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Multimodal MRI of Cerebral Small Vessel Disease

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1. Inroduction

Cerebral small vessel disease (cSVD) is a spectrum of clinical and imaging abnormalities linked to the pathology of small penetrating arteries and arterioles in the brain irrigating subcortical structures[1]. Accumulating data suggest that cSVD is the most prevalent neurological disorder in the ageing society of the developed world[2, 3]. The prevalence of its seemingly asymptomatic manifestations –silent brain infarcts- increases with age from approximately 6-7% at 60 years to 28% at 80 years of age according to a recent review[4]. In another study lacunar infarcts were found in 23% of all subjects over 65 years, and in 43% of subjects over 80 years of age[5]. Its acute, symptomatic manifestations –lacunar strokes- account for approximately 20% of all ischemic strokes[6-8]. Thus improved management of cSVD based on better understanding of the disease is of great importance.

cSVD is characterised by the arteriolosclerosis and/or microatheromatosis of small calibre (50-500 μm) cerebral arterial vessels caused by various pathologies[1]. Its most common, sporadic form is related to age and vascular risk factors including hypertension and diabetes in particular. Inherited forms are increasingly recognised with CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) being the most prevalent genetic cSVD caused by the mutation of NOTCH 3 gene encoding a transmembrane receptor of vascular smooth muscle cells[9, 10]. CADASIL -affecting young to middle aged, otherwise healthy individuals- provides a pure model for cSVD and therefore has been extensively studied [11]. Inflammatory, infective and immunologically mediated forms are usually part of systemic diseases of diverse origin characterised by central nervous system vasculitis [12]. Cerebral amyloid angiopathy (CAA) –a pathological hallmark of Alzheimer's disease- affects small vessels both cortically and subcortically and may also lead to ischemic changes, although it is particularly associated with recurrent lobar haemorrhages[12]. In this chapter we will only focus on the most common and well studied age and vascular risk factor related form of cSVD and CADASIL.

cSVD predominantly affects perforating end-arteries branching usually perpendicularly from a large parent artery. These penetrating arteries irrigate the so called perforator areas including the basal ganglia and internal capsule (lenticulostriate arteries from the anterior cerebral artery (ACA) A1 segment and middle cerebral artery (MCA) M1 segment), the

thalamus (thalamoperforators from the posterior cerebral artery (PCA) and posterior communicating artery (PCoA)), the pons (pontine perforators from the basilar artery (BA)) and the hemispheric deep white matter -centrum semiovale (perforators from the cortical, leptomeningeal arteries)[13-16].

The pathological changes in cSVD lead to luminal narrowing, decreased autoregulation and vasoreactivity, and vessel wall damage in the cerebral microvessels resulting in their i. gradual stenosis, ii. sudden occlusion or iii. rupture. As a consequence the subcortical brain tissue suffers from i.: diffuse chronic hypoperfusion and ischemia leading to the progressive disintegration of cerebral white matter[17]; ii.: acute localised ischemia resulting in lacunar infarcts[18]; ad iii.: acute major haemorrhages or microbleeds [12, 19]. In an advanced state of the disease cerebral atrophy invariably occurs as a remote and/or diffuse consequence of vascular lesion burden[20]. The pathogenesis of cSVD manifestations is summarized in **Figure 1**. The gradual ischemic tissue damage clinically manifests in progressive vascular cognitive impairment (mainly executive dysfunction) and physical disability (gait disturbances, pseudobulbar palsies, urinary incontinence etc.), whereas acute focal ischemia presents with the so-called lacunar syndromes. Cerebral microbleeds are usually asymptomatic and their clinical significance is yet to be determined.

In this chapter we will summarize recent knowledge about the MRI characteristics of cSVD. Since the cerebral microvasculature cannot be currently visualized in vivo, the consequent parenchymal lesions (lacunar infarcts, white matter lesions, microbleeds and atrophy) have been adopted as markers of cSVD[12]. We will not discuss the issue of major haemorrhages.

2. Lacunar infarcts

2.1 Definition

According to the "lacunar hypothesis" first proposed by Fisher small subcortical infarcts of a diameter less than 15 mm –called lacunar infarcts (LI)- result from the sudden occlusion of penetrating arteries due to cSVD in typical locations -the perforator areas (see above) [18]. Infarcts of this type have been linked to particular clinical syndromes with a relatively good prognosis called the lacunar syndromes, most frequent of which are the classical ones: pure motor stroke, pure sensory stroke, ataxic hemiparesis, dysarthria-clumsy hand syndrome and sensorimotor stroke. The concept of lacunar stroke that entered stroke classifications was based on postmortem and CT based studies both with considerable limitations. The pathological studies were limited by the low mortality of lacunar strokes and by the anatomical changes occurring in the chronic stage and/or during fixation. CT has a low sensitivity to detect small infarcts in certain locations (posterior fossa, cortex) and in the acute stage and cannot differentiate between fresh and old lesions. The advent of MRI and especially its newer techniques such as diffusion weighted imaging (DWI), perfusion weighted imaging (PWI) and diffusion tensor imaging (DTI) has slightly modified our understanding of LIs[21].

2.2 Conventional MRI

Because of their small size visualizing LIs is much more problematic than that of larger territorial infarcts. Compared to CT conventional MRI sequences such as T1 weighted, T2

