (e.g. lacunar infarcts).

As mentioned in Sect. 4.4, white and deep grey matter hyperintensities on T2-weighted images and FLAIR images are generally considered surrogate markers of ischaemic small vessel disease in elderly subjects. Given that white matter hyperintensities progressively accumulate with age, they are usually

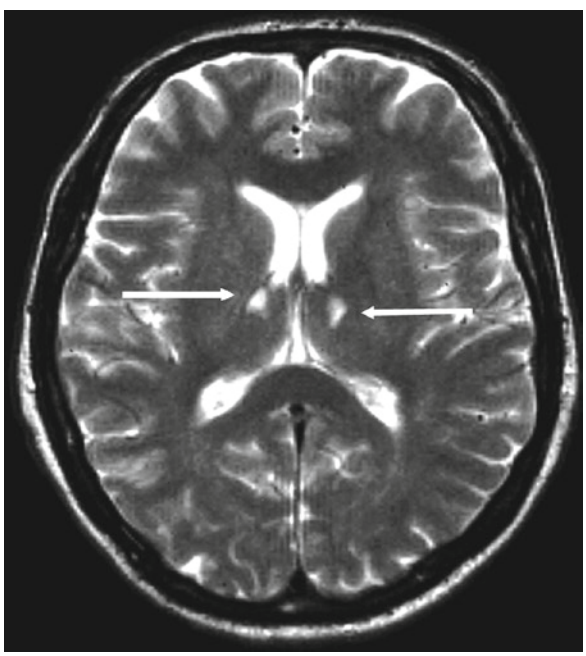

Fig. 6.4 Bilateral thalamic infarcts. Axial T2-weighted image showing bilateral thalamic infarcts (*white arrows*), a feature sufficient to diagnose VaD according to the NINDS-AIREN criteria

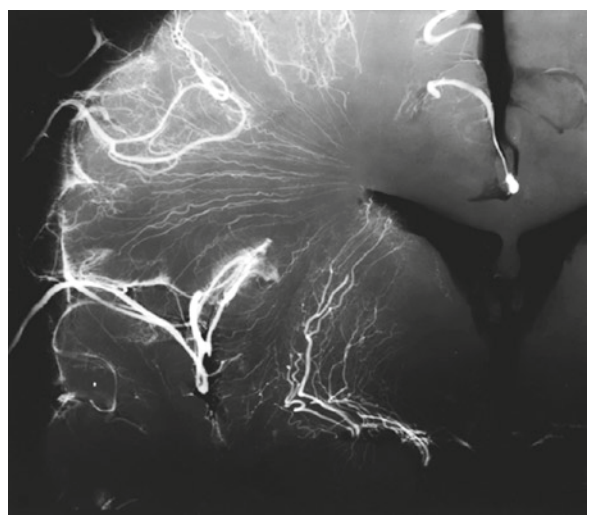

Fig. 6.5 Deep white matter vasculature. Post-mortem radiograph of a normal cerebral hemisphere after the injection of a barium sulphate-gelatin suspension into the right middle cerebral artery. This X-ray demonstrates that the periventricular and deep white matter, and the deep grey matter nuclei are irrigated by long, perforating medullary arteries that are relatively small in diameter (small vessels), exit at right angles from their 'parent' vessels, and give few or no collaterals. As such, the regions supplied by these small vessels constitute a 'watershed territory' susceptible to ischaemia in the presence of decreased cerebral perfusion (Reproduced with permission from Coffey CE, Figiel GS. Neuropsychiatric significance of subcortical encephalomalacia. In: Carrol BJ, Barret JE, editors. Psychopathology and the brain. Raven; 1991)

referred to as age-related white matter changes, or ARWMC. Moreover, they are associated with vascular risk factors as well as with other types of cerebrovascular lesions. According to the NINDS-AIREN criteria, white matter changes alone may be sufficient to cause dementia when at least ¼ of the white matter is involved (Table 6.2). Although this proportion has been defined arbitrarily, it is in accordance with the finding that only severe white matter disease is associated with cognitive dysfunction.

Diffuse confluent ARWMC are always abnormal for age. In fact, extensive white matter changes predominantly involving the periventricular and deep white matter, but relatively sparing the U-fibres, are the imaging correlate of Binswanger's disease. By contrast, in patients with CADASIL, diffuse white matter signal abnormalities involving the U-fibres predominantly occur in the temporal, temporopolar and frontal regions. Microbleeds (see Sects. 3.2, 3.3 and 4.3.1) are also present in a considerable proportion of patients with CADASIL, as well as in patients with CAA.

The occurrence of multiple enlarged Virchow–Robin spaces in the basal ganglia, a condition referred to as 'etát criblé' (see Sect. 4.3) is also pathological. The association of 'état criblé' with diffuse confluent white matter lesions (Fig. 6.6), and cognitive impairment is a frequent finding.

6.4.2 Subcortical Ischaemic Vascular Dementia

Most patients with a diagnosis of VaD have small vessel rather than large vessel disease. Subcortical ischaemic VaD is now recognised as the most broad and homogeneous subtype of small vessel VaD. It encompasses both Binswanger's disease and 'état lacunaire'.

6.4.2.1 Aetiology, Pathology and Genetics

The risk factors for subcortical ischaemic VaD also include risk factors for stroke, in general, especially those leading to small vessel disease, such as hypertension and diabetes. The aetiology and pathology of subcortical ischaemic small vessel VaD may be classified by either the type of brain lesion or the underlying type of vessel abnormality:

- Brain lesions
  - Small vessel cortical microinfarcts
  - Infarcts of the perforating deep small vessels
  - 'État criblé' (multiple enlarged deep grey matter Virchow–Robin spaces)
  - Microbleeds
  - Diffuse white matter lesions (incomplete infarctions)

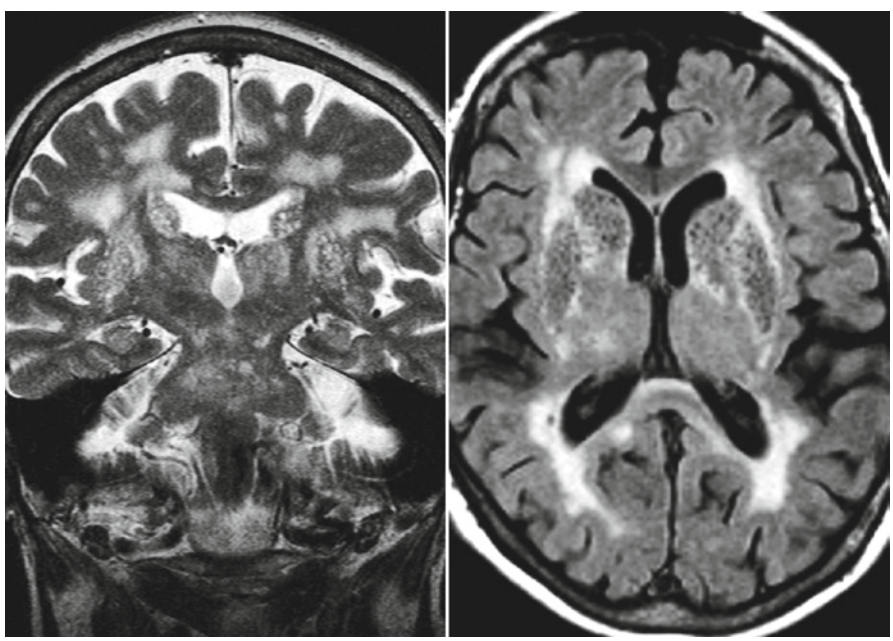

Fig. 6.6 'État criblé' with extensive white matter hyperintensities (WHM). Coronal T2-weighted (*left*) and axial FLAIR (*right*) images showing multiple enlarged perivascular spaces in the basal ganglia ('état criblé') and diffuse confluent WMH highly suggestive of ischaemic small vessel disease

- Vessel abnormalities include:
  - Atherosclerosis
  - Arteriolosclerosis
  - Amyloid angiopathy
  - Embolic sources

The two major pathological expressions of small vessel disease are lacunar infarcts (complete infarction) and white matter changes (incomplete ischaemic changes). Although small vessel disease is more likely to cause white matter changes, it certainly causes grey matter abnormalities as well (e.g. microinfarcts). Microinfarcts are not currently depicted by means of the available conventional neuroimaging modalities (Fig. 6.7).

Lacunar infarcts are complete infarcts of deep small vessels. Some authors also consider this definition dependent on size (from 2–3 to 15–20 mm in diameter). Enlarged Virchow–Robin spaces correspond to extensions of the subarachnoid space around small vessels and may be misclassified as cystic lacunar infarcts, especially when they are large or irregular. Diffuse white matter lesions usually represent incomplete infarcts. From the pathological point of view, they may correspond to diffuse myelin and axonal loss (demyelination), oedema, gliosis, spongiosis (vacuolation) and to breakdown of ependymal lining.

Genes that determine brain vulnerability to cerebrovascular disease seem to play a relevant role in subjects with ARWMC – including those related to AD, for example presenilins, amyloid precursor protein and the apolipoprotein E genes (see also Sect. 6.7).

6.4.2.2 Clinical Presentation, Epidemiology and Treatment

Many individuals with microvascular ischaemic VaD have a significant amount of white matter changes before presenting with a clinically recognised transient

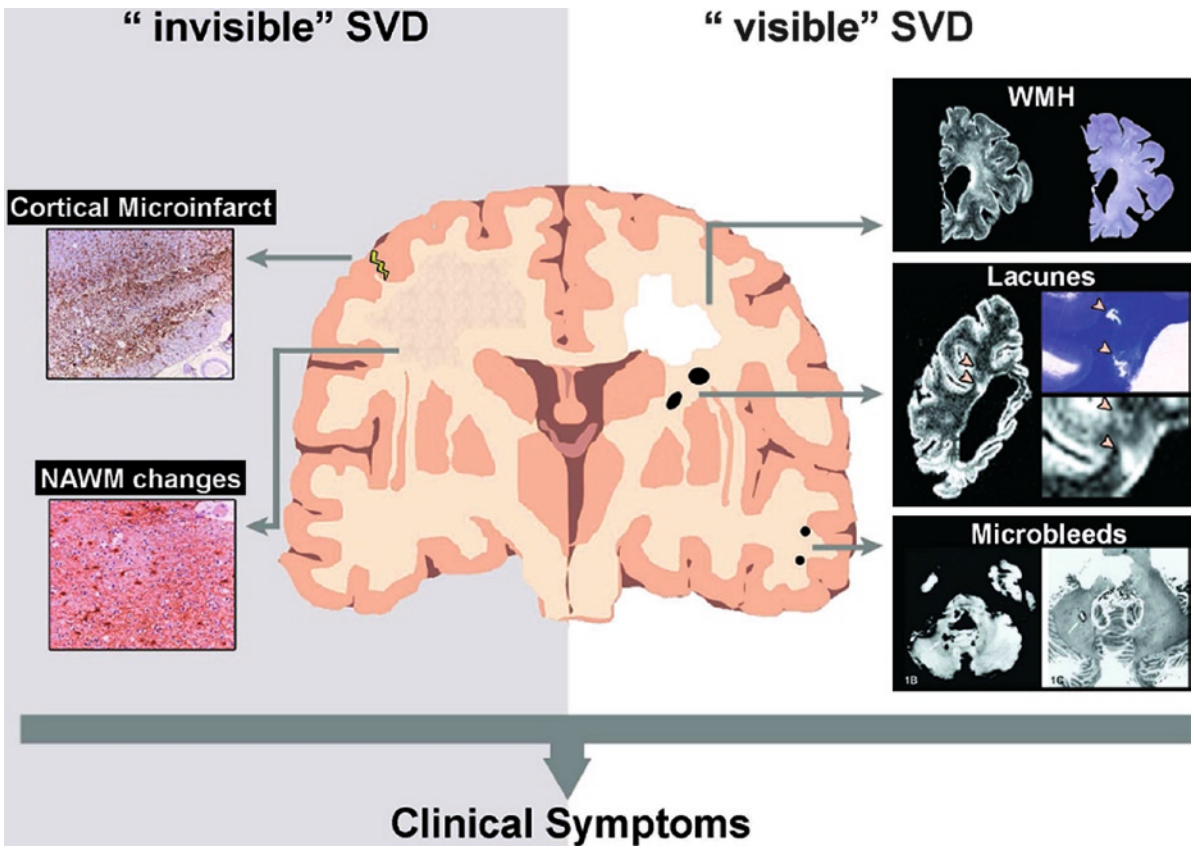

Fig. 6.7 A schematic representation of small vessel disease (SVD). Different expressions of SVD are shown, including post-mortem fluid-attenuated inversion recovery magnetic resonance images and histological sections. Note that cortical microinfarcts and normal-appearing white matter changes are only histopathologically depicted. (Illustration kindly provided by Dr. Alida A. Gouw)

ischaemic attack or stroke. As the disease may be slowly progressive, it usually lacks the so-called stepwise decline more typical of large vessel VaD. Neuroimaging is, therefore, even more relevant for the diagnosis. From the neuropsychological point of view, the most striking characteristics are executive dysfunction, mental slowness, problems with decision making, poor organisational ability, difficulties in adjusting to change (impaired executive functions of the frontal lobe), attention difficulties and apathy. This clinical syndrome has been called subcortical dementia. Whereas present, memory dysfunction is not the principal feature. Gait abnormalities may be a clinical clue.

Vascular disease of the brain, particularly hypertensive small vessel disease, is a more important factor in producing cognitive impairment and dementia than previously thought. Due to the possible concomitance between vascular and neurodegenerative pathology, the true incidence of vascular versus mixed dementia is unknown. However, subcortical ischaemic VaD represents the most broad and homogeneous subtype of patients with dementia attributable to cerebrovascular disease.

The primary treatment for subcortical ischaemic VaD is the control of vascular risk factors. It is expected that with an early identification and treatment of risk factors, vascular cognitive impairment and dementia could decrease, but this still remains uncertain. In addition to classical vascular risk factors (smoking, hypertension, diabetes, cholesterol) it may be worthwhile to exclude less common risk factors, for example vitamin B deficiency, mild hyperhomocysteinaemia and even Fabry disease and clotting disorders.

Once cognitive problems are present, studies have shown that cholinesterase inhibitors are effective. As in AD, the results are modest and only seen in some patients, but they are useful and should be considered when deciding to start treatment.

6.4.2.3 Neuroimaging Strategy and Key Findings

White matter changes on MRI are visible as diffuse hyperintense abnormalities on T2 and FLAIR (Fig. 6.8), but usually not prominently hypointense on T1-weighted images as in true infarction with liquefaction (Fig. 6.1). On CT, white matter changes appear as mildly hypodense areas, sometimes referred to as leukoaraïosis.

Patients with subcortical ischaemic VaD have widespread (diffuse or multifocal) cerebrovascular supratentorial pathology. In addition, infratentorial abnormalities are also frequent among these patients (Fig. 6.9).

The combination of different types of MR images is important to correctly detect and classify brain abnormalities. As previously mentioned, hypointensity on T1-weighted MR usually represents tissue destruction, a surrogate marker for complete infarcts. Conversely, ischaemic abnormalities, hyperintense on T2 and isointense on T1 (e.g. ARWMC), represent incomplete infarcts. FLAIR images enable identification of cystic lesions, and the combination of FLAIR with T1 may be useful to differentiate the more aggressive lesions from those that might be less likely to cause cognitive impairment.

Lacunar infarcts are focal complete infarcts of deep small vessels. Contrary to focal incomplete infarcts, lacunar infarcts are markedly hypointense on T1 (Fig. 6.9) and FLAIR. Actually, lacunar infarcts may have signal intensity similar to CSF on all MR sequences, although FLAIR may often reveal an irregular rim of hyperintensity around the lacune; see Fig. 3.12. Finally, the sensitivity of T2-weighted images to depict thalamic lesions is superior to FLAIR and, given the well-known clinical relevance of these lesions, FLAIR should not be used as the only T2-weighted sequence to detect thalamic lesions in patients suspected of having VaD (Fig. 3.5).

Perfusion-weighted imaging is an advanced MR technique that constitutes a good alternative to nuclear medicine for the evaluation of microvascular changes in the brain. In particular, arterial spin labelling (ASL) represents a promising MR technique to evaluate brain perfusion in patients with or at risk of having VaD (Sect. 3.4.2).

Neuroimaging modalities other than MR or CT may also play a role in small vessel VaD. Transcranial Doppler sonography is now able to provide valuable information on cerebrovascular resistance, cerebrovascular reserve and cerebral perfusion. Patients with small vessel VaD have a significant increase in vascular resistance and a decrease in vascular reserve.