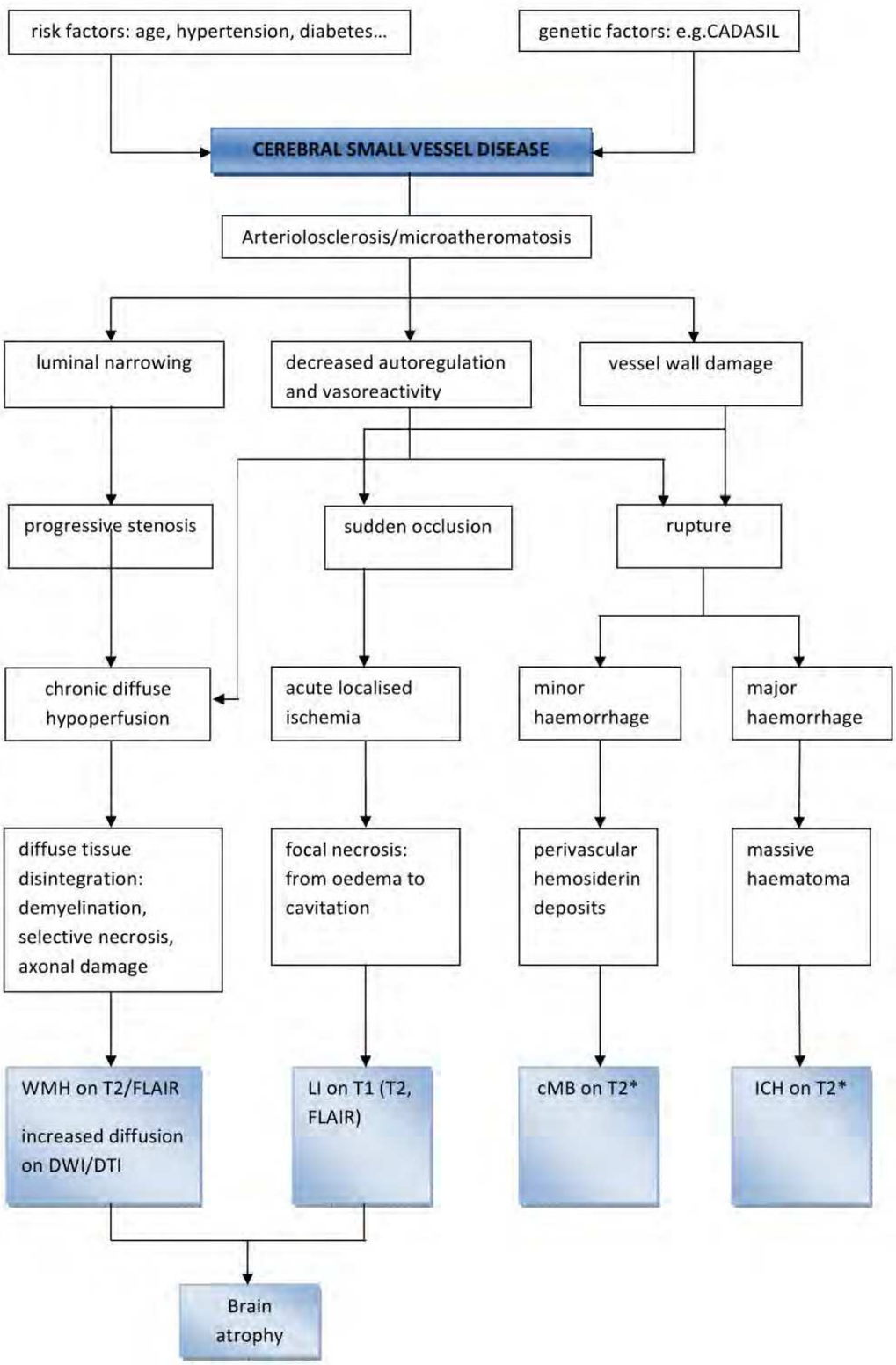


Fig. 1. Pathogenesis of cSVD manifestations. Abbreviations can be found in the text.

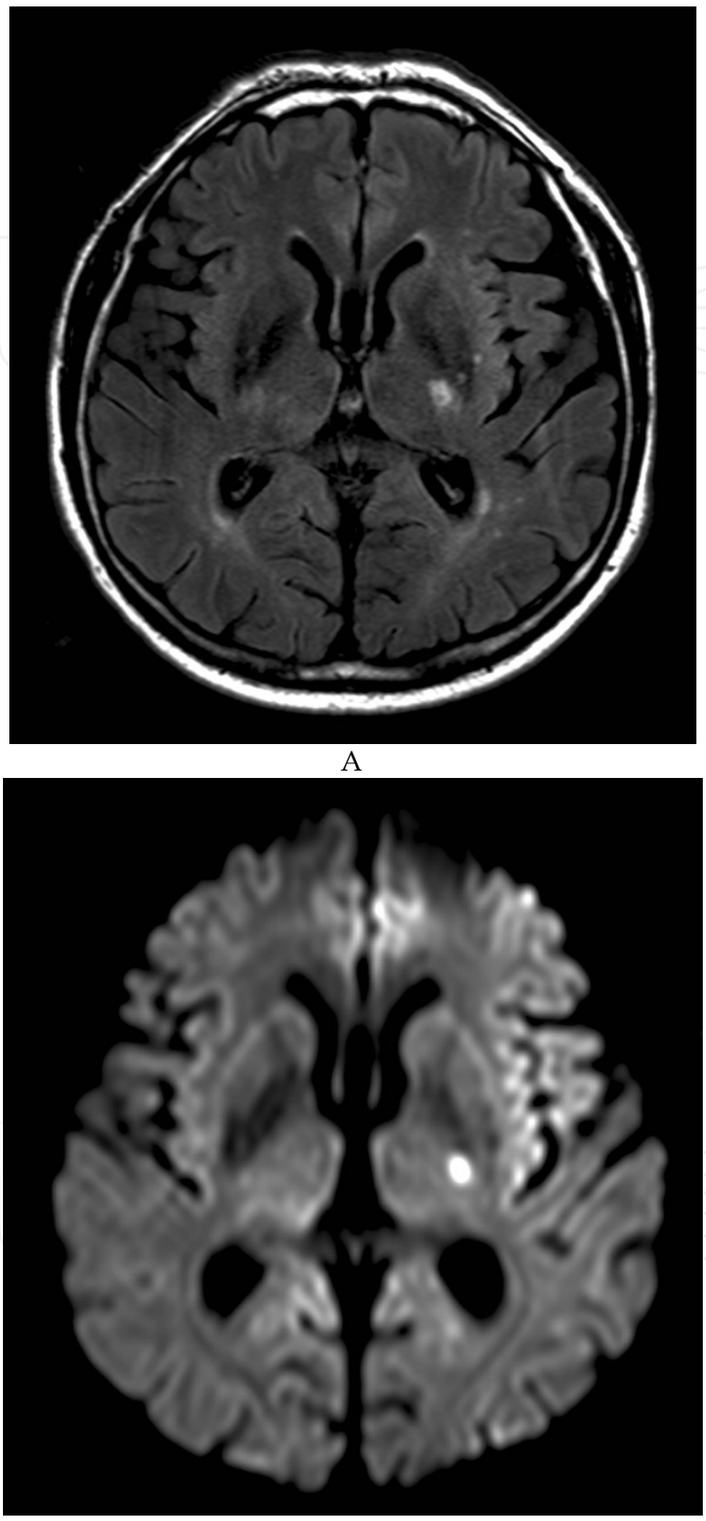
weighted imaging (T1/2WI) have a better spatial resolution, can image the posterior fossa without artifacts and have a better signal/noise ratio. LIs in the chronic stage appear as fluid filled cavities: hypointensities (black holes) on T1WI and hyperintensities on T2WI isointense with CSF. More recent LIs can be seen as hyperintensities on T2WI corresponding to brain tissue with increased water content (oedema). The widely used T2 based fluid attenuation inversion recovery (FLAIR) sequence that nulls the hyperintense signal of free water (mainly CSF) has some advantages over the T2WI. FLAIR is more sensitive in the detection of small, recent infarcts in the proximity of CSF spaces like those in the cortex or next to the ventricles. It can better estimate the age of LIs, because the signal of bulk water in chronic infarcts (cavitations) is nulled as well, whereas the increased bound water content of acute infarcts (solid tissue) is hyperintense [22]. Acute lesions on FLAIR give a relatively stable high signal for several weeks as opposed to the fluctuations in intensity seen on T2W images [23, 24] (**Figure 2**). However very early ischaemia within the first few hours especially in the lacunar dimension cannot be seen on any of the conventional MR sequences, because the signal abnormality only appears 6-8 hours after symptom onset.

2.3 DWI

Acute stage imaging has been revolutionised by the introduction of diffusion weighted imaging (DWI) that shows intracellular cytotoxic oedema resulting from critical cerebral ischaemia within the first few minutes after stroke onset [25]. The energy failure of brain cells results in the accumulation of intracellular bound water leading to a reduced diffusion of free water. This appears as marked hypointensity on the apparent diffusion coefficient (ADC) map which translates into high DWI signal [26-28]. In the case of cortical ischemia the reduced ADC returns to normal in 5-10 days [24, 29], while it stays low for a considerably longer period in subcortical disease. Consequently the hyperintensity due to diffusion restriction is also visible for longer[30]. Finally the ADC increases in the chronic stage indicating tissue disintegration/necrosis and vasogenic oedema [31]. At the same time the lesion appearing hyperintense on DWI may remain visible further on as the developing T2 lesion is also seen as high signal (T2 shine through). Therefore DWI and ADC map images have to be interpreted together to judge the age of an ischaemic infarct [32, 33]. The sensitivity of this sequence within 6 hours of symptom onset is of 95% and its specificity is of practically 100% for territorial infarcts [34]. Although understandably less for small subcortical infarcts, it is still the only reliable tool to visualise hyperacute LIs making it indispensable for acute phase therapy decisions (**Figure 2**).

2.4 DTI

A great proportion of LIs occur along the course of motor pathways whose affection well correlates with the severity of clinical symptoms and mainly determines prognosis. The extent of damage to these pathways can be judged by the diffusion tensor imaging (DTI) that is capable of visualizing white matter tracts [35]. This imaging method is based on the principle that cell membranes constrain the diffusion of water molecules which therefore diffuse longitudinally along axons in the white matter. By measuring diffusion from several directions the net orientation of axons in a voxel of white matter can be determined as a 3 dimensional vector –a „tensor". From these vectors projections of fibres can be generated and displayed as maps of white matter anatomy e.g. in a color-coded way where different colors stand for different directions, and colour brightness for the degree of anisotropy



A

B

Fig. 2. Subacute lacunar infarct in the posterior limb of the left internal capsule in a hypertensive patient on axial FLAIR (A) and DWI trace (B) image.

(color-coded directional image)[36, 37]. Fiber tracking is a further development that enables examiners to visualize fibers passing through a certain region of interest (ROI) or linking two ROIs thus delineating functional systems such as the corticospinal tract (CST). This method has been used to specifically localize small infarcts with regard to the functional pathway of the CST with good topographical accuracy [38-40] . Nevertheless, only a limited number of such tractography studies have been published to date, and few techniques have been assessed for their ability to track through lesions which disrupt tracts.

2.5 Size criterion

The size of LIs according to the classical definition is less than 15 mm –a rather arbitrary criterion based on early autopsy studies representing a healed, chronic state [18]. Since then we know that LIs in the acute stage can be significantly larger later undergoing shrinkage by about half their original size [41]. Furthermore surprisingly large infarcts can be caused by single perforator occlusion due to anatomic variations of the branching pattern of the lenticulostriate arteries. More or even all of the penetrating arteries may arise from one common stem [15, 42]. Therefore the size criterion for LIs can lead to stroke type misclassification and should be reconsidered[43].

2.6 Differentiation of underlying mechanisms

Apart from cSVD small subcortical infarcts may be caused by emboli of arterial or cardiac origin or critical hypoperfusion in watershed areas due to stenosing large artery disease (LAD). As determining stroke subtype is crucial for further management it is important to make an early etiological diagnosis. Acute lesion patterns on DWI help us to differentiate between the underlying pathomechanisms [44]. The co-existence of a small striatocapsular and one or more distal small cortical lesions points to an embolus originally stuck in the M1 segment obstructing the orifices of the lenticulostriate arteries and later on fragmented and washed further up into one or more small cortical branches of the MCA[45, 46]. This scenario is also possible in the posterior circulation -although much less frequently- with the picture of a small brainstem lesion together with a PCA territory thalamic or cortical infarct. Multiple small subcortical lesions in the same vascular territory are associated with LAD (arterio-arterial embolism), whereas those in different territories/bilaterally suggest a proximal embolic origin (heart or aortic arch) [47]. In the latter case it is not clear whether they result from repeated embolism or a single embolic shower [44].

It has also been proposed that multiple small infarcts may also be due to cSVD affecting several vessels contemporaneously [48]. As mentioned earlier subcortical lesions can remain hyperintense on DWI for much longer than cortical ones. Thus several lesions in diffferent vascular territories could arise contemporaneously (i.e. within a few weeks of each other) but not simultaneously and all appear hyperintense on DWI falsely raising the suspicion of an embolic origin. In addition the small perforators arising perpendicularly from large vessels seem hardly accessible for fast moving emboli from an anatomical point of view. Therefore the purely embolic origin of multiple small subcortical DWI lesions in multiple vascular territories remains debated.

Partial borderzone infarcts in the watershed of superficial and deep perforators of the MCA and/or ACA may also appear similar to LIs. They can be seen as a single small lesion or a chain of them (rosary-like pattern) in the centrum semiovale alongside and slightly above the lateral ventricle. The demonstration of ipsilateral carotid artery disease and consequent

hypoperfusion shown by a perfusion deficit on perfusion weighted imaging (PWI) far exceeding the lesion area leads to diagnosis [49, 50].

2.7 Differentiation from other small cerebral lesions

LIs –especially when occurring without overt clinical symptoms, as incidential findings- may be difficult to distinguish from other hyperintense focal abnormalities on T2 weighted images. Studies correlating these lesions on in vivo and postmortem MR images with brain autopsy findings have identified the following pathologies: silent LIs, dilated Virchow-Robin spaces (VRS), foci of demyelination [51] due to incidental multiple sclerosis [52] or insufficient circualtion [53 54], gliosis, minute cysts and ventricular diverticuli [55, 56]. Distinction between an infarct, a focal gliosis and a plaque of demyelination is usually impossible on entirely imaging grounds, while the relationship of a diverticulum or cyst to the ventricles and their round shape are differential features [56].

VRSs are small perivascular spaces surrounding cerebral perforating arteries along their way through the parenchyma serving as drainage pathways for the cerebral interstitial fluid [57]. They are small (<1 mm) CSF isointense foci round shaped in cross section or linear in longitudinal section and run perpendicular to the brain surface [58-60]. Dilated VRSs, that can resemble lacunes, appear as an irregular or ectatic focal expansion of the otherwise regular and smooth VRSs [60]. They are still generally smaller than lacunes usually not exceeding 3 mm in diameter [61], whereas lacunes are larger and wedge shaped [59, 60]. Dilated VRSs have been associated with ageing [62], hypertension [63], widespread white matter lesions [64], sporadic cSVD[65 61], CADASIL[66], reduced cognitive function [64], and vascular dementia [65, 67]. However their real clinical significance is a subject of controversy. It is generally accepted that dilated VRSs are related to brain shrinkage around perforating vessels thus representing brain atrophy[68]. In this perspective they can both be regarded as common ageing phenomenon or as a marker of various pathologies. The distinction between normal and pathologically dilated VRSs can be made by judging the appearance of the adjacent brain tissue and the clinical context [60].

2.8 Silent cerebral infarcts

With the increasing use of MRI and the improving image quality an increasing number of patients are found to harbour small cerebral infarcts without any apparent stroke-like symptoms. It has now become clear that LIs only cause clinically evident stroke if they hit main sensorimotor pathways or occur in deep, subcortical nuclei. However the majority of them fall outside of these strategic locations and thus remain silent. Studies have shown that in the general population the prevalence of silent infarcts is fivefold higher than that of stroke, and they can be present in more than one fourth of people over 60 years of age [69-72]. They have approximately the same risk factors as symptomatic lacunes with hypertension being the most important [71, 72]; and their presence more than doubles the risk of subsequent vascular events, cognitive impairment and dementia [4, 73]. The extent of asymptomatic small vessel disease at the time of index stroke has a significant prognostic value for all outcomes [41, 73]. These findings have led to a modified understanding of cerebrovascular disease according to which strokes and TIAs –i.e. overt clinical symptoms- are only the tip of the iceberg of cSVD manifestations[21]. Silent infarcts are the underwater majority. It has not yet been evaluated though – and remains doubtful at present- whether the same diagnostic workup and risk factor management would be

justifiable upon finding a silent infarct as for a clinical stroke. Although by definition silent infarcts lack clinically overt stroke symptoms they progressively lead to less evident cognitive dysfunction, general physical disability and depression. Therefore these infarcts should be referred to as "covert" rather than "silent"[4, 74].

3. White matter lesions

3.1 Definition

White matter lesions seen in elderly patients and those with arterial hypertension are usually bilateral and more or less symmetrical areas of increased signal on T2 and FLAIR images (hence the name: white matter hyperintensities, WMH) located in the hemispheric deep white matter, the basal ganglia and the pons (**Figure 3**). The term "leukoaraiosis" meaning rarefaction of white matter is a description from the CT era of the same phenomenon[75]. WMHs are generally regarded as a consequence of ischemic brain tissue disintegration due to cSVD. Pathological studies found varying degrees of tissue damage appearing as WMH: from selective loss of myelin, to loss of myelin, axons and oligodendroglia consistent with incomplete infarcts, to near complete infarcts with astrogliosis[76-79].