6.4.2.4 Differential Diagnosis

The causal relation between vascular lesions alone and dementia is not always clear. Such a relation may be expected when patients are young and unlikely to have associated Alzheimer's pathology; when cognitive

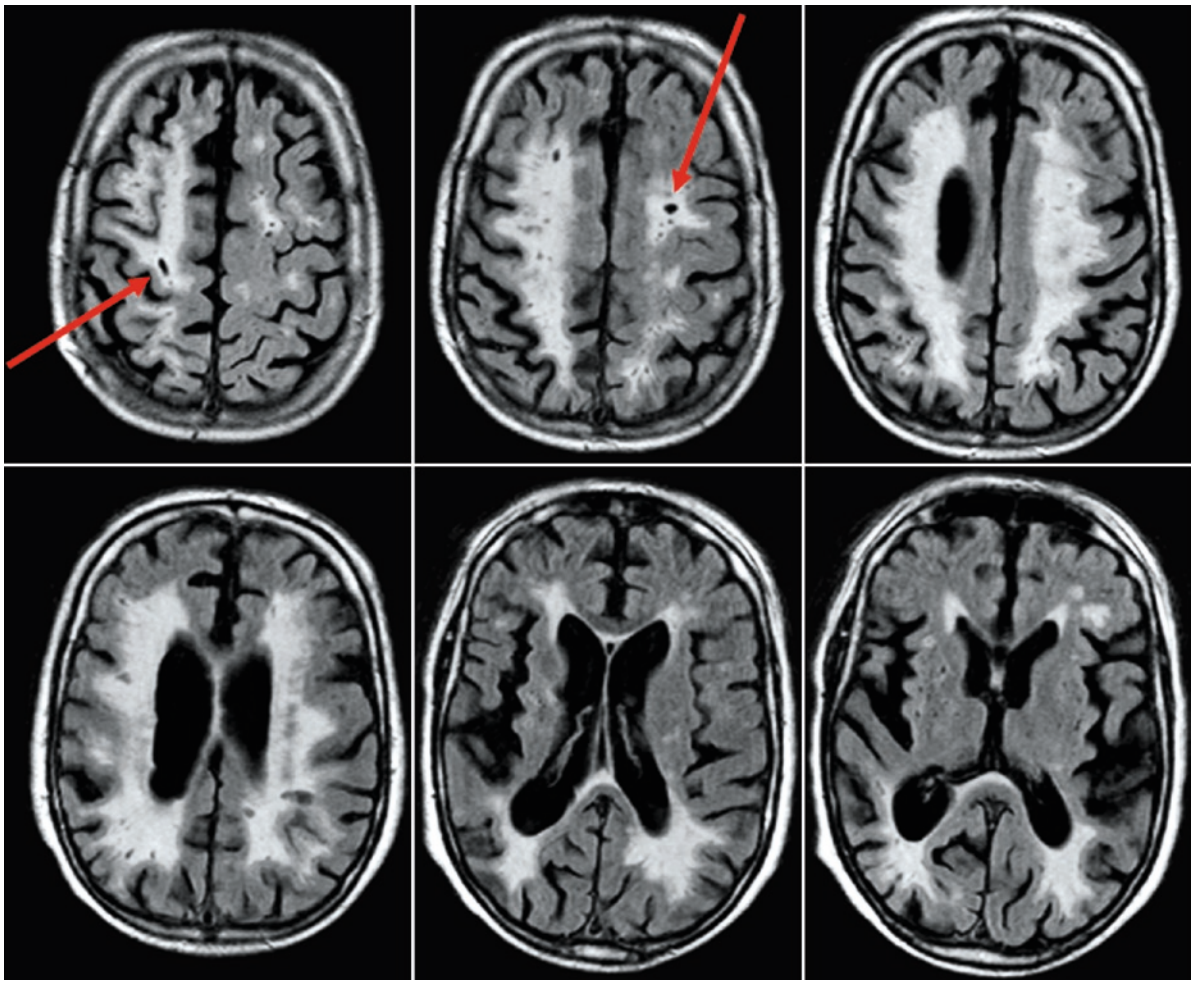

Fig. 6.8 Extensive and diffuse WMH. Axial FLAIR shows white matter hyperintensity (WMH) predominantly involving the deep and periventricular white matter, but relatively sparing the U-fibres, a pattern typical of Binswanger's disease. Scattered lacunar infarcts (*red arrows*) in the white matter are also identifiable

functions are normal before stroke, impaired immediately after, and do not worsen over time; when vascular lesions are located in strategic regions and when well-defined vasculopathies known to cause dementia are proven, for example CADASIL and CAA (see Sect. 6.4.3). In other circumstances, it is possible that both neurodegenerative and vascular pathology may contribute to cognitive impairment. Therefore, the overlap between cerebrovascular and neurodegenerative disease is significant, which makes 'mixed dementia' (see Sect. 6.7) the most relevant differential diagnosis of subcortical ischaemic VaD.

Specific types of microangiopathy will be discussed in Sect. 6.4.3, but the differential diagnoses for small vessel VaD otherwise includes:

- Vasculitis (Sect. 6.5)
- HIV encephalitis (Sect. 7.2.2)
- Progressive multifocal leukoencephalopathy (PML - Sect. 8.3.2)
- Subacute sclerosing panencephalitis (SSPE, Sect. 7.2.2.)
- Acute disseminated encephalomyelitis (ADEM) and MS (Sect. 7.3.2)
- Adult polyglucosan body disease (Sect. 7.4.6)
- Leukodystrophies (see Sect. 7.4)
- Mitochondrial diseases (see Sect. 7.4.3)
- Encephalopathy secondary to cytotoxic drugs; for example methotrexate (Sect. 7.5)
- Carbon monoxide poisoning (see Sect. 7.5.4)
- Post-radiation encephalopathy (Sect. 7.6)

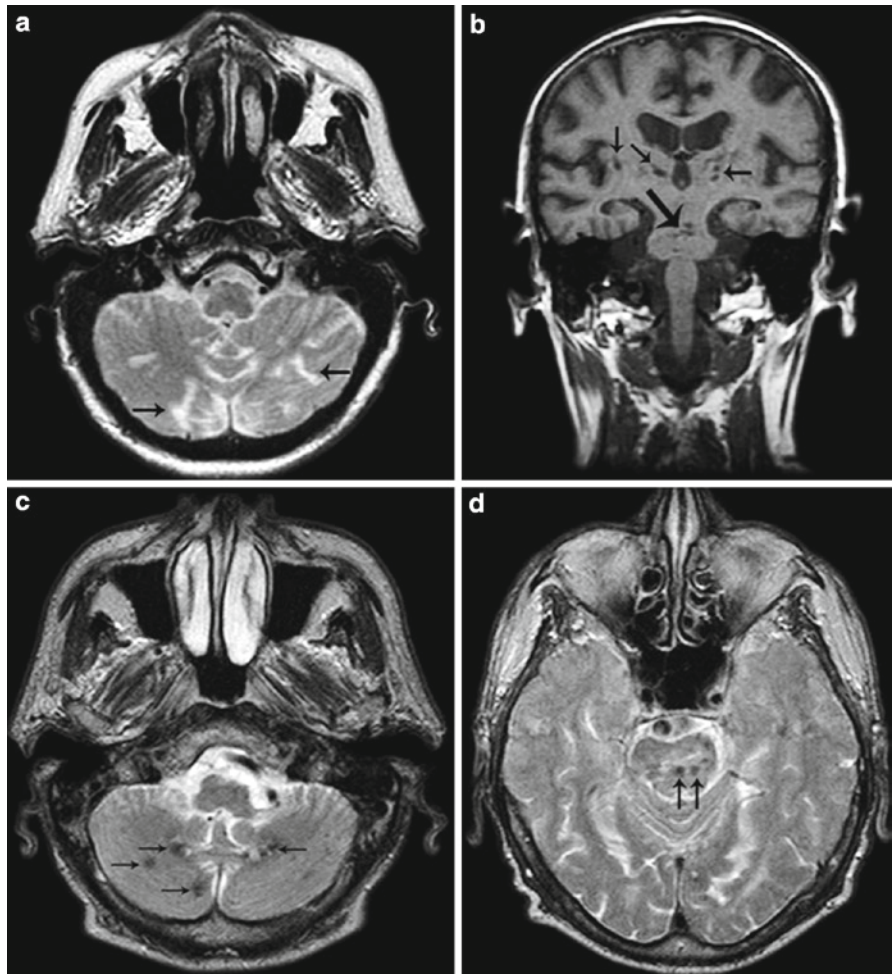

Fig. 6.9 Examples of focal lesions in patients with small vessel vascular dementia. (**a**) Axial T2-weighted image of a 78-year-old patient showing multiple small vessel cerebellar infarcts, some involving the cerebellar cortex (*arrows*). (**b**) Coronal T1-weighted image of an 80-year-old patient showing multiple infratentorial lacunes in the basilar pons (*large arrow*), and supratentorial lacunes occurring in the right basal ganglia region and in both thalami (*small arrows*). (**c**, **d**) Axial T2-weighted images of a 66-year-old patient showing multiple deep cerebellar and pontine microbleeds (*arrows*). (Reproduced with permission from Stroke 2006;37:105–110)

6.4.3 Specific Types of Microangiopathy

6.4.3.1 Introduction and Classification

The majority of cases with small vessel disease will be sporadic or idiopathic; that is the underlying pathophysiology is not attributable to a specific cause, but rather to general vascular risk factors (e.g. hypertension, diabetes) leading to arteriosclerosis, hypoperfusion and to white matter damage. In a small fraction of patients, specific diseases can be discerned with an established aetiology. Recognising those subtypes is clinically meaningful in terms of management, prognosis and genetic counselling. Therefore, in the following sections, we will separately discuss several types of microangiopathy with microhaemorrhages (e.g. amyloid angiopathies), as well as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and Fabry's disease.

6.4.3.2 Microangiopathy with Microhaemorrhages

Introduction

Cerebral microhaemorrhages or microbleeds (MBs) have mostly been identified by radiologists on MRI rather than by histopathological examination. They correspond to small intramural and perivascular haemorrhages. MBs are defined as small foci of low signal intensity on T2* or susceptibility-weighted images not attributable to vessels, calcification or other pathology like cavernomas (see Chap. 3.3.2.5). MBs occur in sporadic small vessel disease (SVD), often in a central

distribution involving the basal ganglia. By contrast, their distribution is mostly cortical–subcortical (lobar) in specific disorders such as cerebral amyloid angiopathies (CAA). Amyloid angiopathy may also occur secondarily in prion diseases, such as Creutzfeldt–Jakob disease and Gerstmann–Sträussler–Scheinker syndrome. Table 6.4 provides a radiological differential diagnosis of cerebral MBs.

Sporadic CAA

Aetiology, Genetics and Histopathology

In addition to the hereditary types of CAA discussed in the following sections, sporadic cases of CAA may also present with symptomatic or subclinical (imaging only) intracerebral haemorrhage. Sporadic CAA is a common cerebrovascular pathology of the elderly and is caused by the deposition of β-amyloid in the media and adventitia of small-to-medium sized cerebral arteries. The prevalence of CAA in autopsy specimens increases from 2% at the age of 50 years to 74% in subjects above the age of 90 years. In western countries, CAA is the leading cause of lobar intracerebral haemorrhage as opposed to hypertensive bleeding occurring in the basal ganglia. In addition, severe CAA is a risk factor for dementia, in general, and is a feature of AD, in particular. Specific amyloid precursor protein (APP) mutations (e.g. APP693) and APP duplications lead to severe CAA. In 'sporadic' CAA, the apolipoprotein E (APOE) ε2 and ε4 alleles are risk factors: the latter leads to a higher propensity for amyloid β (Aβ) 40 to be deposited in vessel walls. Histopathologically, degenerative vascular changes may accompany amyloid deposition, including fibrous thickening with an 'onion skin' appearance of the vessel wall, 'double barrelling', thinning of the degenerated vessel wall (sometimes with microaneurysm formation), fibrinoid necrosis and evidence of blood breakdown products around the affected blood vessels. In severe CAA, the smooth muscle cell layer is completely lost and degenerative changes of the affected vessel walls are often accompanied by evidence of leakage of blood. In some cases, a marked inflammatory response occurs, probably underlying an angiitis-like illness occurring in a subset of patients.

Clinical Presentation, Epidemiology and Management

Sporadic CAA may present as subcortical vascular dementia, stroke or as an acute vasculitis-type of illness.

Table 6.4 Differential diagnosis of cerebral MBs

Disease	MB distribution	Additional MR features	Clinical clues
Sporadic SVD	Basal ganglia	Lacunes, extensive WML	Hypertension, other vascular risk factors
CAA	Cortico-medullary	Subpial blood, macroscopic haematoma	TIA, stroke
HCHWA APP mutations (e.g. APP693) and duplications; and other familial amyloidoses	Cortico-medullary	Frequently macroscopic haematoma, but sometimes just extensive white matter changes	Stroke, seizures, family history
FBD/FDD	Unknown	Rarely macroscopic haematoma	Ataxia
CADASIL	Cortico-medullary	Temporal WML	Migraine, family history
Cavernomas	Random	Popcorn lesions, high signal on T1	Epilepsy
Collagen type 4 mutations	Brainstem and cerebellum	Extensive WML, dilated VRS	Stroke, migraine, retinal artery tortuosity
Radiation vasculopathy	Random	Atrophy and WML	Radiation therapy
DAI	Cortico-medullary, corpus callosum, brainstem	Cortical contusions	History of trauma

For abbreviations, see text and list on page XV

Table 6.5 Boston criteria for CAA

1. Definite CAA. Full post-mortem examination demonstrating: • Lobar, cortical, or cortical–subcortical haemorrhage • Severe CAA with vasculopathy • Absence of other diagnostic lesion
2. Probable CAA with supporting pathology. Clinical data and pathologic tissue (evacuated haematoma or cortical biopsy) demonstrating: • Lobar, cortical, or cortical–subcortical haemorrhage • Some degree of CAA in specimen • Absence of other diagnostic lesion
3. Probable CAA. Clinical data and MRI or CT demonstrating: • Multiple haemorrhages restricted to lobar, cortical or cortical–subcortical regions (cerebellar haemorrhage allowed) • Age of 55 years and over • Absence of other cause of haemorrhage
4. Possible CAA. Clinical data and MRI or CT demonstrating: • Single lobar, cortical or cortical–subcortical haemorrhage • Age of 55 years and over • Absence of other cause of haemorrhage

Source: Neurology 2001;56:537–539

The diagnosis of CAA can be made with varying levels of confidence using the Boston criteria (Table 6.5). In subjects with stroke/haemorrhage, anti-coagulants convey an increased risk for repeated haemorrhage (particularly when multiple MBs are present). Patients with an inflammatory type of CAA may benefit from steroid treatment, certainly when there is marked oedema on MR imaging; see also Sect. 8.9. In subjects with AD, multiple MBs (and presumably severe CAA) convey a worse prognosis.

Neuroimaging Strategy and Findings

Structural imaging is important to assess macroscopic haemorrhage in both symptomatic (Fig. 6.10a) and asymptomatic (Fig. 6.10b) subjects. Demonstration of MBs requires T2*-weighted imaging techniques, such as gradient echo. Susceptibility-weighted imaging (SWI) is a particularly sensitive technique that uses phase information to enhance visibility of MBs. The sensitivity to detect MBs is dependent on many technical factors, including field strength, echo time and slice thickness. Higher field strength leads to many more MBs being detected. Due to this variation in acquisition, generalisable normative data are hard to provide, but as a rule-of-thumb, more than 3 MBs in a lobar distribution at 1.5 T are indicative of CAA. Amyloid PET imaging (e.g. ^{11}C-PIB) shows increased uptake in CAA.

Neuroimaging strategy and findings in CAA
Structural imaging • Evidence of past lobar haemorrhage on CT or MR • Multiple MBs at the corticomedullary junction on T2*-images • Subpial siderosis on T2*-images • White matter hyperintensities (WMH) and lacunes
PET scanning (unconfirmed) • Increased binding on amyloid imaging

HCHWA

Synonyms

Hereditary cerebral haemorrhage with amyloidosis (HWHWA), Dutch type (HCHWA-D), icelandic type (HCHWA-I), oculo-leptomeningeal amyloidosis, APP-related CAA

Aetiology, Genetics and Histopathology

Several autosomal dominant single-gene disorders cause cerebral haemorrhage with amyloidosis. The best studied of these involve certain specific point mutations in the APP gene on chromosome 21. Such disorders result in early-onset cerebral amyloid angiopathy and/or cerebral 'parenchymal' amyloidosis: cerebral haemorrhage is a common, but not inevitable, feature in members of these families. The Dutch mutation (at position 693) is the prototypical example (HCHWA-D), but other mutations are well described and all encode changes at a similar position on APP within the sequence of the Aβ peptide (clustered around the alpha secretase site); e.g. Flemish (692), Italian (693), Iowa (694) and Arctic (693) mutations. In all these APP-related CAAs, meningocortical arteries are affected by β-amyloid deposits, leading to aneurysmal dilatation or thinning of the vessel wall and to fibrinoid necrosis. Vessels in the deep hemispheric structures (e.g. thalamus and basal ganglia) and brain stem are relatively spared. Duplications in APP also cause CAA, but cerebral haemorrhage is less frequent.

In the Icelandic-type (HCHWA-I), a mutant of the cysteine protease inhibitor cystatin-c occurs on chromosome 20. In oculo-leptomeningeal amyloidosis, the affected protein is transthyretin (TTR), whose gene is located on chromosome 18. In HCHWA-I, the amyloid angiopathy is more widely distributed, involving arteries in the cerebrum, cerebellum and the brain stem. In oculo-leptomeningeal amyloidosis, deposition of abnormal TTR occurs in the vitreous and the leptomeningeal blood vessels.

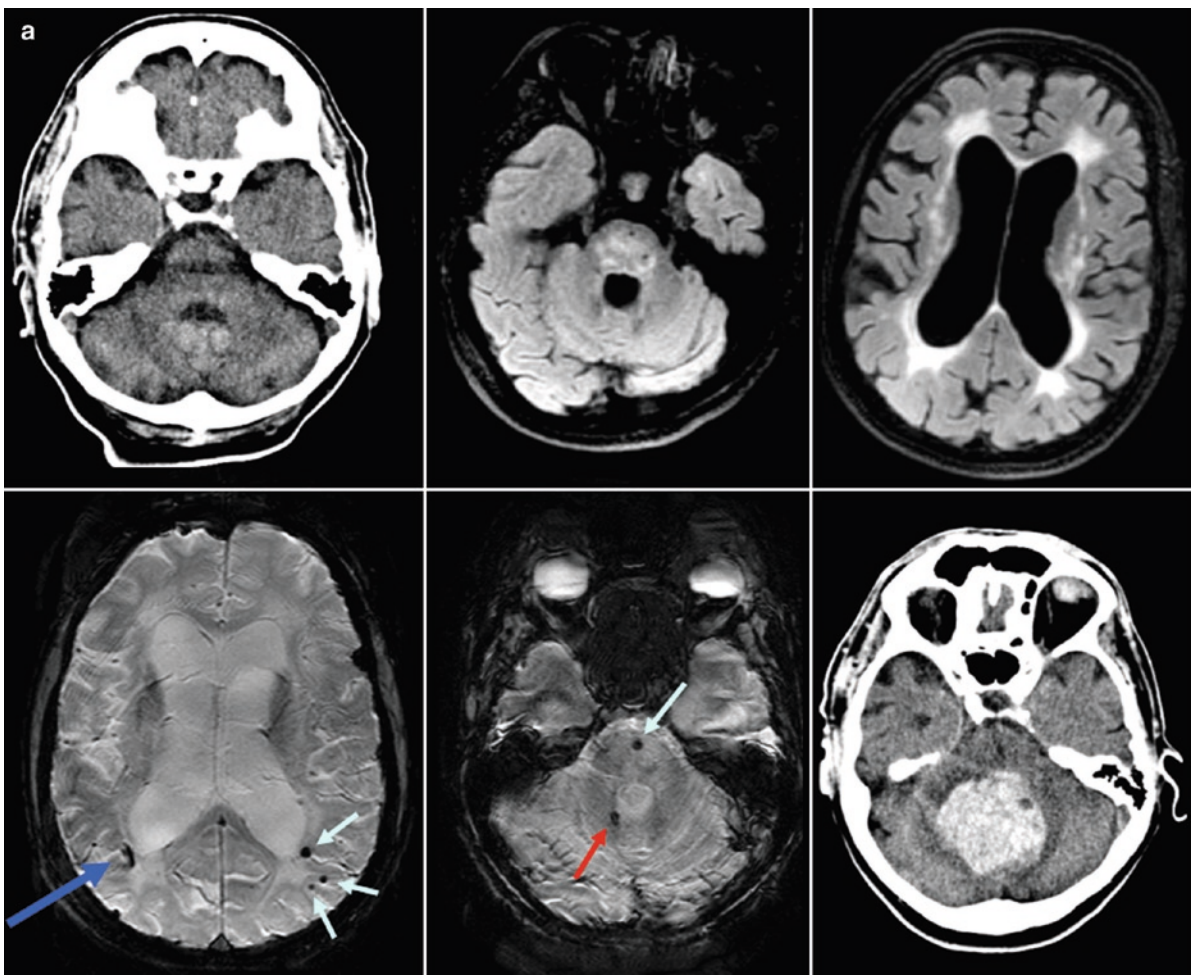

Fig. 6.10 (**a**) Symptomatic CAA. This 62-year-old woman had diabetes type II and a history of cardiac disease, for which she was treated with oral anti-coagulants. She was recently forced to stop working due to forgetfulness. Baseline CT (*upper left*) and MRI showed confluent ischaemic white matter lesions with multiple microbleeds (*light blue arrows*), but also evidence of a silent macroscopic bleeding (*dark blue arrow*) consistent with CAA. A few months later she was admitted with a stroke and the corresponding CT (*lower right*) showed a large cerebellar haematoma, in close proximity to a previous cerebellar microbleed (*red arrow*)

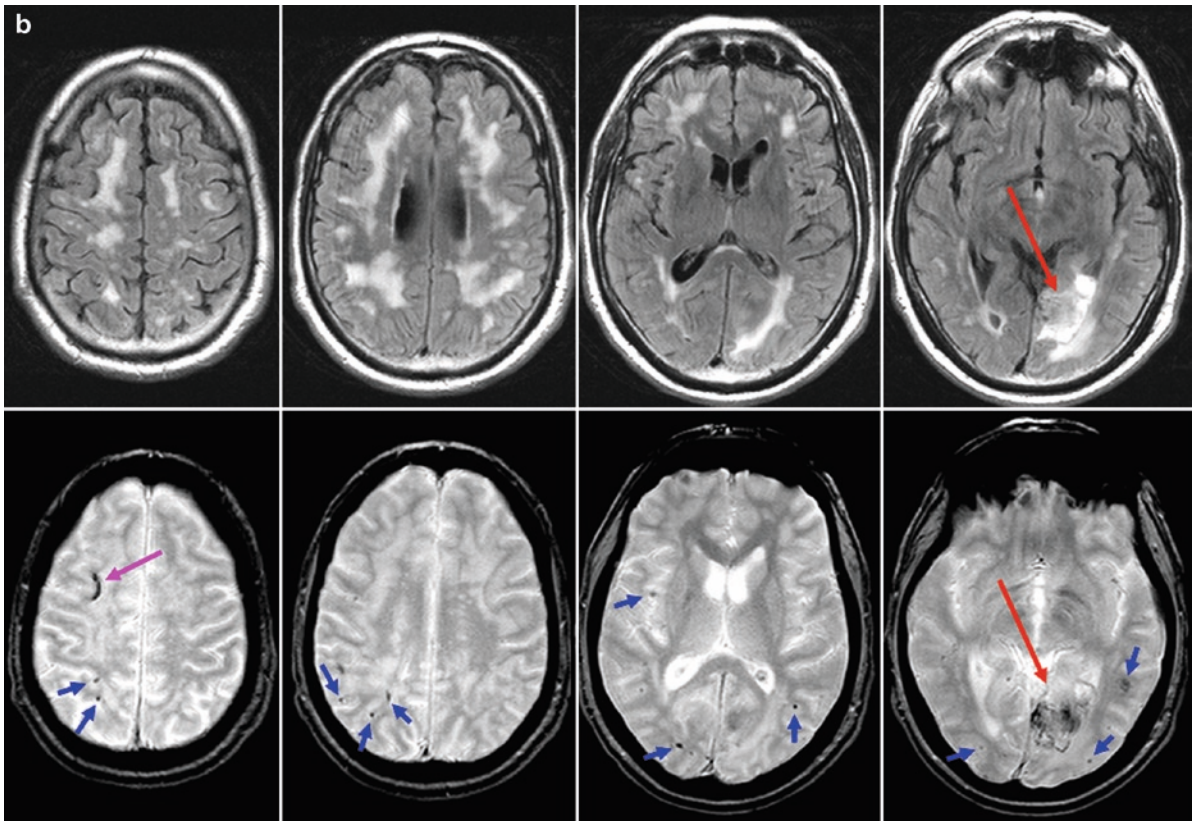

Fig. 6.10 (continued) (**b**) Asymptomatic CAA. This 67-year-old man presented with mild memory disturbances and cognitive slowing clinically diagnosed as MCI (MMSE 30/30). MR revealed confluent ischaemic white matter lesions (Fazekas grade III) on FLAIR (*upper row*) and multiple microbleeds (*blue arrows*) on gradient echo T2*-weighted images (*lower row*). However, there is also evidence of past (*purple arrow*) and recent (*red arrow*) haemorrhages, consistent with a diagnosis of CAA

Clinical Presentation, Epidemiology and Management

HCHWA-D usually presents in the 6th decade, mostly with intracranial haemorrhage or dementia without stroke. Patients with HCHWA-I usually present their first episode of haemorrhage in the 3rd or 4th decade of life. The TTR variants may manifest in many ways, usually with sensorimotor polyneuropathy with or without associated autonomic neuropathy.

Neuroimaging Strategy and Findings

Structural imaging may reveal multiple haemorrhages and multiple MBs in a typical lobar distribution. In advanced cases, the central regions become affected as well. Additional white matter lesions develop as the disease progresses.

Familial British and Danish Dementia with Amyloid Angiopathy

Synonyms

Familial British dementia (FBD), Worster-Drought syndrome, familial cerebral amyloid angiopathy – British type, familial Danish dementia (FDD), heredopathia ophthalmo-oto-encephalica

Aetiology and Genetics

Both FBD and FDD are extremely rare early-onset autosomal dominant disorders characterised by progressive cognitive impairment, spasticity and cerebellar ataxia. Both are associated with a stop codon mutation in the BRI gene located on chromosome 13, resulting

in the production of amyloidogenic fragments. Histopathologically, there is hippocampal neurofibrillary degeneration and widespread parenchymal and vascular amyloid deposits.

Symptoms and Course

Both diseases present over the age of 60 years. FBD is characterised by impaired recognition and memory recall progressing to dementia, progressive spastic tetraparesis and cerebellar ataxia. FDD is additionally characterised by cataracts and deafness. In contrast to HCHWA and CAA, cerebral haemorrhage is less common.

Neuroimaging Findings

FBD patients have extensive periventricular white matter hyperintensities mostly affecting the occipital lobe and corpus callosum as well as lacunar infarcts, but no signs of frank intracerebral haemorrhage. No data are available on the occurrence of MBs. The corpus callosum can be severely atrophic as in some forms of hereditary spastic paraparesis. Amyloid imaging may show increased cerebellar rather than cerebral uptake in FBD. Imaging findings in FDD are lacking.

6.4.3.3 CADASIL

Synonyms

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), hereditary multi-infarct dementia, familial Binswanger's disease

Aetiology, Genetics and Histopathology

In 1977, Stevens et al. described a hereditary disorder with recurrent subcortical infarctions and progressive neurological deficits leading to dementia, pseudobulbar palsy and severe disability; similar cases were perhaps also described by van Bogaert in 1955. The acronym CADASIL was coined by Elizabeth Tournier-Lasserve et al. in 1993. CADASIL is caused by a mutation in the NOTCH3 gene. NOTCH3 codes for a transmembrane receptor protein on the surface of smooth muscle cells surrounding arteries. Accumulation of pathologic NOTCH3 receptor protein in small and medium-sized cerebral arteries results in thickening and fibrosis of the walls of small and medium-sized arteries, leading to cerebral infarctions (Fig. 6.11). CADASIL is the most common hereditary disease presenting with stroke.

Clinical Presentation, Epidemiology and Management

The clinical picture is dominated by recurrent subcortical ischaemic infarctions and cognitive decline typically beginning around 40–60 years of age. Other clinical manifestations include migraine with aura and prominent mood disturbance with apathy. The cognitive profile in CADASIL is characteristically subcortical and is similar to that seen in small vessel VaD in general. A definite diagnosis of CADASIL can be made when the clinical findings are supported by a mutation of the NOTCH 3 gene on chromosome 19 or with histopathological confirmation from skin or brain biopsy. Probable CADASIL is suggested by brain imaging findings (Table 6.6). CSF, blood and neurophysiology are typically non-contributory. There is no specific treatment beyond anti-platelet treatment and management of vascular risk factors.

Neuroimaging Strategy and Findings

Whereas CT may reveal leukoaraïosis, MR imaging is the critical imaging modality in CADASIL due to its sensitivity to show the characteristic involvement of the temporal pole (Figs. 6.12 and 6.13), which has a very limited differential diagnosis (multiple sclerosis, myotonic dystrophy and adult polyglucosan body disease). Additional findings include lacunes, MBs and widened Virchow–Robin spaces at the cortico-medullary junction. Diffusion-weighted imaging may show restricted diffusion in recent infarcts, and diffusion tensor imaging (DTI) may show a more generalised involvement of the (partially normal appearing) brain tissue. MR spectroscopy may reveal lactate (Fig. 6.14). The imaging findings are summarised in Table 6.6.

6.4.3.4 Fabry's Disease

Synonyms

Fabry's disease (FD), Anderson-Fabry disease, α-galactosidase A deficiency

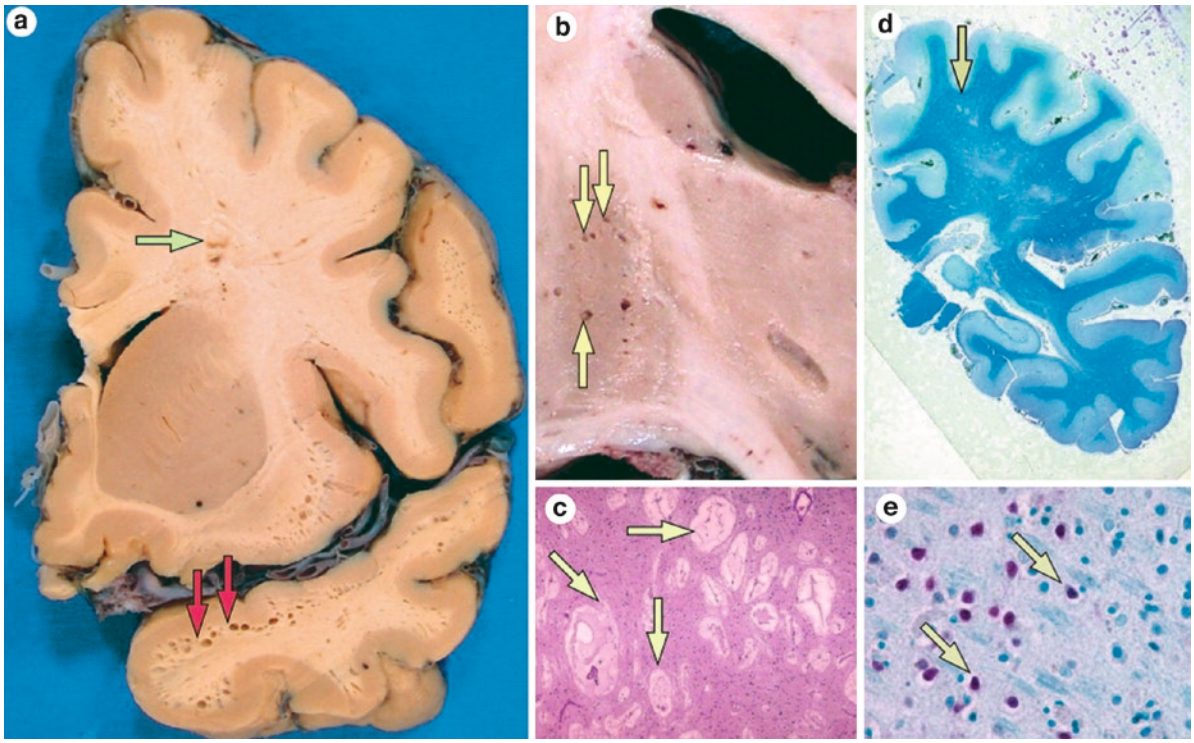

Fig. 6.11 Pathological features of cerebral lesions in CADASIL. (**a**) Coronal section of the left hemisphere at the level of the caudate nucleus. Multiple subcortical lacunes (*small infarcts*) corresponding to dilated perivascular spaces are detected at the cortico–subcortical junction in the temporal lobe and insula (*red arrows*). Other lacunes are present in the centrum semi-ovale (*green arrow*). (**b**) Macroscopic section of the striatum and thalamus showing a notable area of status cribrosus (*arrows*) with (**c**) microscopy (haematoxylin and eosin, ×40) confirming accumulation of dilated perivascular spaces (*arrows*). (**d**) Coronal section of the right hemisphere at the level of the pulvinar nucleus. Klüver-Barrera stain (*luxol cresyl violet*) shows myelin loss in the centrum semi-ovale and small lacunes in the white matter (*arrow*). Note the relative sparing of the cortex by ischaemic lesions. (**e**) Neuronal apoptosis in layer 3 of the occipital cortex (TUNEL technique). Several neurons are positively stained, some of which have pyknotic nucleus (×400; *arrows*). (Reprinted with permission from Lancet Neurology 2009;8: 643–653–and with thanks to Françoise Gray, Department of Pathology, Hôpital Lariboisière, Paris, France)

Table 6.6 Neuroimaging strategy and findings in CADASIL

Structural imaging – MRI is the preferred modality
• Extensive/confluent white matter lesions
– Temporal pole involvement (one of the earliest features)
– U-fibre involvement at the vertex
– Deep white matter and basal ganglia
External capsule involvement (not specific)
• Lacunes in the basal ganglia, thalamus and deep white matter
• Widened Virchow–Robin spaces
– 'État criblé' in the basal ganglia
– Lacune-like lesions at the cortico-medullary junction
• Cerebral MBs–especially in the thalamus and brainstem
• Hypointensity on T2 in the basal ganglia
Additional MR findings
• MR angiography – typically normal
• DWI may show restricted diffusion in recent lesions
• Spectroscopy may reveal lactate
NB – contraindication for catheter angiography (DSA), because of a high complication rate

Aetiology, Genetics and Histopathology

FD is an X-linked recessive disorder resulting from α-galactosidase-A deficiency. Progressive accumulation of globotriaosylceramide in lysosomes leads to pathological lipid storage in many organs, including the vascular endothelium throughout the CNS. Thickening of vessel walls and their obstruction leads to ischaemic infarctions and aneurysm formation.