3.2 Differential diagnosis

Multifocal or diffuse white matter lesions resembling those caused by cSVD can be found in a wide range of central nervous system (CNS) pathologies. These are summarized in **Table 1**. Their differential diagnosis is based on the complex evaluation of patient history, clinical context, other diagnostic tests and some differences in MRI appearance. Some of these WMHs are also ischemic in origin such as those caused by hypoperfusion 1. in watershed areas due to large artery stenosis, or 2. in different vascular territories due to various types of CNS vasculitis. These latter can occur either as an isolated CNS affection (primary CNS vasculitis), or as part of a systemic disease (SLE, Sjörgen syndrome, Behcet disease, antiphospholipid syndrome, sarcoidosis etc.) Others are a consequence of multifocal demyelination in multiple sclerosis (MS) and its variants or in central pontine/extrapontine myelinolysis. As opposed to cSVD MS is characterized by ovoid-shaped lesions perpendicular to the ventricles (Dawson fingers), frequently found in the corpus callosum, some of which may enhance contrast material. Plaques may also be located in the optic nerves, cerebellum and spinal cord. WMH caused by transient vasogenic edema due to the neurotoxic effect of various complex conditions (preeclampsia/eclampsia, severe hypertension, allogenic bone marrow transplantation, organ transplantation, autoimmune diseases and high dose chemotherapy) has been termed as Posterior reversible encephalopathy syndrome (PRES). The typical pattern of WMH in PRES resembles the watershed zones with a parietal and occipital (posterior) predominance. The subcortical white matter but also the cortex is involved to varying degrees and the lesions always regress[80]. White matter lesions of unclear nature can be seen in some infective diseases /postinfective conditions such as HIV, Lyme-disease or Syphilis related encephalopathies, Progressive multifocal leukoencephalopathy (PML), Subacute sclerosing panencephalitis (SSPE) or Acute disseminated encephalomyelitis (ADEM); and metabolic disorders like leukodystrophies, phenylketonuria and mitochondrial diseases (MELAS)[81, 82].

Ischemia
- Watershed hypoperfusion in large artery stenosis
- Primary CNS vasculitis
- Secondary CNS vasculitis (SLE, Sjörgen syndrome, Behcet disease, antiphospholipid syndrome, sarcoidosis etc.)

Demyelination
- Multiple sclerosis and variants
- Central pontine/extrapontine myelinolysis

Vasogenic oedema
- PRES

Unclear origin
- Infective/postinfective: HIV-, Lyme-, Syphilis- encephalopathy, PML, SSPE, ADEM
- Metabolic: leukodystrophies, phenylketonuria, MELAS

Table 1. CNS pathologies causing multiple/diffuse white matter lesions. Abbreviations can be found in the text.

3.3 Evaluation with conventional MRI

The severity of white matter damage on T2 and FLAIR images can be assessed semiquantitatively by various visual rating scales (proposed by Fazekas[83], Schmidt[84], Scheltens[85], Wahlund[86] and others) that take into account the location, pattern and extension of WMH[87]. The mostly used Fazekas-scale which evaluates WMH in two distinct locations: periventricular and deep subcortical white matter is presented in Table 2. The mildest forms are seen as smooth periventricular and punctuate deep WMH, whereas irregular periventricular, early confluent and confluent deep WMH represent an increasing severity of tissue damage. Furthermore the three dimensional extension of WMH can be quantified by volumetric evaluation[88, 89]. WMH volumetry is more reproducible and more sensitive for lesion progression than visual scales[90]. However the severity of white matter lesions as assessed by any of the above methods showed only moderate correlations with the clinical status represented by scores of disability and cognitive impairment[91-93].

	periventricular	**deep subcortical**
0	absence	no or a single punctate lesion
1	„caps" or pencil-thin lining	multiple punctate lesions
2	smooth „halo"	beginning confluency of lesions
3	irregular PVH extending into deep WM	large confluent lesions

Table 2. Fazekas visual rating scale for WMH (0-6 points)[83]

3.4 Evaluation with non-conventional MRI

The whole spectrum of microscopic brain tissue changes due to cSVD appears uniformly as WMH on conventional T2 based MR sequences. In order to obtain information on the degree of underlying tissue damage, non-conventional MRI techniques have been developed such as T1- and T2 relaxation time mapping, magnetisation transfer imaging (MTR) and diffusion tensor imaging (DTI)[94, 95]. This latter technique, that measures the degree and orientation of tissue water diffusivity, has been widely used in various cerebral diseases and conditions including cSVD[96]. As diffusivity partly depends on the density of cells in a given tissue volume (cell membranes and intracellular particles restrict water diffusion), the increase in diffusivity (as measured by a non-oriented derivate of the tensor, the mean diffusivity, MD) is proportional to the degree of ultrastructural tissue disintegration[97, 98]. Region of interest (ROI) based measurements detected increased MD inside but also outside of WMH, in the normal appearing white and subcortical grey matter[99, 100]. DTI can thus show tissue damage „invisible" for conventional MRI. In diffuse cerebral pathologies however -such as cSVD - a global, approach of whole brain diffusion histograms is more informative about the overall disease severity than a ROI analysis. Accordingly, MD histogram parameters have been reported to correlate more with clinical scores than WMH visual rating scales and volumetric data in cSVD both cross sectionally and longitudinally. Furthermore they were more sensitive than clinical scales in detecting change over time [101-106]. There are data indicating that the much simpler, quicker and widely available (DWI) derived ADC can be used similarly to DTI derived MD to quantify brain damage due to cSVD (findings of Gunda et al. to be published)(**Figure 3 and 4**). Therefore these quantitative MRI techniques seem to be a promising tool in the quantified monitoring of cSVD and could possibly act as surrogate markers in future therapeutic trials.

4. Cerebral microbleeds

4.1 Definition

Gradient echo (or T2* weighted) imaging is a sequence highly sensitive of blood. With its increasing use the number of visible haemorrhagic brain lesions has grown considerably and even millimetre-sized bleedings in the parenchyma have become detectable. Cerebral microbleeds (cMB) appear as small (<5 mm), homogenous, rounded foci of low signal intensity on T2* images[107](**Figure 5**). The signal loss is caused by hemosiderin –a paramagnetic blood degradation product that remains in macrophages for several years after haemorrhage indicating previous blood extravasation[108]. Thus the age of cMBs cannot be determined by MRI but the total haemorrhage burden can be assessed. Cerebral microbleeds appear larger on T2* images than the real tissue lesions due to the "blooming effect" of the MR signal[109]. The few studies relating cMBs on MRI to histopathological findings revealed focal hemosiderin deposits from the rupture of small vessels showing evidence of arteriolosclerosis or occasionally amyloid angiopathy clearly indicating an underlying small vessel pathology[110, 111].