Clinical Presentation, Epidemiology and Management

The prevalence of FD is probably underestimated; FD accounts for ~1% of young male stroke cases and should be considered when proteinuria is present. Characteristic clinical manifestations of FD include acroparaesthesias,

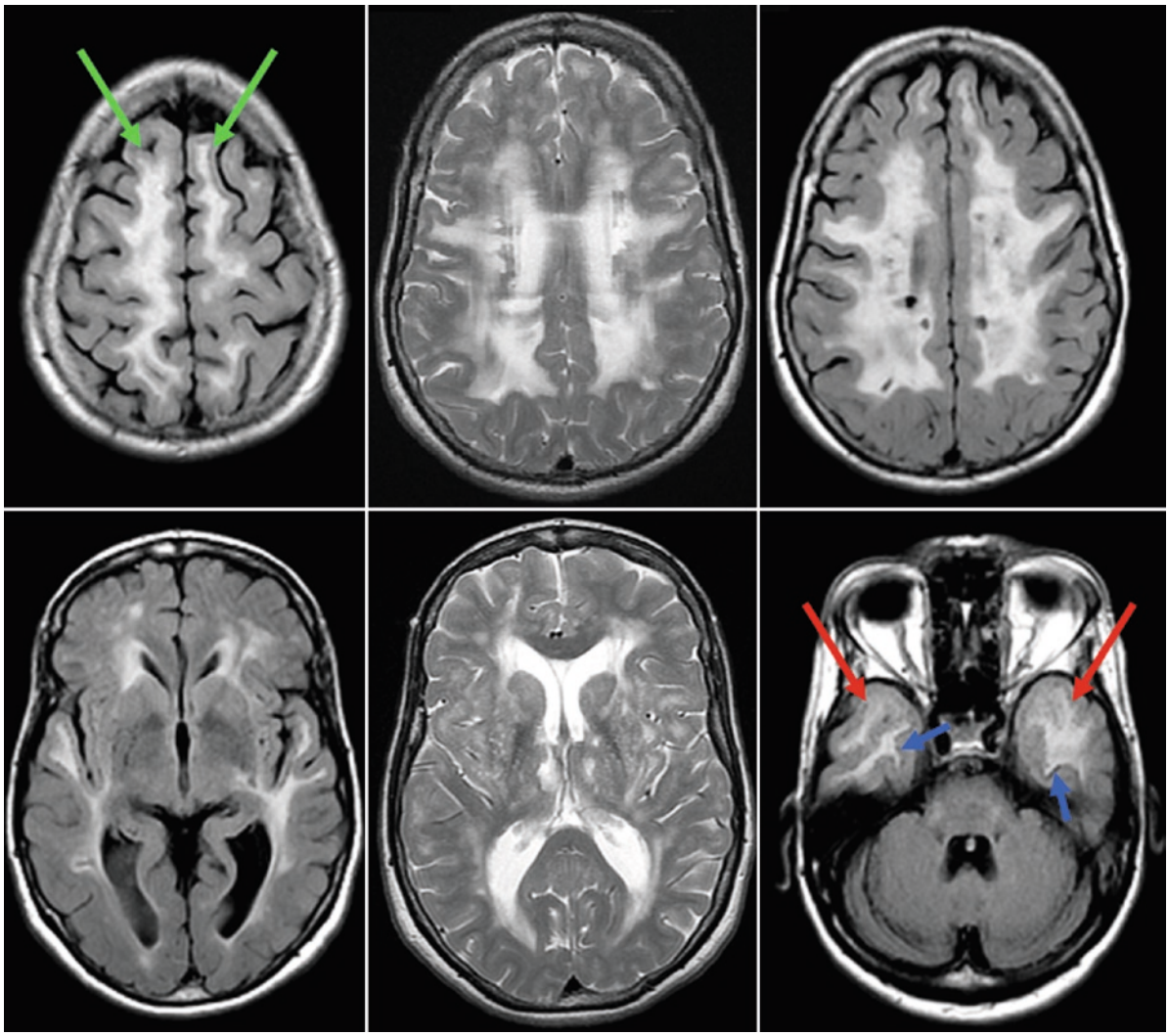

Fig. 6.12 MRI findings in CADASIL. This 57-year-old woman presented with memory disturbances, disorientation and difficulties in walking and speaking. Her MMSE was 26/30. MRI revealed confluent white matter changes on FLAIR and T2 (*middle*), with a characteristic involvement of the U-fibres at the vertex (*green arrows*) and temporal pole (*red arrows*); note also juxtacortical fluid spaces in the temporal pole on FLAIR. Genetic testing revealed a notch-3 mutation

angiokeratoma, corneal opacity, hypohidrosis, gastrointestinal symptoms, renal, and cardiac dysfunction. CNS manifestations include hemiplegia, hemianaesthesia, aphasia and seizures. In men developing stroke below the age of 65 years, FD should be routinely excluded. The diagnosis of FD is established by demonstrating a deficiency of α-galactosidase in plasma, leukocytes, urine or by means of genetic testing. Enzyme replacement therapy has been available since 2001.

Neuroimaging Strategy and Findings

The imaging findings in FD are mostly non-specific small and large vessel pathology on CT or MRI.

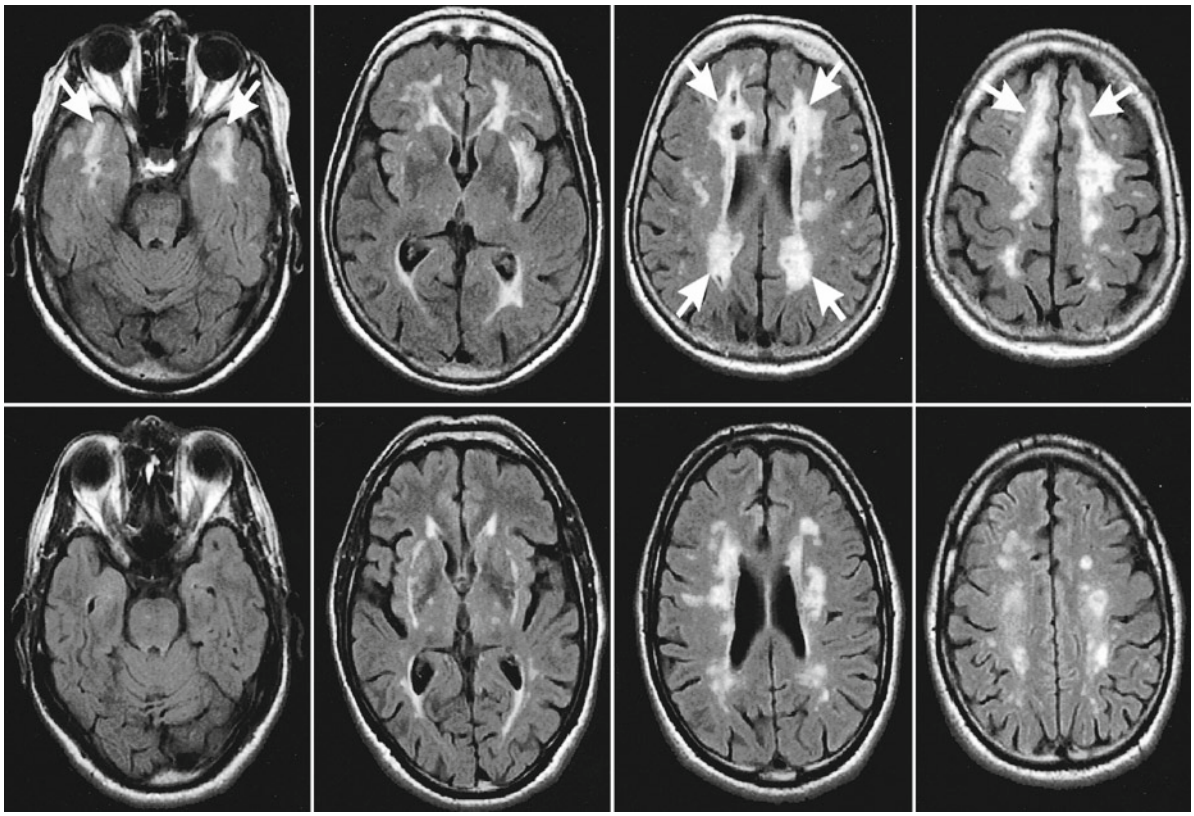

Fig. 6.13 CADASIL versus sporadic small vessel disease.The characteristic involvement of the anterior frontal lobes and the temporal poles in the CADASIL patient (*arrows in the upper row*) is not seen in the patient with sporadic small vessel disease (*lower row*). Note that involvement of the external capsule is not a distinguishing feature. (Reprinted with kind permission from Radiology 2000;218: 443–445)

Dolichoectasia may occur, especially in the vertebrobasilar system. Small vessel disease may manifest as diffuse white matter changes or multiple bilateral lacunar infarcts. Large vessel territorial infarcts may occur as well.

A relatively specific MR imaging finding is signal change in the pulvinar. Twenty to 30% of the patients have high signal intensity in the pulvinar on T1-weighted images, and low signal intensity on T2*-weighted images in the more severe cases. These changes correspond to calcification on CT (Fig. 6.15). The proportion of subjects showing pulvinar changes increases with age. Increased cerebral blood flow in the posterior circulation, particularly in the thalamus, suggests that the dystrophic calcification may be secondary to cerebral hyperperfusion and to a selective vulnerability of the pulvinar and adjacent thalamic nuclei. CT may show more extensive calcium deposits, particularly in more severely affected patients, involving the cerebral cortical–subcortical junction, globus pallidus, pulvinar and the cerebellar cortico-medullary junction – a pattern similar to Fahr's disease.

Beyond focal vascular lesions, quantitative MR techniques may show diffusely abnormal DTI characteristics of the normal appearing WM and reduced NAA/Cr ratio as well as enhanced brain activity on fMRI, probably as a compensatory mechanism.

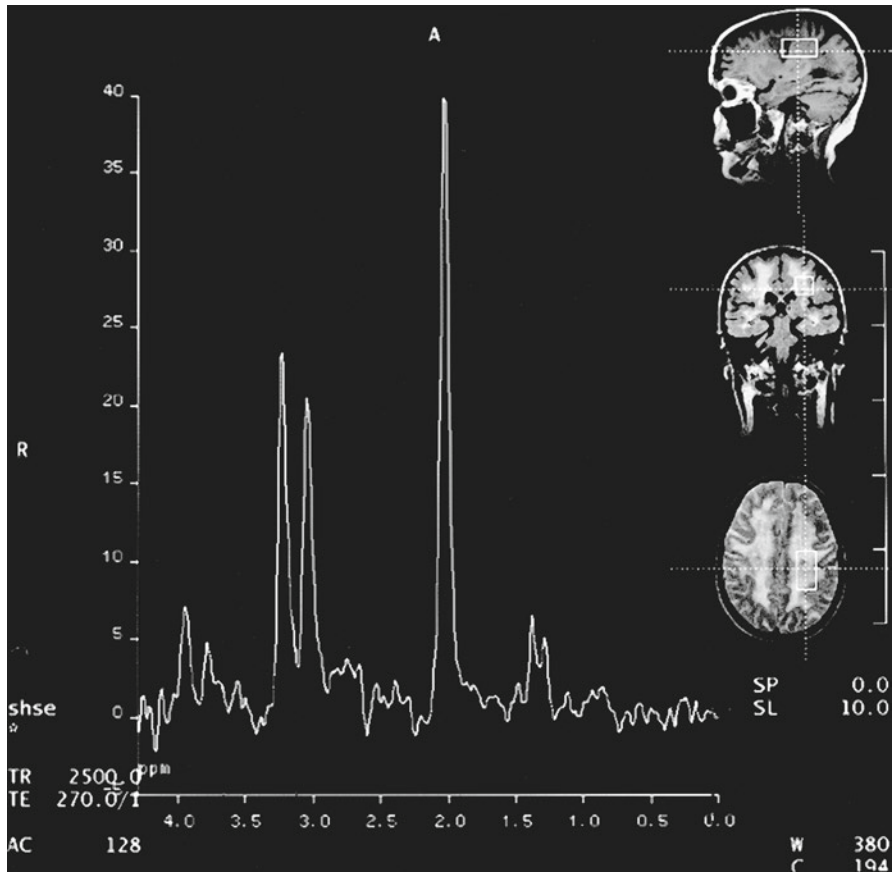

Fig. 6.14 Proton MR proton spectroscopy in CADASIL. Long-echo spectrum shows reasonably preserved ratios of N-acetylaspartate, creatine and choline. At 1.3 ppm there is a lactate doublet

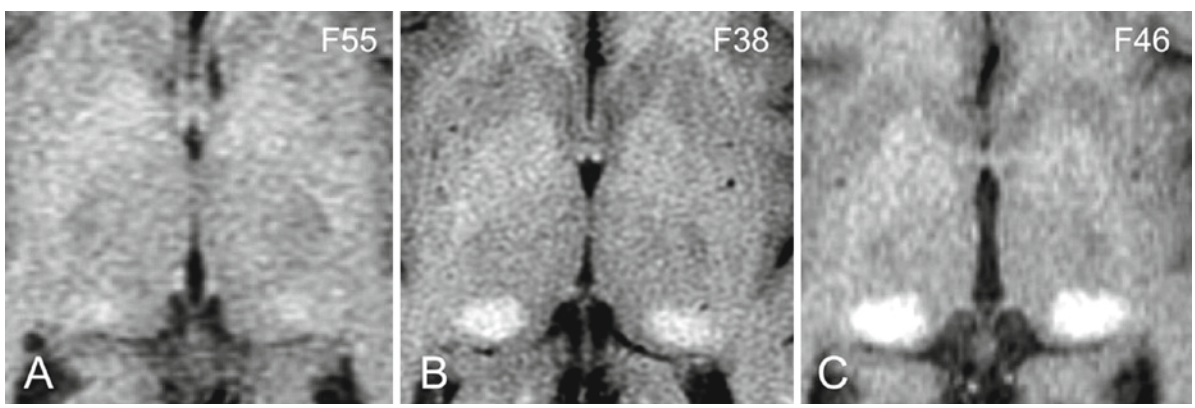

Fig. 6.15 Comparison of CT and MR findings in the posterior thalamus. (**a**–**c**), T1-weighted images through the thalamus in three patients with mild (**a**), moderate (**b**), and marked (**c**) hyperintensity, respectively. (**d**–**f**), Corresponding CT scans demonstrate increased attenuation indicating calcification is present only in the moderate and marked cases. (**g**–**i**), Corresponding gradient-echo T2*-weighted images demonstrate that susceptibility-induced signal intensity loss is seen in the pulvinar in only the moderate and marked cases. Numbers in upper right are patient identifiers. (Reprinted with permission from Am J Neuroradiol 24:1096–1101)

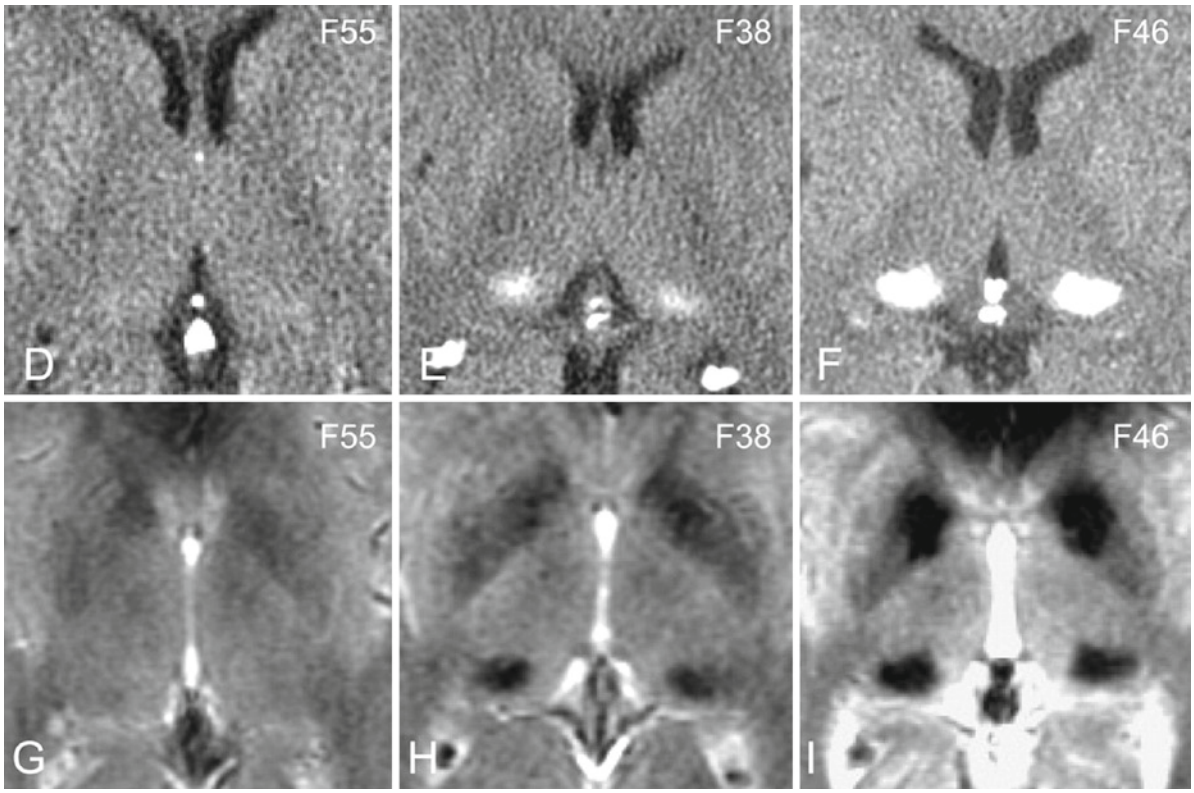

Fig. 6.15 (continued)

6.5 Vasculitis

In this chapter, we discuss primary central nervous system (CNS) vasculitis, and several causes of secondary CNS vasculitis.

6.5.1 Primary CNS Vasculitis

Synonyms

Primary CNS vasculitis, primary angiitis of the CNS (PACNS), granulomatous angiitis of the nervous system, isolated CNS vasculitis

6.5.1.1 Aetiology and Histopathology

Primary angiitis of the CNS is a disease with unknown aetiology with patchy inflammation preferentially affecting small leptomeningeal and parenchymal vessels. Histologically, two subtypes exist: granulomatous angiitis and benign angiopathy.