4.2 Differential diagnosis

CMBs need to be distinguished from other causes of focal signal loss on T2* images. These include: flow voids of small arteries in cross-section that can be followed on

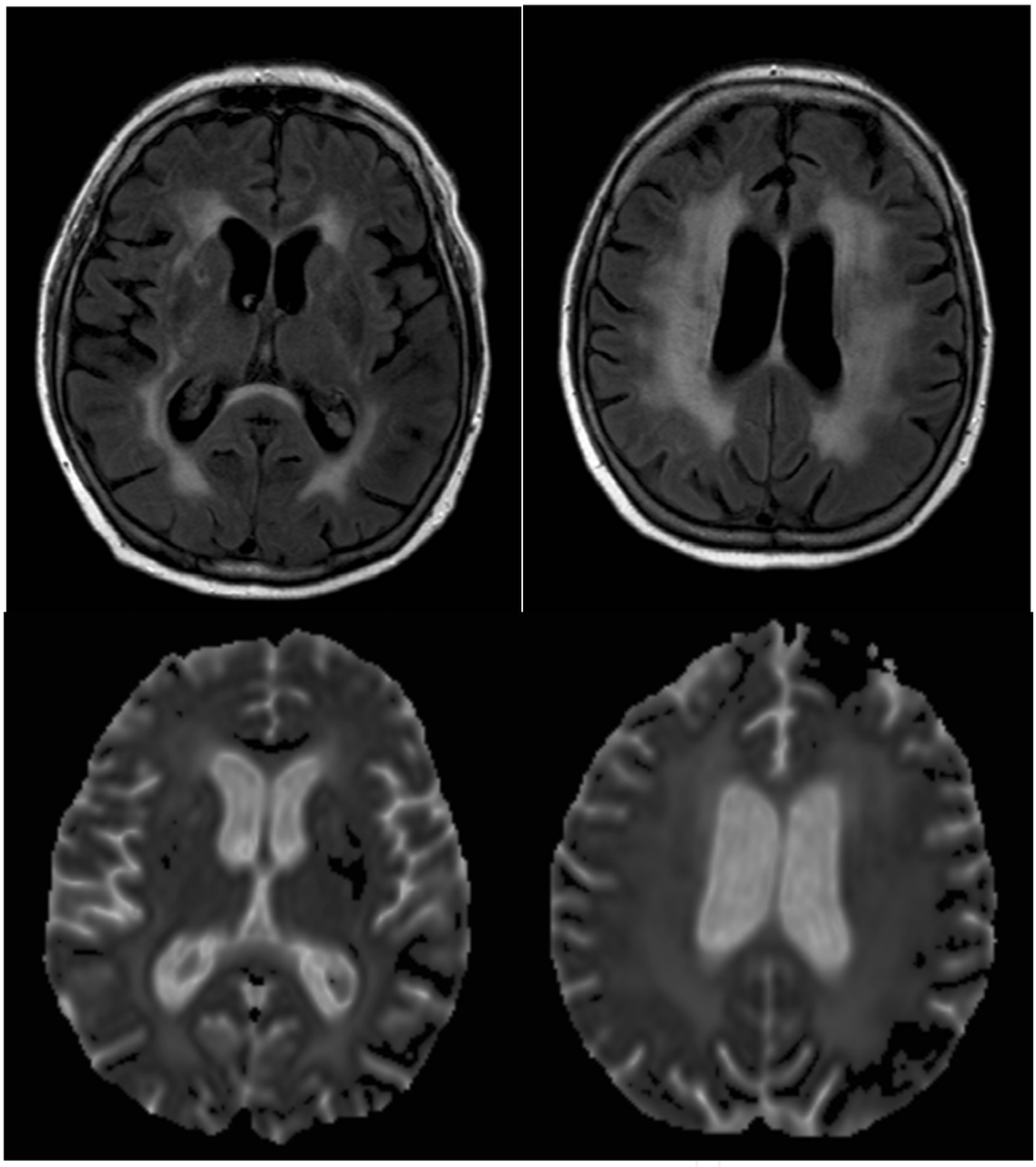


Fig. 3. Diffuse white matter lesions in a 70 year-old hypertensive patient on axial FLAIR image (upper row) and ADC map (lower row). Note the increased diffusion (ADC) corresponding to areas of WMH (FLAIR).

consecutive/neighbouring slices; the usually symmetrical calcifications or iron deposits in the globi pallidi that appear hyperdense on CT; type IV cavernous malformations and capillary teleangiectasias; foci of hypointensity compatible with hemorrhagic shear injury in head trauma, and even artefacts of metallic materials released from mechanical heart valves[112, 113]. Etiological differentiation of signal loss is based on the location, number and distribution of lesions, associated imaging findings and patient history.

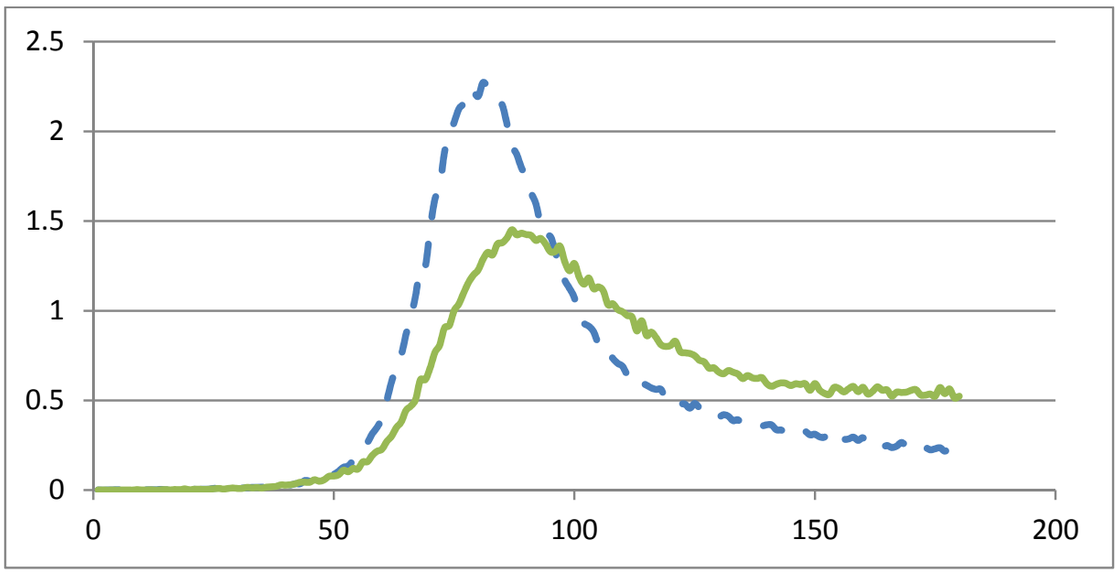


Fig. 4. ADC histogram of the patient on Figure 3 (green line) compared to a normal control (dashed blue line) (X: diffusivity in 10^{-5} mm^2/s, thresholded at 180; Y: relative frequency of voxels in %).

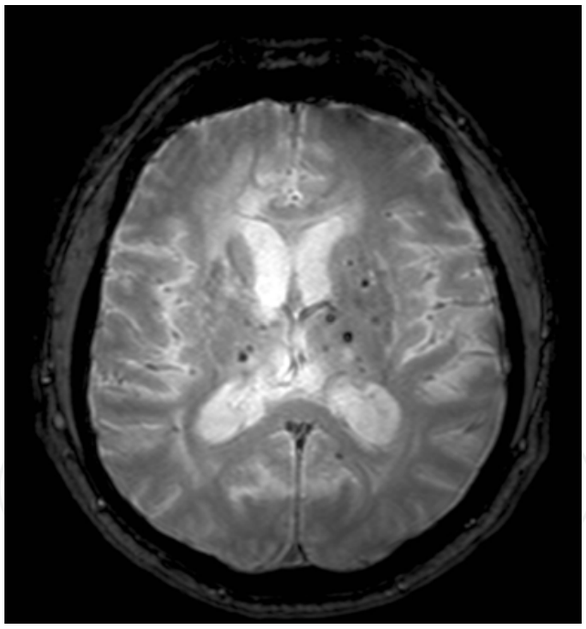


Fig. 5. Multiple cMBs in a 48 year-old hypertensive patient on axial T2* image.