6.5.1.2 Clinical and Laboratory Findings

Presentation of PACNS is quite variable, and classically involves a triad with headache, organic brain syndrome and multifocal neurological deficits. The course may be fluctuating, multiple sclerosis-like or gradually progressive with subcortical dementia. Being isolated to the CNS, patients with PACNS often lack systemic manifestations. In addition, routine laboratory blood tests, including the erythrocyte sedimentation rate (ESR), may be normal in a variable proportion of cases; brain biopsy (including leptomeninges) is the only definitive proof. As a result, suspicion of vasculitis is a major indication for brain biopsy, since the diagnosis is elusive otherwise and the condition is potentially treatable. Therapeutic options include steroids and cyclophosphamide treatment.

6.5.1.3 Neuroimaging Strategy and Findings

Conventional digital subtraction angiography (DSA) may show beading produced by alternating stenosis and dilation, but this finding is not specific and negative catheter angiography is an invasive procedure that does not rule out vasculitis. MRI is a more sensitive test, being abnormal in perhaps 80% of patients, but often is non-specific by showing hyperintense lesions on T2-weighted or FLAIR images in the white matter and cortex. The pattern of gadolinium enhancement (punctiform in multiple locations) may suggest PACNS, but the differential diagnosis includes other vasculitides, malignancies and infectious disease (Fig. 6.16).

6.5.2 Secondary CNS Involvement

Secondary vasculitis of the CNS is more common than primary CNS vasculitis, and encompasses several systemic illnesses, including generalised autoimmune diseases like systemic lupus erythematosus (SLE), Behçet's disease, Sjögren's syndrome, Susac's syndrome and a variety of systemic vasculitides including Wegener's granulomatosis and polyarteritis nodosa. Secondary CNS vasculitis can be induced by hard drugs like amphetamine, cocaine, but also by over-the-counter drugs like ephedrine.

In this section, only two disorders are discussed in some more detail: SLE, given its high prevalence (of neuropsychiatric involvement), and Susac's syndrome, for its typical imaging appearance. Imaging findings in other secondary vasculitides include non-specific vascular lesions and, occasionally, punctiform gadolinium enhancement.

6.5.3 Systemic Lupus Erythematosus (SLE)

SLE is an autoimmune disease of unknown origin that can be drug induced. The most common cerebral manifestation of SLE is an organic encephalopathy that can be detected by using MRI and PET/SPECT. It may be due to cytokine-mediated effects on vascular endothelium and antiphospholipid antibodies. In addition to small vessel vasculopathy, true vasculitis may occur in large-to-medium sized vessels, which may lead to a stroke-like presentation (that may also be caused by emboli from Libman–Sacks endocarditis). The diagnosis is based on the criteria of the American College of Rheumatology, as well as on laboratory tests including the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and anti-nuclear antibodies (ANA).

Neuropsychiatric symptoms are frequently found in SLE, and incidental cases have been described where dementia is the manifesting symptom. While multi-infarct dementia can be caused by SLE, chronic encephalopathy and inflammation due to active vasculitis can affect cognition as well. MRI findings in acute presentations include multiple infarcts, swelling of the basal ganglia, and punctiform contrast enhancement (Fig. 6.17). In chronic cases, the most common correlate of NP-SLE is generalised brain atrophy, including the hippocampus, and non-specific WM lesions. Quantitative MR techniques (MTR, DTI) may show abnormal tissue integrity in neuropsychiatric SLE, and SPECT/PET may show reduced cerebral perfusion and metabolism.

6.5.4 Susac's Syndrome

Susac's syndrome is a microangiopathy caused by endothelial dysfunction affecting the precapillary arterioles of the brain, retina and the inner ear. It mostly affects middle-aged women. Clinical symptoms include encephalopathy, branch retinal artery occlusions and hearing loss. Headache is often the presenting feature, but neuropsychiatric disturbances can occur and include memory loss, confusion and dementia.

Typical (characteristic) MRI findings in Susac's syndrome
- Multiple lesions (sometimes small, but also 'snow-ball'-like)
  - Centred on the corpus callosum
- Enhance with gadolinium in the acute phase
  - May have associated leptomeningeal enhancement
- May have restricted diffusion in acute phase
- Progress to a 'punched-out' appearance on follow up

Although any part of the corpus callosum may be involved (Figs. 6.18 and 6.19), the central fibres are

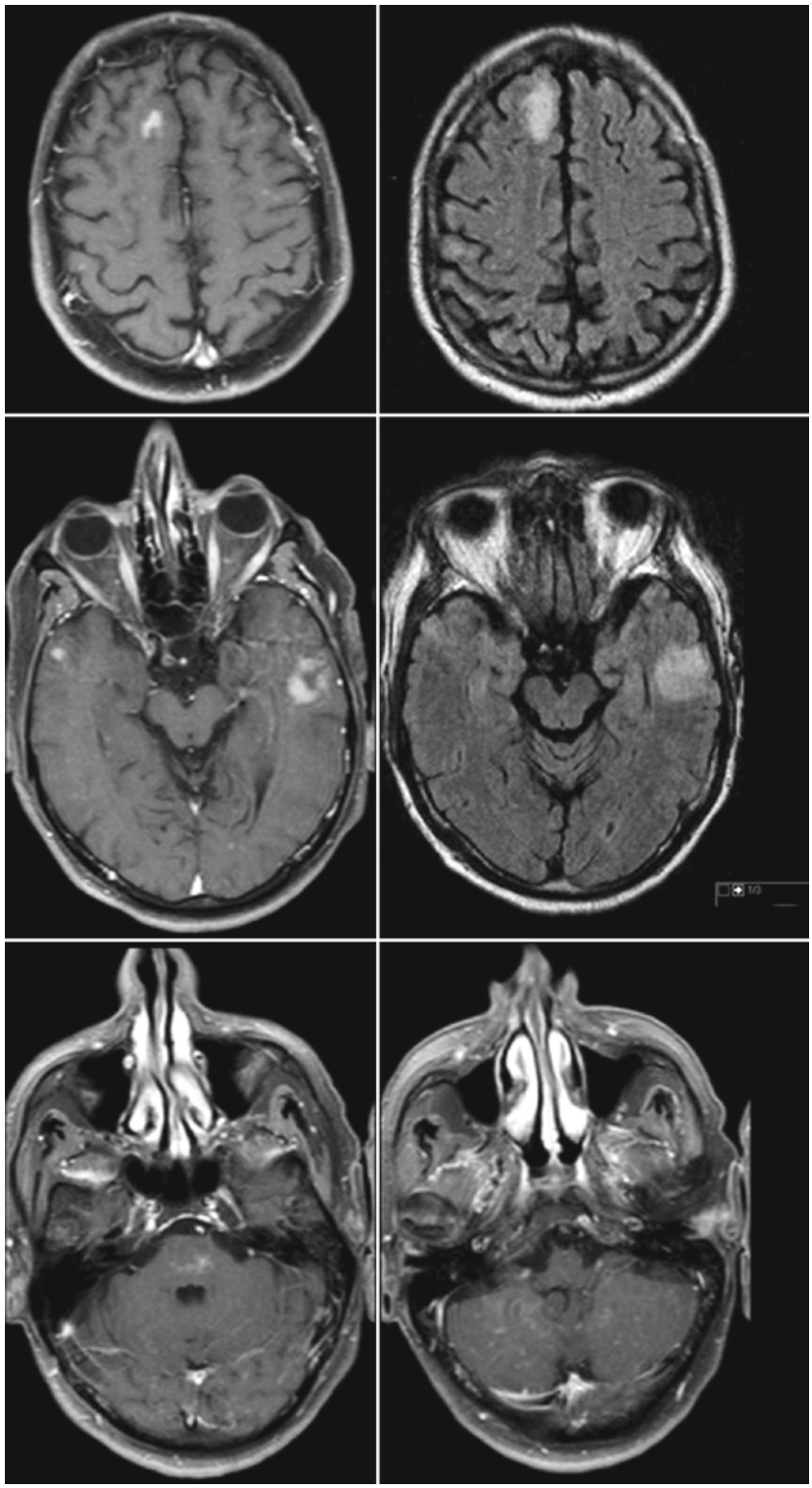

Fig. 6.16 PACNS. This 48-year-old patient presented with multifocal neurological symptoms, a high erythrocyte sedimentation rate and eosinophilia. FLAIR images (*upper-right*) show hyperintense lesions in multiple cortical areas, with patchy punctiform contrast enhancement on T1-weighted images (*left column and bottom-right*), both supra and infratentorially. The major vessels to the brain were normal on MRA (not shown). The patient was diagnosed (and successfully treated) as having a PACNS

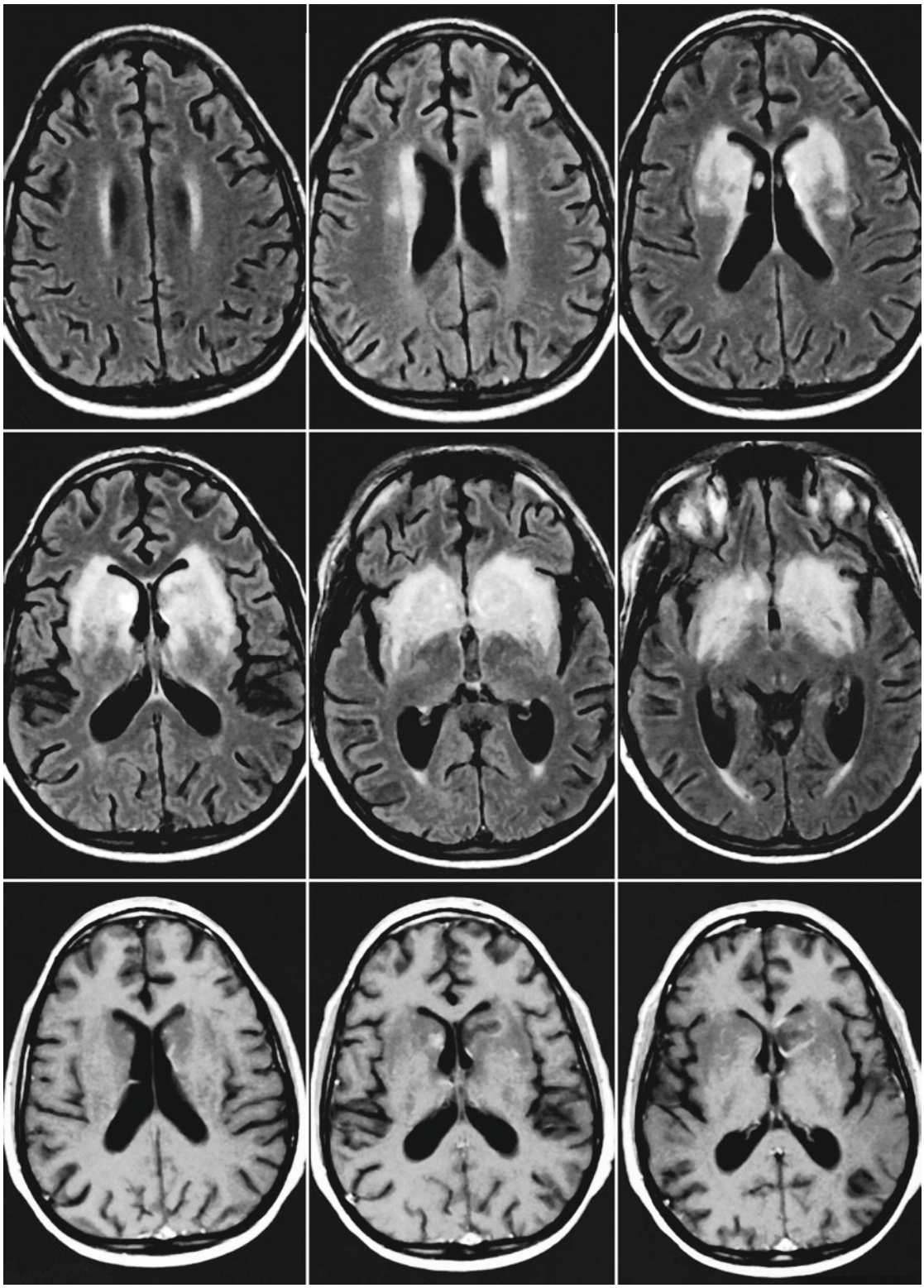

Fig. 6.17 SLE. This 36-year-old woman with SLE presented with confusion. The *upper two rows* represent transverse FLAIR images showing severe involvement of the striatum with swelling and oedema. CT did not show calcification. The *bottom row* shows contrast-enhanced T1-weighted images, illustrating some punctiform enhancement in the caudate nuclei

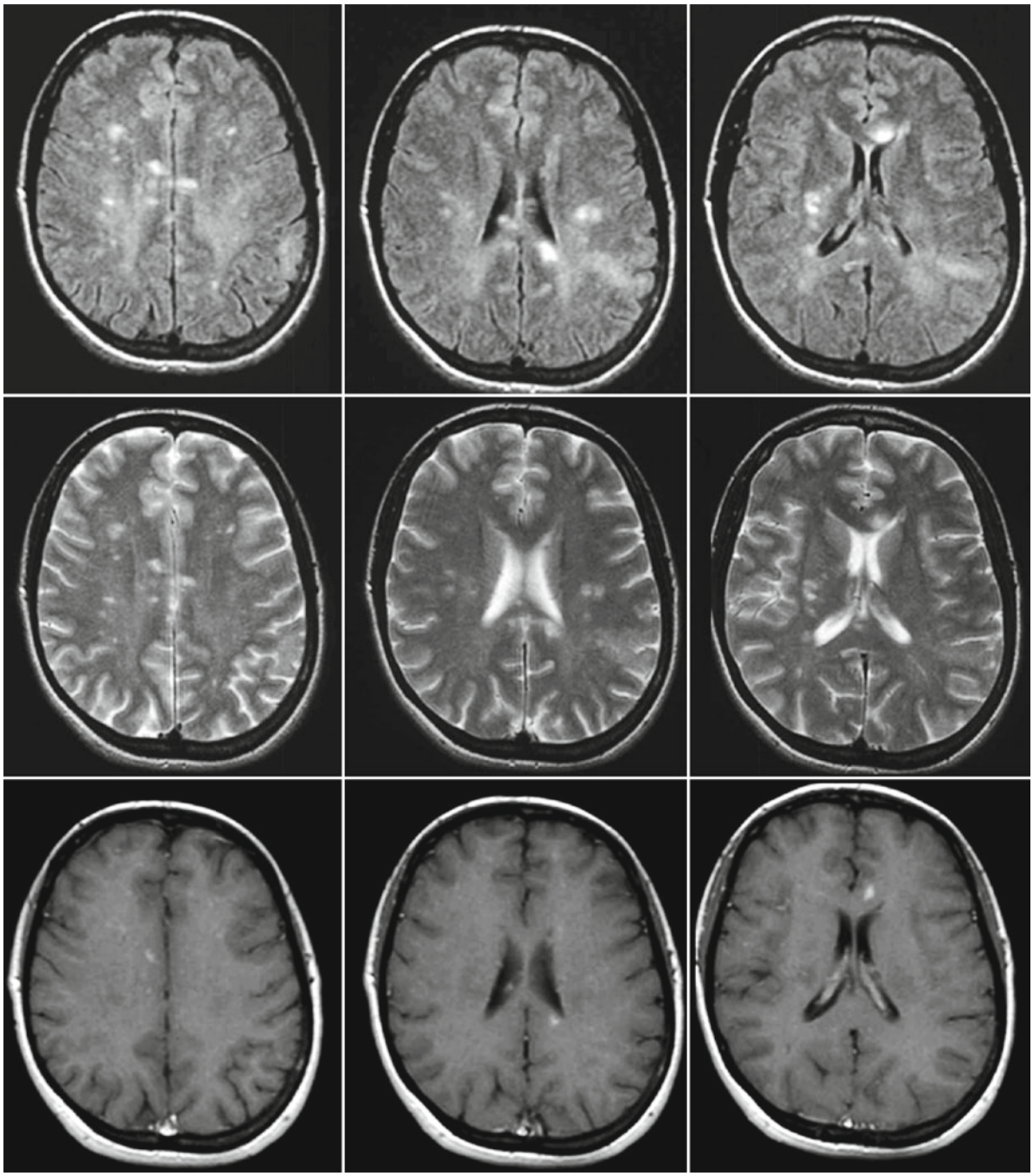

Fig. 6.18 This 33-year-old woman presented with a picture of mental slowing, memory disturbances, headache and drowsiness that developed over a month. MRI showed multiple white matter lesions on FLAIR (*top row*) and T2-weighted (*middle row*) images that mainly involved the corpus callosum, and partly enhanced after gadolinium (*bottom row*). While reminiscent of MS, the 'cotton wool-ball' or 'snow-ball' appearances suggest Susac's syndrome, which was subsequently diagnosed based on auditory loss and retinal vessel abnormalities (Thanks to Alex Rovira, Barcelona, for providing this case)

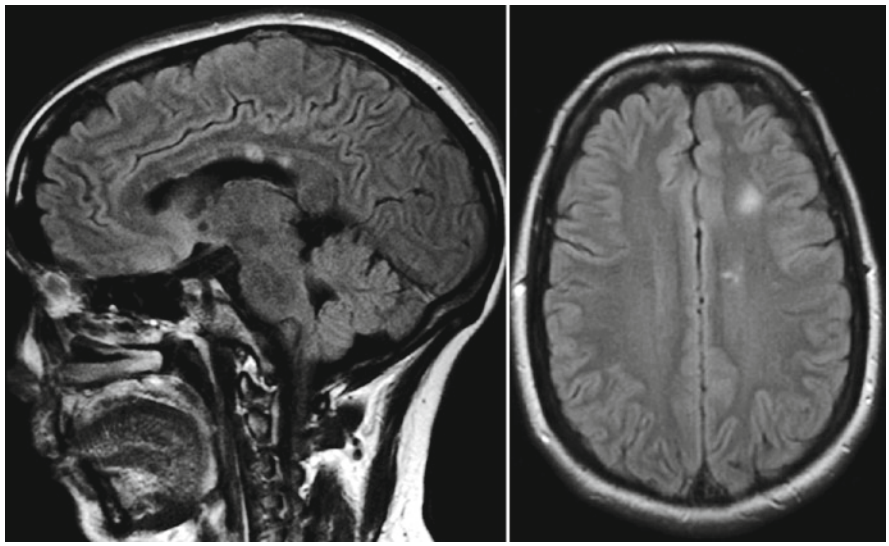

Fig. 6.19 Callosal involvement in Susac's syndrome. Sagittal and axial FLAIR images of a middle-aged woman presenting with behavioural disturbance and cognitive decline that had progressed over several weeks: a psychiatric condition or a rapidly progressive dementia were considered. The sagittal FLAIR image shows two characteristic 'snow-ball' lesions, the smaller one (also displayed on the axial image) predominantly involves the central fibres of the corpus callosum, but relatively spares the peripheral ones. The diagnosis was confirmed by means of retinal examination. A good response was seen with immunosuppression. However, frontal deficits persisted

predominantly involved and there is relative sparing of the peripheral ones. Extensive miliary and leptomeningeal enhancement can also occur. Cerebral angiography findings are almost always normal, because the involved precapillary arterioles can not be depicted, but the diagnosis can be confirmed by fluorescein angiography of the retina that often shows branch retinal artery occlusions, as well as the pathognomonic multifocal fluorescence of the branch arterioles. The pathogenesis of this syndrome is unknown, but it is believed as an autoimmune endotheliopathy. Patients tend to spontaneously improve, but treatment options include immunosuppressants like steroids, cyclophosphamide and immunoglobulin, often combined with aspirin.

6.6 Systemic Hypoxia

In addition to ischaemia caused by vascular wall changes, as discussed in the preceding sections, systemic disorders can also cause ischaemia and lead to cognitive dysfunction and ultimately dementia. Systemic causes of ischaemia include cellular dysfunction (mitochondrial disease, discussed in Sect. 7.4.3), but also anaemia and hypotension.

6.6.1 Anaemia

Cerebral function and neuronal survival depends on oxygen availability at the cellular level and may be adversely affected by a number of contributing factors including a susceptibility to failure of local energy production (e.g. mitochondrial disorders) exacerbated by hypoxia, regionally impaired oxygen delivery (e.g. atherosclerosis) or general oxygen delivery failure (e.g. due to anaemia; cardiopulmonary arrest or failure).

Anaemia is associated with an increased incidence of cognitive impairment, probably through diffuse anoxic damage to vulnerable (grey matter) regions. Such damage may lower the threshold for the development of neurodegenerative processes, such as AD or may contribute to cognitive deficits through a lowering of cognitive reserve. In fact, vascular dementia and AD

share many vascular risk factors, including anaemia. Anaemia is also often associated with other co-morbidity, such as with chronic obstructive pulmonary disease (COPD), which may, in itself, lower the threshold for cognitive decline. The reverse situation (i.e. increased levels of haemoglobin), including polycythaemia, carries the risk of thrombotic vascular events in the brain. Polycythaemia, probably due to a hyperviscosity state, is reversibly associated with subcortical (speed and attention) cognitive deficits.

Macrocytic anaemia is a feature of vitamin B12 deficiency which in itself is associated with (potentially reversible) dementia, mostly secondary to white matter demyelination (see Sect. 7.5.2). Similarly, transient low blood oxygenation, leading to delayed white matter demyelination and cognitive impairment, will be discussed in Sect. 7.5.5.

Special cases of anaemia include sickle cell disease and cerebral malaria.

In sickle cell disease (haemoglobin SS), a low haematocrit per se predisposes to cognitive impairment, probably through diffuse ischaemic damage to grey matter. The occurrence of infarctions (caused by abnormal coagulability) additionally predisposes to cognitive impairment. Infarctions may manifest themselves either as evident strokes or be clinically silent (MRI only); subclinical cognitive decline may occur in childhood.

In cerebral malaria, anaemia also is combined with intravascular occlusion of capillaries, and a complex inflammatory process with alterations in the blood–brain barrier, leading to impaired homeostasis and cerebral oedema. In the short term, this may cause seizures, altered consciousness and coma. In the long term, structural damage and cognitive impairment ensue.

6.6.2 Transient Global Amnesia

Synonym

Acute transient amnesia

6.6.2.1 Aetiology and Histopathology

Although first recognised by Morris Bender in 1956, the name transient global amnesia (TGA) was coined by C. Miller Fisher and Raymond Adams in 1958. It occurs in 5–25 of 100,000 individuals. The pathophysiology of TGA remains speculative; suggested causes include epilepsy, a vascular (TIA) event, and migraine-related phenomena. In a proportion (~30%) of cases a precipitating event such as emotional stress or physical exertion can be identified. Venous ‘congestion’ in the context of a Valsalva manoeuvre has also been suggested as a mechanistic cause and may explain the history of precipitating events.

Although the pathological substrate for TGA is unclear there have been suggestions that damage to CA1 neurons of the cornu ammonis (the so-called Sommer – or vulnerable – sector of the hippocampus) may be responsible. The existence of a watershed area within the CA1 vulnerable sector of Sommer, secondary to the existence of an anastomosis between the upper and lower hippocampal arteries, has been suggested as a predisposing factor. Some support for hippocampal involvement has been provided by diffusion imaging studies discussed below.

6.6.2.2 Clinical and Laboratory Findings

TGA is a clinical syndrome characterised by an abrupt onset of profound anterograde and retrograde amnesia, without further neurological deficits, resolving within 24 h. A typical feature is perseverance (i.e. constantly repeating the same statements or questions). Diagnostic criteria include:

- A reliable witness report of definite loss of recent memory (anterograde amnesia)
- Absence of clouding of consciousness or any other cognitive impairment other than amnesia.
- No focal neurological signs or deficits during or after the attack.
- No features of epilepsy in the past 2 years, and no recent head injury.
- Resolution within 24 h

There are no established laboratory tests. Depending on the clinical features, MRI and/or EEG are indicated; transient epileptic attacks are an important differential. The differential diagnosis otherwise includes basilar artery thrombosis, cardioembolic syndrome, migraine variants, syncope or related paroxysmal spells.

6.6.2.3 Neuroimaging Strategy and Findings

The most informative imaging modality is MRI including DWI. Foci of abnormal high signal intensity with corresponding low apparent diffusion coefficient (ADC) in the Sommer sector of the hippocampus may be seen in the first few days (max 48–72 h) after the onset of symptoms, suggesting a vascular cause (Fig. 6.20). Such abnormalities may be unilateral or bilateral, and may subsequently become visible on high-resolution T2-weighted images. TGA abnormalities do not evolve into cystic lesions, and should be differentiated from benign cavities of the vestigial hippocampal sulcus that occur with normal ageing (Chap. 4).

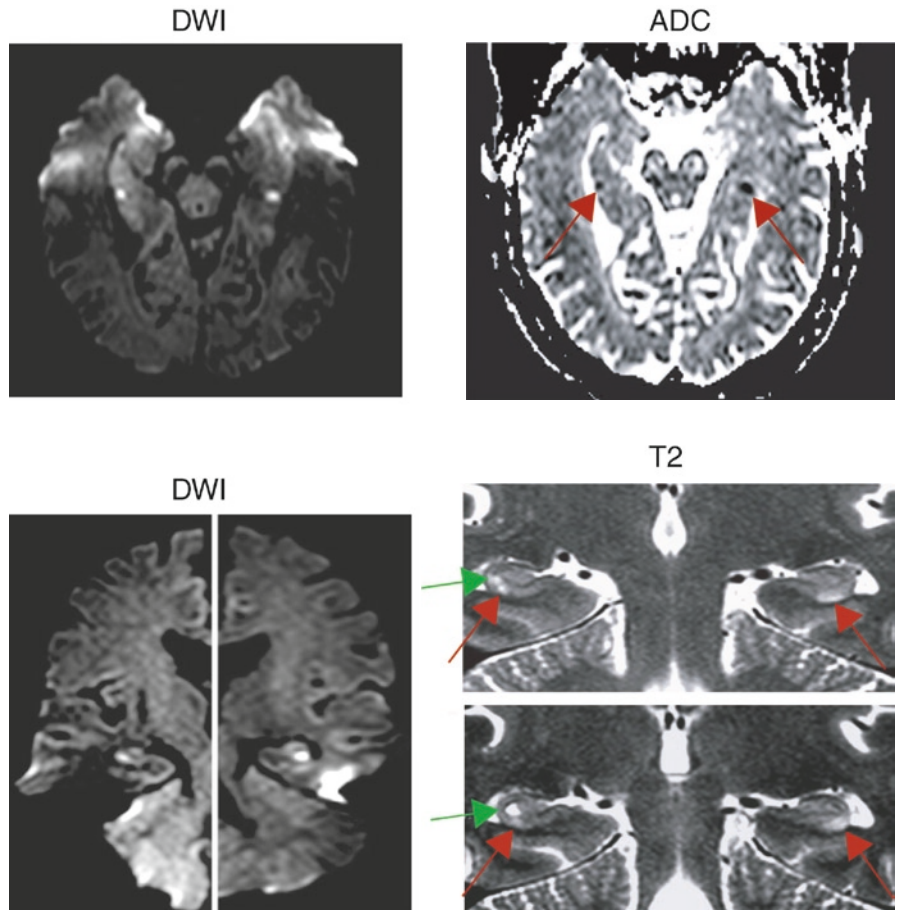

Fig. 6.20 Representative 3T MRI showing typical increased DWI signal and lowered ADC corresponding to lesions on T2-weighted images. On the high-resolution T2-weighted images, note the bilateral lesions in the CA1 sector of the cornu ammonis (*red arrow*) extending over 4–5 mm (slice thickness 2 mm), which are clearly separated from the cavity of the pre-existing vestigial hippocampal sulcus (*green arrow*) more deeply located, between the cornu ammonis and the dentate gyrus. (Reprinted with permission from Brain 2006;129:2874–2884)

6.7 Mixed Dementia and Interrelationship of Vascular Pathology and Alzheimer's Disease

Wiesje van der Flier

6.7.1 Introduction

Traditionally, demented patients are diagnosed with a specific label, on the basis of clinical criteria and ancillary investigations. MRI is an essential part of the diagnostic work-up, and can provide positive evidence for the presence of neurodegenerative (e.g. atrophy) and cerebrovascular disease (e.g. infarcts, white matter hyperintensities, microbleeds). The majority of patients receive a diagnosis of AD. The second most frequently diagnosed type of dementia in the elderly is VaD. Whereas neuropathologically, senile plaques and neurofibrillary tangles are presumed to underlie AD, cerebrovascular pathology, by definition, causes VaD. However, it is increasingly recognised that these two types of neuropathological damage are often concomitantly observed, and their effects may not be easily disentangled. In this section, we will focus on the interrelationship between these two types of pathology, and their manifestation on MRI. We first provide evidence for the role of additional cerebrovascular pathology in AD. Subsequently, we will focus on the opposite, describing neurodegenerative changes in VaD. We will then discuss several hypotheses regarding the relationship between neuropathological and cerebrovascular brain changes. Finally, a future perspective is sketched, where MRI may have a decisive role in the choice of therapy for individual patients, regardless of the specific diagnostic label.

6.7.2 The Contribution of Cerebrovascular Pathology to Alzheimer's Disease

Since the first description of AD at the beginning of the twentieth century, there has been debate about the putative interaction between neurodegenerative and cerebrovascular brain changes in causing AD. For a long time, 'senile dementia' was thought to be caused by intracranial atherosclerosis, while by contrast AD (with young onset, as exemplified by the first patient Auguste D who was only 51 years old) was caused by senile plaques and neurofibrillary tangles. In the course of the twentieth century, senile dementia was discovered to be the same disease as initially described by Alois Alzheimer, caused by plaques and tangles. In this period, atherosclerosis was abandoned as a causative disease mechanism for AD. To date, however, interest is picking up again; as the amyloid cascade hypothesis has not provided definitive answers, and evidence is accumulating that cerebrovascular disease should be taken into account to fully understand the disease.

AD is the most common form of dementia, accounting for more than half of dementia cases. An increasing number of neuropathological studies, however, have shown that, especially in elderly patients over the age of 75 years, mixed disease underlies the clinical syndrome of dementia, whereas pure AD is relatively less common. Persons with multiple neuropathological diagnoses are three times more likely to develop dementia, and most are clinically classified as 'probable' AD. Cerebrovascular disease refers to a variety of abnormalities, including large vessel infarcts, lacunar infarcts and white matter lesions. Intracranial atherosclerosis of the circle of Willis has been related to a diagnosis of AD, and a relationship with the burden of plaques and tangles suggests a direct relationship between the two disease processes. In addition, (cortical) microinfarcts seem to have significant impact on cognitive function. Expressions of cerebrovascular disease on MRI can also be highly diverse. In addition to large vessel infarcts, there are several expressions of small vessel disease that can be appreciated on MRI, including lacunar infarcts, white matter hyperintensities (WMH) and microbleeds. With current methods, cortical microinfarcts cannot be visualised by using MRI.

There is a growing body of literature that illustrates interrelationships between AD and cerebrovascular disease. Not only VaD, but also AD is predicted by a history of stroke. In population studies, clinically silent infarcts predict the subsequent development of dementia, believed to be of the Alzheimer type. Infarcts are, therefore, a risk factor for AD. Having a stroke doubles the risk of developing dementia, often AD. It seems that the stroke may serve to exacerbate pre-existing,

subclinical pathology. In line with this, baseline atrophy of the medial temporal lobe, rather than WMH, predicts subsequent cognitive decline in stroke survivors.

WMH are considered to reflect ischaemic, small vessel pathology. Severe WMH may suffice to cause VaD, but WMH are also frequently observed in AD. Subjects with severe WMH have a modestly, but non-significant, increased risk of AD, whereas atrophy of the medial temporal lobe is clearly associated with AD. However, patients in whom both abnormalities are observed on MRI mostly have a clinical diagnosis of AD, implying that the known association between hippocampal atrophy and AD is amplified by the additional presence of WMH (Table 6.7). These results support the view that WMH contribute to the clinical syndrome of AD.

Microbleeds are an expression of cerebrovascular disease that has recently received an increasing amount of attention. Microbleeds have long been considered to be specific for populations such as stroke. In the context of dementia, they are often observed in VaD, cerebral amyloid angiopathy (CAA) and CADASIL. However, it has become clear that microbleeds also frequently occur in patients with AD. One out of five patients with AD has at least one microbleed on T2*-weighted imaging. Of these, the majority has only one microbleed. A small proportion of patients with AD has many (>5) microbleeds; probably reflecting amyloid angiopathy (Fig. 6.21). Amyloid angiopathy typically reflects the combination of Alzheimer's pathology and vascular damage, as it refers to the deposition of amyloid in small-to-medium sized blood vessels of the brain and leptomeninges. The amyloid deposits may cause breakdown of the blood vessel wall, resulting in haemorrhage.

The clinical relevance of microbleeds is not yet clear. In stroke patients without cognitive impairment and in those with subcortical vascular dementia, microbleeds have been associated with cognitive decline. In AD, patients with many microbleeds seem to perform worse on a cognitive screening test than AD patients without any microbleed, regardless of the degree of atrophy, WMH, or disease duration. Such patients also tend to have more abnormal levels of amyloid-beta 1–42 in the CSF than AD patients without any microbleeds, suggesting a direct link with neurodegenerative pathology. In addition, microbleeds convey a more than 2-fold increased risk of mortality, regardless of other expressions of small vessel disease on MRI, or vascular comorbidity (Fig. 6.22). Microbleeds might predispose for future haemorrhages, although the benefits of antithrombotic agents in secondary prevention of vascular diseases seem to outweigh the potential risks.

6.7.3 The Contribution of Neurodegenerative Pathology to VaD

VaD is the second most prevalent type of dementia, certainly over the age of 75 years. Although by definition, cerebrovascular disease underlies dementia in VaD, atrophy is also commonly observed. Neuropathologically, pure VaD is a rare condition, as cerebrovascular disease is often accompanied by neurodegenerative changes. According to the radiological National Institute of Neurological Disorders and Stroke (NINDS)–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) criteria, involvement of more

Table 6.7 Odds ratios for AD dependent on medial temporal lobe volume and WMH

Medial temporal lobe	Large	Large	Small	Small
White matter hyperintensities	Mild	Severe	Mild	Severe
AD (number)	9	10	16	23
Control (number)	14	10	4	0
Odds ratio	1.0	1.6	6.2	Infinity
(95% CI)	(Reference)	(0.4–6.2)	(1.3–32.7)	(6.3–inf.)