4.3 Epidemiology

CMBs have been found in various patient populations as well as healthy elderly. Their occurrence was the most frequent in patients with intracerebral haemorrhage (ICH) and lacunar infarcts (due to hereditary or sporadic cSVD), less so in ischemic stroke patients of other subtypes. The most comprehensive review on cMB published in 2007 pooled data from comparable studies and found the overall prevalence of cMBs to be 5% among healthy

adults; 34% in ischemic stroke patients; and 60% in patients with ICH. The prevalence according to ischemic stroke subtype was 54% in lacunar-, 36% in atherothrombotic - and 19% in cardioembolic stroke. 38% of CADASIL patients had cMB. CMBs were more prevalent among patients with recurrent than first-ever stroke (44 vs 23% for ischemic and 83 vs 52% for haemorrhagic stroke)[114].

4.4 Clinical significance

CMBs were found to be associated with age, hypertension, other manifestations of cSVD (lacunar infarcts and WML), previous ischemic stroke and ICH, and an increased risk of recurrent lacunar infarct or ICH in those with lacunar infarct or ICH[114]. These findings further emphasize the common pathophysiological basis for cMB, LI, WML and ICH. Studies have shown that the anatomical distribution of ICHs is similar to that of cMBs in individual patients, but it is not the pre-existing cMBs that evolve into major haemorrhages[115]. Similarly several cases have been reported where patients with cMBs developed major haemorrhage after thrombolysis or antiplatelet therapy remote from the cMBs[116]. Thus cMBs can be considered as markers of a diffuse, bleeding-prone microangiopathy. This raised the important question whether patients with cMB are at an increased risk of ICH when treated with antiplatelet, anticoagulant or thrombolytic agents. For the time being there is no sufficient evidence to give a definite answer (some studies reported an increased risk, others not, all of them underpowered to draw firm conclusions)[116-120]. However some stroke centres already incorporate cMBs in their treatment decisions.

In conclusion cMBs are markers of a haemorrhage-prone cSVD and predictors of recurrent vascular events (be it ischemic or haemorrhagic). At present they cannot be considered as a contraindication to antithrombotic or thrombolytic therapies, but may play a role in the individual stratification of haemorrhagic risk, and may be incorporated in the design of clinical trials of anticoagulation/antiaggregation drugs.

5. Brain atrophy

Brain atrophy is best evaluated on T1WI and appears as shrinkage of brain parenchyma with a reduction of cortical thickness and an increase of internal and external CSF spaces. It can be assessed by visually rating the degree of ventricular dilatation and sulcal widening, by measuring the width of sulci or ventricles in a standard location, or by different three-dimensional volumetric methods that have now become the methods of choice.

Brain atrophy is a common phenomenon in normal ageing that increases progressively beyond the age of 65 years[121]. This process can be accelerated by numerous cerebral pathologies causing diffuse brain tissue loss such as degenerative diseases (like Alzheimer's disease and other primary dementias)[122], demyelinating diseases (MS)[123] and cerebrovascular disorders (**Figure 6**). In these latter conditions, the importance of brain atrophy has only recently been recognised. A number of imaging studies using quantitative brain volumetry demonstrated atrophy in both focal and diffuse cerebrovascular diseases[124-127]. Brain atrophy correlated strongly with the clinical status and cognitive scores, and proved to be a sensitive marker of disease progression in cSVD[104, 128, 129]. It is now widely accepted that purely subcortical cSVD can lead to cortical volume loss[129, 130]. How subcortical ischemic damage leads to cortical atrophy is not fully elucidated, but the diffuse and/or remote effect of lacunar lesions and tissue microstructural changes through Wallerian degeneration, secondary axonal loss due to deinervation and local or remote neuronal apoptosis are possible mechanisms[20, 124, 131, 132].

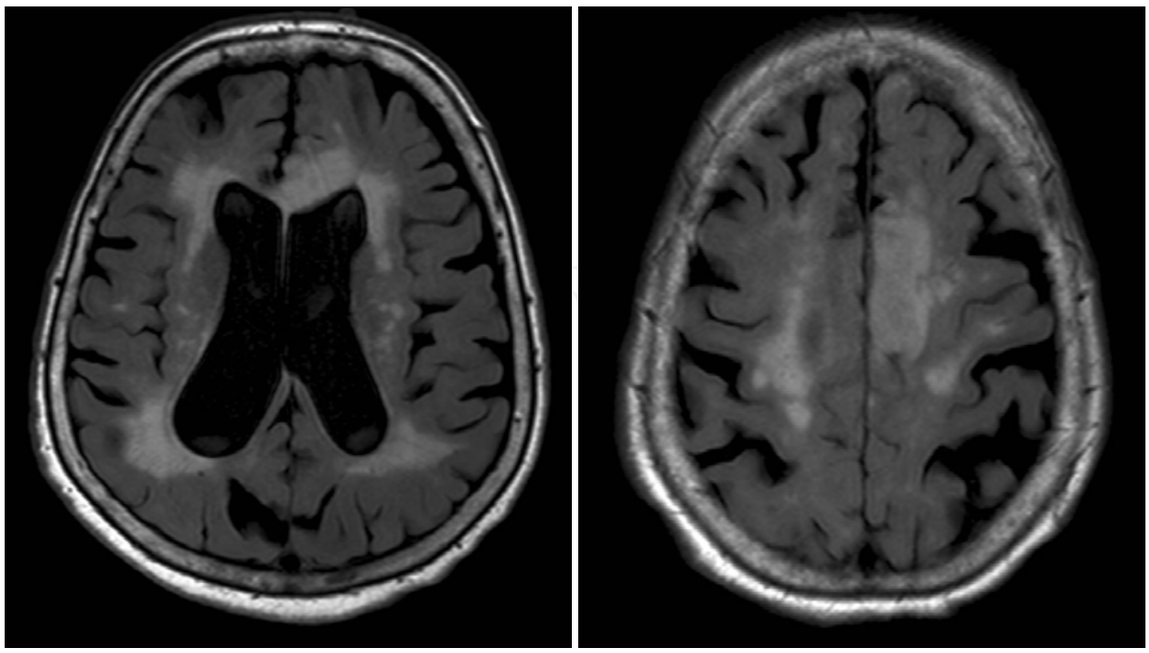


Fig. 6. Widespread WMH and diffuse brain atrophy in a 89 year-old hypertensive patient on axial FLAIR images.

T1
• cavitated, chronic LIs appear hypointens („black hole")
• good for evaluation of brain atrophy and cortical thickness, volumetry as surrogate marker
T2
• subacute LIs appear hyperintens (fluctuating); good visualisation of VRS
• white matter damage appears as WMH; good for judging deep WMH
FLAIR
• (sub)acute LIs give more stable high signal; good for detection of periventricular LIs, differentiates acute (hyperintens) from chronic (hypointens) LIs
• white matter damage appears as WMH; good for judging both deep and periventricular WMH
T2*
• cMBs appear as small, hypointense foci, marker of bleeding-prone microangiopathy
DWI
• the only method to visualize (hyper)acute LIs that give high signal on DWI, low signal on ADC; acute lesion patterns guide differential diagnosis
• chronic LI gives low signal on DWI, ultrastructural tissue damage causes increased diffusivity (high signal on ADC map), whole brain ADC histogram as surrogate marker?
DTI
• localisation of LIs in relation to WM tracts (tractography)
• ultrastructural tissue damage causes increased diffusivity (high signal on MD map), whole brain MD histogram as surrogate marker

Table 3. Utility of different MRI sequences in cSVD. Abbreviations can be found in the text.

Brain atrophy is an aspecific finding and can be regarded as the final common pathway in the pathophysiology of various cerebral pathologies. As in degenerative diseases, atrophy is now recognized as a strong marker of disease progression in cSVD and thus could serve as a surrogate marker in future clinical trials similarly to whole brain diffusion histogram parameters[133].