Data are presented as odds ratios and their exact 95% confidence intervals. Note that, due to the zero cells, the accompanying OR is indeterminably high

Source: Adapted from Neurology 2004;62(10):1862–1864

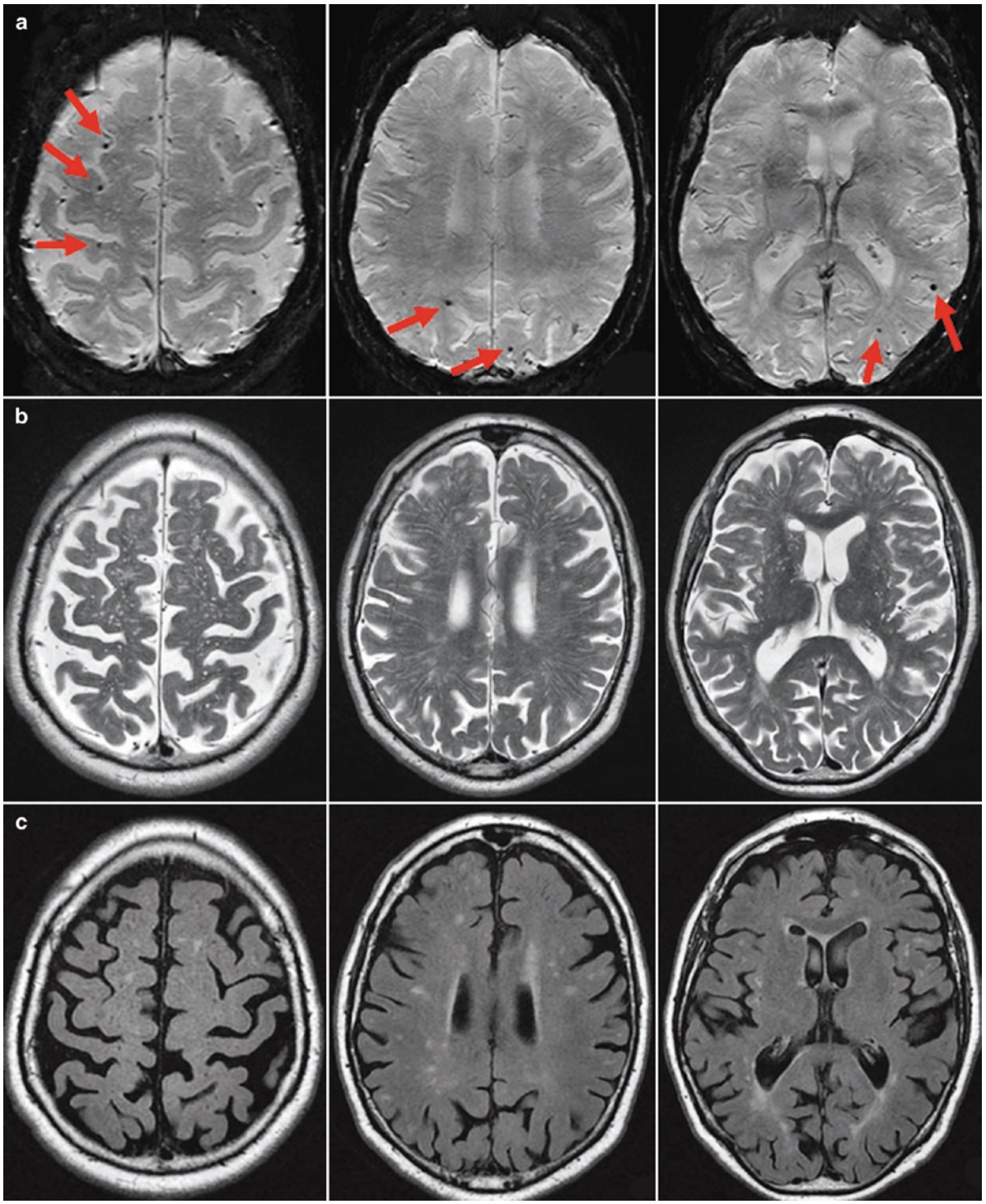

Fig. 6.21 Microbleeds are small, dot-like lesions of low signal intensity in the brain that can be observed on T2*-weighted images. This patient with a clinical syndrome of AD, presented with multiple microbleeds on brain MRI, mostly in the posterior cortex (total count > 50), suggestive of cerebral amyloid angiopathy. Susceptibility-weighted images are presented in **panel A** (examples of microbleeds indicated by *red arrows*). For comparison, matching slices on T2-weighted images (**panel B**) and FLAIR (**panel C**) are shown

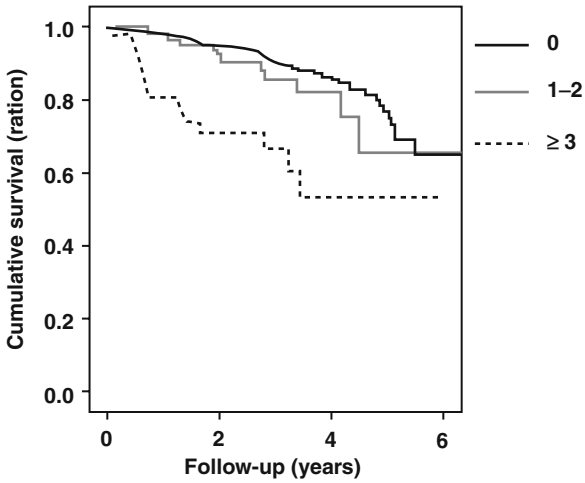

Fig. 6.22 Kaplan-Meier curve illustrating the dose relationship between microbleeds and risk of mortality. Patients with many microbleeds are at increased risk of mortality. Hazard ratio (95% confidence interval): 2.4 (1.4–4.3). (Reproduced with permission from Stroke 2009;40(2):492–498)

than 25% of the total white matter, multiple lacunes, bilateral thalamic lesions and strategic infarcts can lead to a diagnosis of VaD. In clinical practice, the majority of patients with VaD have small vessel disease, rather than large vessel disease.

In patients fulfilling diagnostic criteria for VaD, atrophy of the medial temporal lobe – generally regarded as an indicator of neurodegenerative (Alzheimer's) pathology – is the strongest predictor of severity of cognitive decline, when compared with measures of cerebrovascular small vessel disease, such as WMH and (lacunar) infarcts. Presumably, the occurrence of medial temporal lobe atrophy (MTA) in patients with VaD is attributable to concomitant Alzheimer's pathology, or even to misdiagnosis (see Fig. 6.23).

Alternatively, MTA may be secondary to vascular pathology, more precisely to small vessel disease and ischaemia. Nonetheless, when there is neuroimaging evidence of mixed pathology (degenerative and

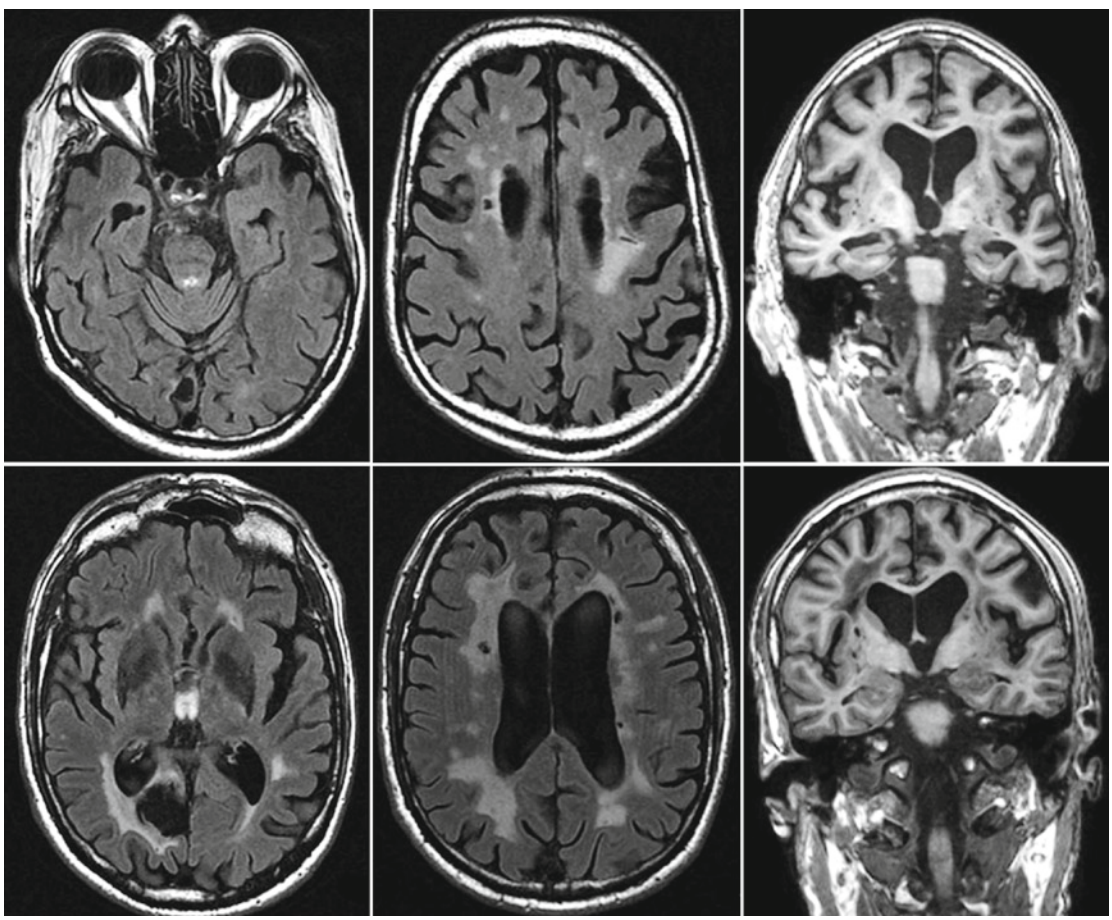

Fig. 6.23 Hippocampal atrophy in VaD. Example of two patients with a diagnosis of vascular dementia, based in both cases on confluent white matter hyperintensities, multiple lacunar infarcts and a large vessel infarct. In the first patient, diagnosis of vascular dementia is accompanied by clear atrophy of the medial temporal lobe (*upper panel*). In the second patient, there is no evidence of any atrophy of the medial temporal lobe (*lower panel*)

vascular), atrophy seems to predict or correlate better with dementia than small vessel disease. Likewise, approximately 10% of patients fulfilling diagnostic criteria for VaD have midbrain atrophy (Fig. 6.24), which also is associated with cognitive impairment even after correction for abnormalities representing degenerative and vascular supratentorial pathology. It is conceivable that midbrain atrophy may also represent concomitance of degenerative pathology, and that its occurrence in the periaqueductal grey matter may explain the association between midbrain atrophy and cognitive impairment by disruption of mesencephalic connections and neurotransmitter systems.

Correlation of post-mortem findings with antemortem MRI measures in a sample of patients with a wide range of cognitive dysfunction has revealed complex relationships of vascular and neurodegenerative pathology with MRI features. During life, volumes of cortical grey matter and hippocampal volumes are the best predictors of cognitive functioning, as opposed to WMH volume and number of lacunes, which are only marginal predictors of cognitive decline. When neuropathological indices are related to MRI findings, cortical grey matter volume on MRI is histopathologically predicted by a combination of the degree of Alzheimer's pathology, arteriosclerosis and subcortical infarcts, whereas the hippocampal volume on MRI is best predicted by the degree of Alzheimer's pathology and hippocampal sclerosis. These findings indicate that observations on MRI are often the result of a combination of different underlying neuropathological changes.

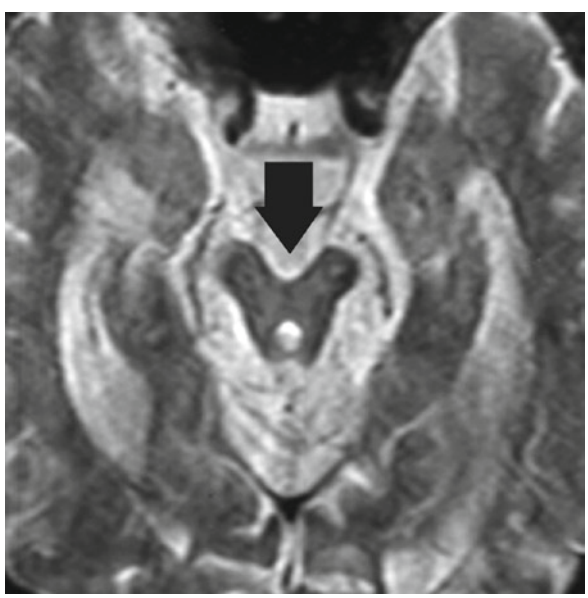

Fig. 6.24 Midbrain atrophy in VaD. Axial T2-weighted image showing midbrain atrophy (*arrow*) in a patient with the clinical diagnosis of vascular dementia. (Reproduced with permission from Stroke 2006;37:105–110)

6.7.4 How Do Neurodegenerative and Cerebrovascular Changes Interact?

To date, there is dispute about the relation between neurodegenerative and cerebrovascular changes. They may be separate and unrelated processes that co-occur incidentally. The majority of dementias may, therefore, be of the mixed type (Fig. 6.25), but it is also possible that misdiagnoses occur. For example, patients that are diagnosed as VaD, just on the basis of the presence of cerebrovascular damage on MRI, may in fact suffer of dementia mostly due to Alzheimer's pathology. Conversely, it is possible that microinfarcts, which cannot be recognised on MRI, underlie the clinical syndrome of dementia labelled as AD.

A second possibility is that different types of pathology add up, until a threshold is reached and clinical dementia ensues, so that, in the presence of additional cerebrovascular damage, a less severe stage of Alzheimer's pathology is sufficient to cause the clinical syndrome. Third, neurodegenerative and cerebrovascular changes may act in synergy, aggravating each other's effect. This is probably most clearly illustrated by the concept of amyloid angiopathy, where Alzheimer's pathology is deposited in the vessel walls, resulting in vascular damage. A theoretical representation of how neurodegenerative and vascular disease might interplay, via the concept of amyloid angiopathy (visible on MRI as microbleeds) is provided in Fig. 6.26.

The e4 allele of the Apolipoprotein E (APOE) gene is associated with an elevated risk of AD. The mechanism through which APOE e4 contributes to the development of AD has not yet been fully clarified, but it is known that this gene is implicated in lipid transportation, and is associated with both (coronary) atherosclerosis and amyloid angiopathy. These links between APOE e4 and cerebrovascular disease suggest that in APOE e4 carriers, AD may develop as a consequence of impaired vessel walls causing reduced clearance of

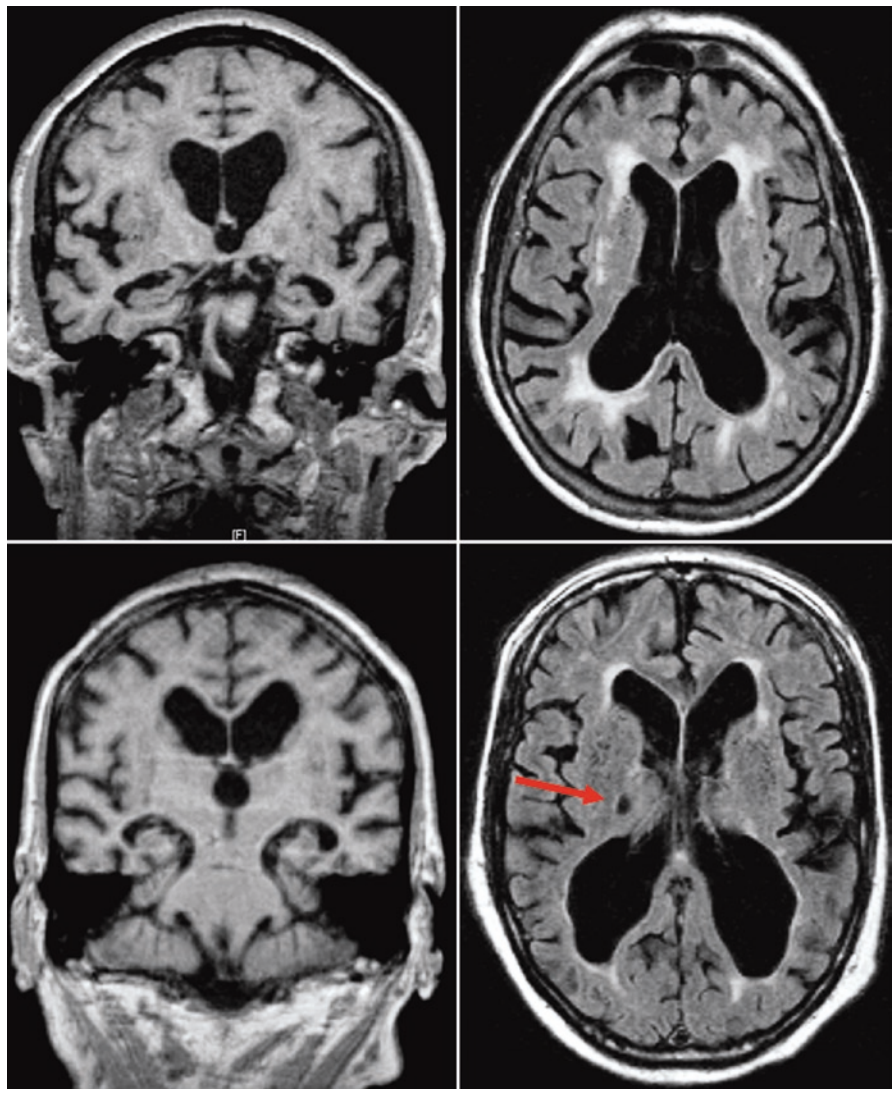

Fig. 6.25 Most patients with dementia at old age have mixed disease. Presented are two patients with pronounced atrophy of the medial temporal lobe, and cerebrovascular disease. The upper patient has severe WMH. The lower patient has a thalamic lesion on the right side (*red arrow*). The clinical diagnosis of both patients was possible AD

amyloid-beta (red route in Fig. 6.26). Conversely, in APOE e4 non-carriers, the disease would be caused by elevated production of amyloid-beta, resulting in more 'pure' AD. Following this line of reasoning, it is conceivable that mixed disease is especially prevalent among APOE e4 carriers. This is a hypothesis that remains to be proven, however.

There are still many questions left unanswered with respect to the relationships between neurodegenerative and cerebrovascular disease. Not in the least, because it is difficult to study their respective contributions during life. Post-mortem studies by definition are post hoc, and may start too late, as it is always the end stage that is studied. Moreover, there is a time lag between in vivo clinical diagnosis and post-mortem observations of neuropathology, often involving several years. As discussed above, observations on MRI are often not specific for type of neuropathology. For example, global atrophy, often considered to be a measure of neurodegenerative disease, is also predicted by underlying vascular disease. Also, MRI observations may reflect multiple types of underlying neuropathology. Additional studies on the association between neuropathological findings, MRI measures and clinical outcome are certainly needed, to shed light on the role of the respective neuropathological substrates in causing cognitive decline and dementia, and to identify MRI measures that more specifically reflect the underlying neuropathological substrates.

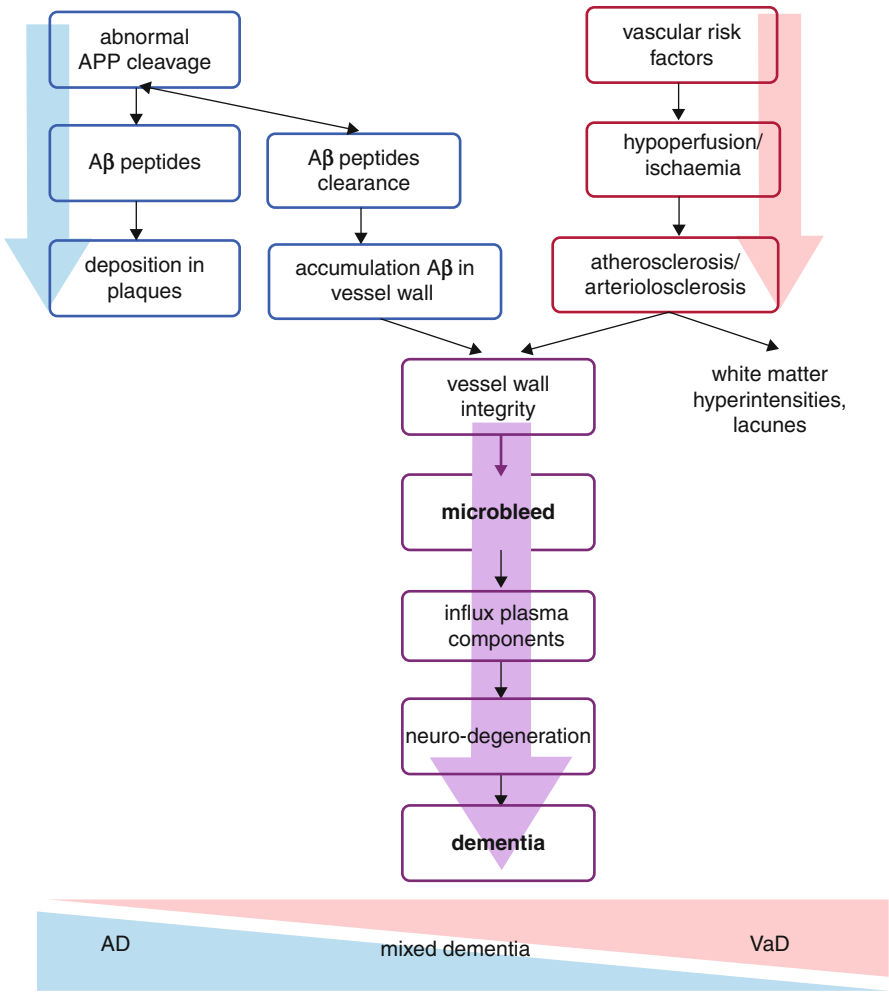

Fig. 6.26 Proposed representation of the interplay between neurodegenerative (*left side, blue representation*; amyloid cascade hypothesis) and vascular (*right side; red representation*; vascular hypothesis) pathological pathways of Alzheimer disease. Amyloid angiopathy (visible on MRI as microbleeds) may play an important role in the interaction between the two. The two routes can both contribute to the clinical syndrome of dementia. Depending on their relative contribution, the diagnosis could be AD, VaD or mixed dementia

6.7.5 Shifting Paradigms

In this section, we have shown accumulating evidence suggesting that patients do not have either AD or VaD; rather, many patients are affected by both types of pathology. Instead of exclusively labelling all patients as either neurodegenerative or cerebrovascular, both disorders could be viewed as a continuum, with purely neurodegenerative disease on one end, and purely cerebrovascular disease on the other end of the spectrum.

Currently, neuroimaging is recommended at least once during the diagnostic work-up of dementia, for the exclusion of surgically treatable disorders, such as tumours or haematomas. In addition, MRI may also add positive evidence for the presence of specific types of neuropathology. It is conceivable that the role of MRI in dementia will change in the future. We propose a new diagnostic paradigm where – irrespective of specific diagnostic labels – MRI is used both as a starting point for treatment choice, and as a means to monitor disease progression and treatment effect. In this paradigm, where a diagnosis would be more than just a label, treatment and management of the patient would directly follow observations of markers on MRI (Fig. 6.27). For example, observing MTA might be a reason to start cholinesterase inhibitors (currently registered for treatment of AD and dementia with Lewy bodies only, while MTA is also frequently observed in vascular dementia). Evidence of cerebrovascular disease should lead to treatment of vascular risk factors and lifestyle modification (e.g. quit smoking and increase physical activity), even when the clinical diagnosis is probable AD. In this framework, other

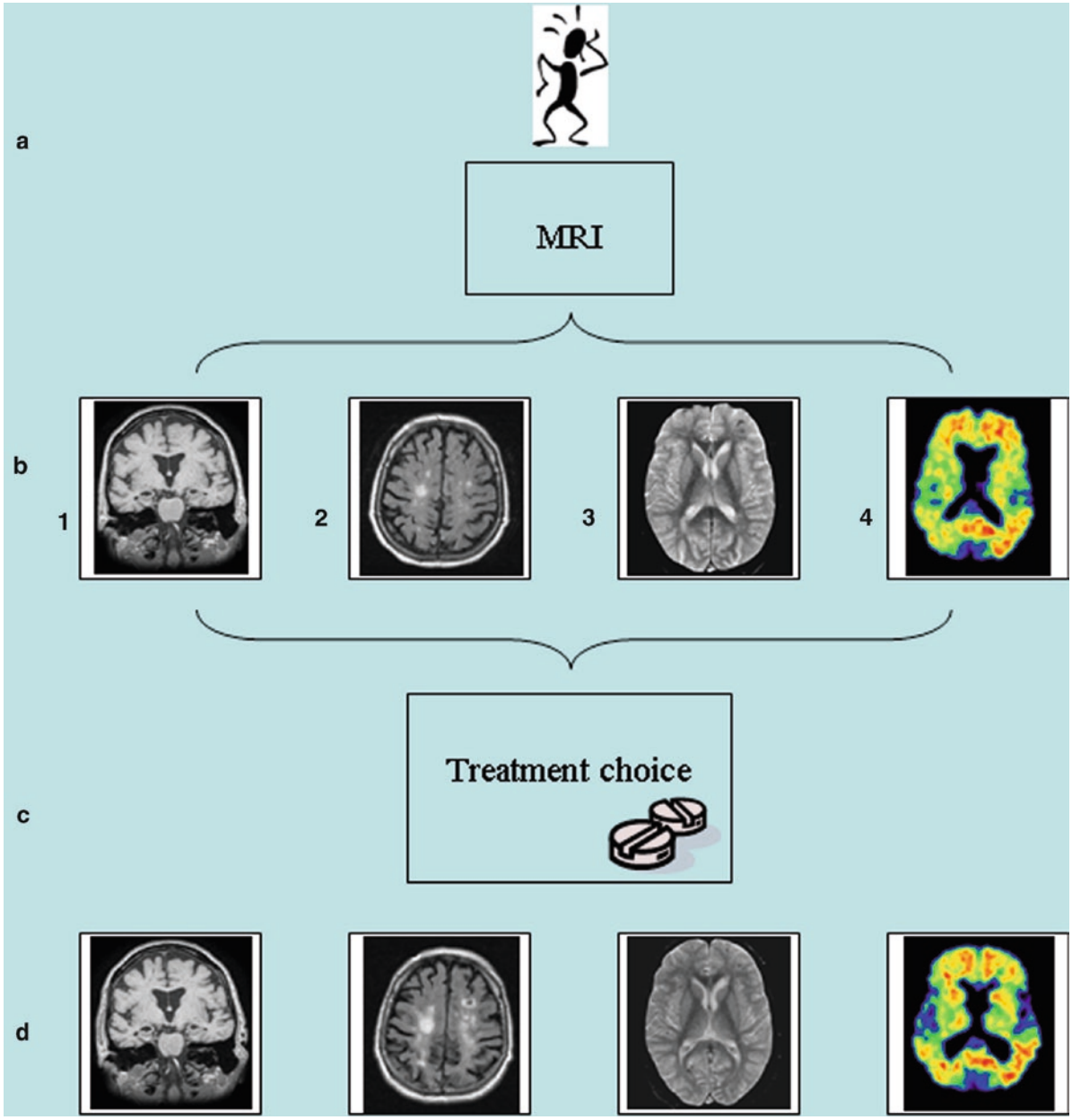

Fig. 6.27 Diagram illustrating the use of MRI as a starting point for treatment choice and monitoring of treatment effect. Please note that this is a representation of a potential future, not an actual recommendation for clinical practise to date. A patient with a clinical syndrome of dementia presents at a memory clinic (**a**). Even when from the specific clinical signs and symptoms it is not perfectly clear which etiological diagnosis best befits this patient, an MRI is made to guide treatment choice. Potential MRI findings with treatment implications could be (**b1**) medial temporal atrophy on coronal T1-weighted images, (**b2**) white matter hyperintensities and/or lacunes on FLAIR images, (**b3**) microbleeds on T2*-weighted images, (**b4**) amyloid load on PIB-PET (as yet, amyloid cannot be demonstrated on MRI, but it is conceivable that this will be the case in the future with ultra-high field MRI). Treatment choice (**c**) will subsequently be based on the observations on MRI, which can be any combination of the observations under (**b**): for example cholinesterase inhibitors in case of atrophy of the medial temporal lobes, treatment of vascular risk factors and explicit advice of lifestyle modification in case of small vessel disease, the observation of microbleeds might prompt carefulness in the use of anticoagulants, and the observation of severe amyloid-load might suggest that vaccination therapy can be useful. Finally, MRI can be used to monitor the effect of the chosen treatment strategy on the evolvement of brain changes (**d**). If necessary, treatment can then be adapted, based on new imaging findings

markers of vascular disease, such as a history of hypertension, diabetes mellitus or hypercholesterolaemia, which have all been related to both the observation of small vessel disease on MRI and to an increased incidence of AD, should be taken into account as well.

By stratification of treatment on the basis of MRI findings, the effectiveness of treatment may be improved. Moreover, with repeated imaging, MRI markers may be used to evaluate treatment effect and to monitor disease progression. Other biomarkers, such as cerebrospinal fluid biomarkers and positron emission tomography, may have added value in combination with the use of MRI.

Suggestions for Further Reading

Bartsch T, Alfke K, Stingele R, Rohr A, Freitag-Wolf S, Jansen O, Deuschl G (Nov 2006) Selective affection of hippocampal CA-1 neurons in patients with transient global amnesia without long-term sequelae. Brain 129(Pt 11):2874–2884

Bastos Leite AJ, van der Flier WM, van Straaten EC et al (2006) Infratentorial abnormalities in vascular dementia. Stroke 37:105–110

Bastos-Leite AJ, van der Flier WM, Van Straaten EC et al (2007) The contribution of medial temporal lobe atrophy and vascular pathology to cognitive impairment in vascular dementia. Stroke 38:3182–3185

Beach TG, Wilson JR, Sue LI, Newell A, Poston M, Cisneros R, Pandya Y, Esh C, Connor DJ, Sabbagh M, Walker DG, Roher AE (Jan 2007) Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. Acta Neuropathol 113(1):13–21

Birnbaum J, Hellmann DB (2009) Primary angiitis of the central nervous system. Arch Neurol 66:704–709

Buechner S, Moretti M, Burlina AP et al (2008) Central nervous system involvement in Anderson-Fabry disease: a clinical and MRI retrospective study. J Neurol Neurosurg Psychiatry 79:1249–1254

Casserly I, Topol E (2004) Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. Lancet 363:1139–1146

Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG (2009) Cadasil. Lancet Neurol 8:643–653

Chao CP, Kotsenas AL, Broderick DF (2006) Cerebral amyloid angiopathy: CT and MR imaging findings. Radiographics 26:1517–1531, http://www.angiopathy.org/index.html

Cordonnier C, van der Flier WM, Sluimer JD et al (2006) Prevalence and severity of microbleeds in a memory clinic setting. Neurology 66:1356–1360

Erkinjuntti T, Inzitari D, Pantoni L et al (2000) Research criteria for subcortical vascular dementia in clinical trials. J Neural Transm Suppl 59:23–30

Fein G, Di SV, Tanabe J et al (2000) Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. Neurology 55:1626–1635

Firbank MJ, Burton EJ, Barber R et al (2007) Medial temporal atrophy rather than white matter hyperintensities predict cognitive decline in stroke survivors. Neurobiol Aging 28:1664–1669

Goos JD, Kester MI, Barkhof F, Klein M, Blankenstein MA, Scheltens P et al (2009) Patients with Alzheimer disease with multiple microbleeds: relation with cerebrospinal fluid biomarkers and cognition. Stroke 40(11):3455–3460

Greenberg SM et al (2009) Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol 8:65–74

Henneman WJ, Sluimer JD, Cordonnier C, Baak MM, Scheltens P, Barkhof F et al (2009) MRI biomarkers of vascular damage and atrophy predicting mortality in a memory clinic population. Stroke 40(2):492–498

Hodges JR, Warlow CP (Oct 1990) Syndromes of transient amnesia: towards a classification. A study of 153 cases. J Neurol Neurosurg Psychiatry 53(10):834–843

Holton JL et al (2002) Familial Danish dementia: a novel form of cerebral amyloidosis associated with deposition of both amyloid-Dan and amyloid-beta. J Neuropathol Exp Neurol 61:254–267

Jagust WJ, Zheng L, Harvey DJ et al (2008) Neuropathological basis of magnetic resonance images in aging and dementia. Ann Neurol 63:72–78

Leys D, Henon H, Mackowiak-Cordoliani MA et al (2005) Poststroke dementia. Lancet Neurol 4:752–759

Mead S et al (2000) Familial British dementia with amyloid angiopathy: early clinical, neuropsychological and imaging findings. Brain 123:975–991

Merino JG, Hachinski VC (2009) Historical perspective. In: Festa JR, Lazar RM (eds) Neurovascular neuropsychology. Springer, pp 1–6

Moore DF, Frank Y, Schiffmann R et al (2003) Increased signal intensity in the pulvinar on T1-weighted images: a pathognomonic MR Imaging sign of Fabry disease. AJNR Am J Neuroradiol 24:1096–1101

Mungas D, Reed BR, Jagust WJ et al (2002) Volumetric MRI predicts rate of cognitive decline related to AD and cerebrovascular disease. Neurology 59:867–873

Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) (2001) Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet 357:169–175

Pantoni L (2010) Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 9:689–701

Pantoni L, Pescini F, Nannucci S, Sarti C, Bianchi S, Dotti MT, Federico A, Inzitari D (2010) Comparison of clinical, familial, and MRI features of CADASIL and NOTCH3-negative patients. Neurology 74:57–63

Peters R, Burch L, Warner J, Beckett N, Poulter R, Bulpitt C (8 Aug 2008) Haemoglobin, anaemia, dementia and cognitive decline in the elderly, a systematic review. BMC Geriatr 8:18

Peterson PL, Axford JS, Isenberg D (2005) Imaging in CNS lupus. Best Pract Res Clin Rheumatol 19:727–739

Revesz T et al (2009) Genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies. Acta Neuropathol 118:115–130

Schneider JA, Arvanitakis Z, Bang W et al (2007) Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 69:2197–2204

Snowdon DA, Greiner LH, Mortimer JA et al (1997) Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 277:813–817

Steen RG, Miles MA, Helton KJ, Strawn S, Wang W, Xiong X, Mulhern RK (Mar 2003) Cognitive impairment in children with hemoglobin SS sickle cell disease: relationship to MR imaging findings and hematocrit. AJNR Am J Neuroradiol 24(3):382–389

Susac JO et al (2003) MRI findings in Susac's syndrome. Neurology 23(61):1783–1787

van den Boom R, Lesnik Oberstein SA, Ferrari MD, Haan J, van Buchem MA (2003) Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: MR imaging findings at different ages-3rd–6th decades. Radiology 229:683–690

van der Flier WM, Middelkoop HA, Weverling-Rijnsburger AW et al (2004) Interaction of medial temporal lobe atrophy and white matter hyperintensities in AD. Neurology 62:1862–1864

van Straaten EC, Scheltens P, Knol DL et al (2003) Operational definitions for the NINDS-AIREN criteria for vascular dementia: an interobserver study. Stroke 34:1907–1912

Vermeer SE, Prins ND, den Heijer T et al (2003) Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 348:1215–1222

Wu CC, Mungas D, Petkov CI et al (2002) Brain structure and cognition in a community sample of elderly Latinos. Neurology 59:383–391