6. Conclusions, perspectives

New and continuously developing MRI sequences and postprocessing techniques have greatly helped to explore and better understand cSVD. Diffusion MRI methods have proved to be particularly useful in: i. visualizing hyperacute LIs thus guiding acute phase therapy and etiologic diagnosis (DWI); ii. detecting ultrastructural changes even in otherwise normal appearing WM, and quantifying the global burden of tissue damage in cSVD (whole brain DTI/DWI histogram measures). Brain atrophy –a phenomenon previously considered to be related to cortical disease- is now recognised as a marker of cSVD based on studies using volumetric measures. In the future an increasing use of quantitative MRI techniques (diffusion histograms, volumetry) can be expected as they are more sensitive to the full spectrum of cSVD expressions, and could provide surrogate markers for disease progression in future therapeutic trials for patients with cSVD. The utility of different MRI sequences in cSVD is summarized in **Table 3**.

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8. References

[1] Lammie GA. Pathology of small vessel stroke. *Br Med Bull*. 2000;56:296-306

[2] Hachinski V. World stroke day 2008: "Little strokes, big trouble". *Stroke*. 2008;39:2407-2420

[3] Thompson CS, Hakim AM. Living beyond our physiological means: Small vessel disease of the brain is an expression of a systemic failure in arteriolar function: A unifying hypothesis. *Stroke*. 2009;40:e322-330

[4] Vermeer SE, Longstreth WT, Jr., Koudstaal PJ. Silent brain infarcts: A systematic review. *Lancet Neurol*. 2007;6:611-619

[5] Bryan RN, Wells SW, Miller TJ, Elster AD, Jungreis CA, Poirier VC, Lind BK, Manolio TA. Infarctlike lesions in the brain: Prevalence and anatomic characteristics at mr imaging of the elderly--data from the cardiovascular health study. *Radiology*. 1997;202:47-54

[6] Bamford J, Sandercock P, Jones L, Warlow C. The natural history of lacunar infarction: The oxfordshire community stroke project. *Stroke*. 1987;18:545-551

[7] Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: A population-based study of incidence and risk factors. *Stroke*. 1999;30:2513-2516

[8] Sacco S, Marini C, Totaro R, Russo T, Cerone D, Carolei A. A population-based study of the incidence and prognosis of lacunar stroke. *Neurology*. 2006;66:1335-1338

[9] Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cecillion M, Marechal E, Maciazek J, Vayssiere C, Cruaud C, Cabanis EA, Ruchoux MM, Weissenbach J, Bach JF, Bousser MG, Tournier-Lasserve E. Notch3 mutations in cadasil, a hereditary adult-onset condition causing stroke and dementia. *Nature*. 1996;383:707-710

[10] Artavanis-Tsakonas S, Rand MD, Lake RJ. Notch signaling: Cell fate control and signal integration in development. *Science*. 1999;284:770-776

[11] Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. Cadasil. *Lancet Neurol*. 2009;8:643-653

[12] Pantoni L. Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*.9:689-701

[13] Herman LH, Ostrowski AZ, Gurdjian ES. Perforating branches of the middle cerebral artery. An anatomical study. *Arch Neurol*. 1963;8:32-34

[14] Kaplan HA. The lateral perforating branches of the anterior and middle cerebral arteries. *J Neurosurg*. 1965;23:305-310

[15] Marinkovic SV, Milisavljevic MM, Kovacevic MS, Stevic ZD. Perforating branches of the middle cerebral artery. Microanatomy and clinical significance of their intracerebral segments. *Stroke*. 1985;16:1022-1029

[16] Umansky F, Gomes FB, Dujovny M, Diaz FG, Ausman JI, Mirchandani HG, Berman SK. The perforating branches of the middle cerebral artery. A microanatomical study. *J Neurosurg*. 1985;62:261-268

[17] Pantoni L. Pathophysiology of age-related cerebral white matter changes. *Cerebrovasc Dis*. 2002;13 Suppl 2:7-10

[18] Fisher CM. Lacunar strokes and infarcts: A review. *Neurology*. 1982;32:871-876

[19] Greenberg SM, Nandigam RN, Delgado P, Betensky RA, Rosand J, Viswanathan A, Frosch MP, Smith EE. Microbleeds versus macrobleeds: Evidence for distinct entities. *Stroke*. 2009;40:2382-2386

[20] Jouvent E, Viswanathan A, Mangin JF, O'Sullivan M, Guichard JP, Gschwendtner A, Cumurciuc R, Buffon F, Peters N, Pachai C, Bousser MG, Dichgans M, Chabriat H. Brain atrophy is related to lacunar lesions and tissue microstructural changes in cadasil. *Stroke*. 2007;38:1786-1790

[21] Gunda B VG, Rudas G, Bereczki D. Challenges in diagnosing cerebral lacunar infarcts. *CMIR*. 2009;5:75-84

[22] Brant-Zawadzki M, Atkinson D, Detrick M, Bradley WG, Scidmore G. Fluid-attenuated inversion recovery (flair) for assessment of cerebral infarction. Initial clinical experience in 50 patients. *Stroke*. 1996;27:1187-1191

[23] Ricci PE, Burdette JH, Elster AD, Reboussin DM. A comparison of fast spin-echo, fluid-attenuated inversion-recovery, and diffusion-weighted mr imaging in the first 10 days after cerebral infarction. *AJNR Am J Neuroradiol*. 1999;20:1535-1542

[24] Lansberg MG, Thijs VN, O'Brien MW, Ali JO, de Crespigny AJ, Tong DC, Moseley ME, Albers GW. Evolution of apparent diffusion coefficient, diffusion-weighted, and t2-weighted signal intensity of acute stroke. *AJNR Am J Neuroradiol*. 2001;22:637-644

[25] Hjort N, Christensen S, Solling C, Ashkanian M, Wu O, Rohl L, Gyldensted C, Andersen G, Ostergaard L. Ischemic injury detected by diffusion imaging 11 minutes after stroke. *Ann Neurol*. 2005;58:462-465

[26] Guadagno JV, Jones PS, Fryer TD, Barret O, Aigbirhio FI, Carpenter TA, Price CJ, Gillard JH, Warburton EA, Baron JC. Local relationships between restricted water diffusion and oxygen consumption in the ischemic human brain. *Stroke*. 2006;37:1741-1748

[27] Hoehn-Berlage M, Norris DG, Kohno K, Mies G, Leibfritz D, Hossmann KA. Evolution of regional changes in apparent diffusion coefficient during focal ischemia of rat brain: The relationship of quantitative diffusion nmr imaging to reduction in cerebral blood flow and metabolic disturbances. *J Cereb Blood Flow Metab*. 1995;15:1002-1011

[28] Lin W, Lee JM, Lee YZ, Vo KD, Pilgram T, Hsu CY. Temporal relationship between apparent diffusion coefficient and absolute measurements of cerebral blood flow in acute stroke patients. *Stroke*. 2003;34:64-70

[29] Schlaug G, Siewert B, Benfield A, Edelman RR, Warach S. Time course of the apparent diffusion coefficient (adc) abnormality in human stroke. *Neurology*. 1997;49:113-119

[30] Munoz Maniega S, Bastin ME, Armitage PA. A quantitative comparison of two methods to correct eddy current-induced distortions in dt-mri. *Magn Reson Imaging*. 2007;25:341-349

[31] Knight RA, Dereski MO, Helpern JA, Ordidge RJ, Chopp M. Magnetic resonance imaging assessment of evolving focal cerebral ischemia. Comparison with histopathology in rats. *Stroke*. 1994;25:1252-1261; discussion 1261-1252

[32] Burdette JH, Elster AD, Ricci PE. Acute cerebral infarction: Quantification of spin-density and t2 shine-through phenomena on diffusion-weighted mr images. *Radiology*. 1999;212:333-339

[33] Geijer B, Sundgren PC, Lindgren A, Brockstedt S, Stahlberg F, Holtas S. The value of b required to avoid t2 shine-through from old lucunar infarcts in diffusion-weighted imaging. *Neuroradiology*. 2001;43:511-517

[34] Lovblad KO, Laubach HJ, Baird AE, Curtin F, Schlaug G, Edelman RR, Warach S. Clinical experience with diffusion-weighted mr in patients with acute stroke. *AJNR Am J Neuroradiol*. 1998;19:1061-1066

[35] Lie C, Hirsch JG, Rossmanith C, Hennerici MG, Gass A. Clinicotopographical correlation of corticospinal tract stroke: A color-coded diffusion tensor imaging study. *Stroke*. 2004;35:86-92

[36] Pajevic S, Pierpaoli C. Color schemes to represent the orientation of anisotropic tissues from diffusion tensor data: Application to white matter fiber tract mapping in the human brain. *Magn Reson Med*. 1999;42:526-540

[37] Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S. Fiber tract-based atlas of human white matter anatomy. *Radiology*. 2004;230:77-87

[38] Lai C, Zhang SZ, Liu HM, Zhou YB, Zhang YY, Zhang QW, Han GC. White matter tractography by diffusion tensor imaging plays an important role in prognosis estimation of acute lacunar infarctions. *Br J Radiol*. 2007;80:782-789

[39] Lee JS, Han MK, Kim SH, Kwon OK, Kim JH. Fiber tracking by diffusion tensor imaging in corticospinal tract stroke: Topographical correlation with clinical symptoms. *Neuroimage*. 2005;26:771-776

[40] Yamada K, Mori S, Nakamura H, Ito H, Kizu O, Shiga K, Yoshikawa K, Makino M, Yuen S, Kubota T, Tanaka O, Nishimura T. Fiber-tracking method reveals sensorimotor pathway involvement in stroke patients. *Stroke*. 2003;34:E159-162

[41] Norrving B. Lacunar infarcts: No black holes in the brain are benign. *Pract Neurol*. 2008;8:222-228

[42] Cho AH, Kang DW, Kwon SU, Kim JS. Is 15 mm size criterion for lacunar infarction still valid? A study on strictly subcortical middle cerebral artery territory infarction using diffusion-weighted mri. *Cerebrovasc Dis*. 2007;23:14-19

[43] Kang DW, Chalela JA, Ezzeddine MA, Warach S. Association of ischemic lesion patterns on early diffusion-weighted imaging with toast stroke subtypes. *Arch Neurol*. 2003;60:1730-1734

[44] Wessels T, Rottger C, Jauss M, Kaps M, Traupe H, Stolz E. Identification of embolic stroke patterns by diffusion-weighted mri in clinically defined lacunar stroke syndromes. *Stroke*. 2005;36:757-761

[45] Donnan GA, Bladin PF, Berkovic SF, Longley WA, Saling MM. The stroke syndrome of striatocapsular infarction. *Brain*. 1991;114 (Pt 1A):51-70

[46] Gerraty RP, Parsons MW, Barber PA, Darby DG, Desmond PM, Tress BM, Davis SM. Examining the lacunar hypothesis with diffusion and perfusion magnetic resonance imaging. *Stroke*. 2002;33:2019-2024

[47] Wessels T, Wessels C, Ellsiepen A, Reuter I, Trittmacher S, Stolz E, Jauss M. Contribution of diffusion-weighted imaging in determination of stroke etiology. *AJNR Am J Neuroradiol*. 2006;27:35-39

[48] Chowdhury D, Wardlaw JM, Dennis MS. Are multiple acute small subcortical infarctions caused by embolic mechanisms? *J Neurol Neurosurg Psychiatry*. 2004;75:1416-1420

[49] Momjian-Mayor I, Baron JC. The pathophysiology of watershed infarction in internal carotid artery disease: Review of cerebral perfusion studies. *Stroke*. 2005;36:567-577

[50] Krapf H, Widder B, Skalej M. Small rosarylike infarctions in the centrum ovale suggest hemodynamic failure. *AJNR Am J Neuroradiol*. 1998;19:1479-1484

[51] Scarpelli M, Salvolini U, Diamanti L, Montironi R, Chiaromoni L, Maricotti M. Mri and pathological examination of post-mortem brains: The problem of white matter high signal areas. *Neuroradiology*. 1994;36:393-398

[52] Gilbert JJ, Sadler M. Unsuspected multiple sclerosis. *Arch Neurol*. 1983;40:533-536

[53] Kirkpatrick JB, Hayman LA. White-matter lesions in mr imaging of clinically healthy brains of elderly subjects: Possible pathologic basis. *Radiology*. 1987;162:509-511

[54] Munoz DG, Hastak SM, Harper B, Lee D, Hachinski VC. Pathologic correlates of increased signals of the centrum ovale on magnetic resonance imaging. *Arch Neurol*. 1993;50:492-497

[55] Haddad FS, Abla A, Allam C. Ependymal brain cyst. *Surg Neurol*. 1982;18:246-249

[56] Braffman BH, Zimmerman RA, Trojanowski JQ, Gonatas NK, Hickey WF, Schlaepfer WW. Brain mr: Pathologic correlation with gross and histopathology. 2.

Hyperintense white-matter foci in the elderly. *AJR Am J Roentgenol*. 1988;151:559-566

[57] Weller RO, Kida S, Zhang ET. Pathways of fluid drainage from the brain--morphological aspects and immunological significance in rat and man. *Brain Pathol*. 1992;2:277-284

[58] Jungreis CA, Kanal E, Hirsch WL, Martinez AJ, Moossy J. Normal perivascular spaces mimicking lacunar infarction: Mr imaging. *Radiology*. 1988;169:101-104

[59] Bokura H, Kobayashi S, Yamaguchi S. Distinguishing silent lacunar infarction from enlarged virchow-robin spaces: A magnetic resonance imaging and pathological study. *J Neurol*. 1998;245:116-122

[60] Groeschel S, Chong WK, Surtees R, Hanefeld F. Virchow-robin spaces on magnetic resonance images: Normative data, their dilatation, and a review of the literature. *Neuroradiology*. 2006;48:745-754

[61] Rouhl RP, van Oostenbrugge RJ, Knottnerus IL, Staals JE, Lodder J. Virchow-robin spaces relate to cerebral small vessel disease severity. *J Neurol*. 2008

[62] Heier LA, Bauer CJ, Schwartz L, Zimmerman RD, Morgello S, Deck MD. Large virchow-robin spaces: Mr-clinical correlation. *AJNR Am J Neuroradiol*. 1989;10:929-936

[63] Hiroki M, Miyashita K. Linear hyperintensity objects on magnetic resonance imaging related to hypertension. *Cerebrovasc Dis*. 2001;11:164-168

[64] Maclullich AM, Wardlaw JM, Ferguson KJ, Starr JM, Seckl JR, Deary IJ. Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *J Neurol Neurosurg Psychiatry*. 2004;75:1519-1523

[65] Patankar TF, Mitra D, Varma A, Snowden J, Neary D, Jackson A. Dilatation of the virchow-robin space is a sensitive indicator of cerebral microvascular disease: Study in elderly patients with dementia. *AJNR Am J Neuroradiol*. 2005;26:1512-1520

[66] Cumurciuc R, Guichard JP, Reizine D, Gray F, Bousser MG, Chabriat H. Dilation of virchow-robin spaces in cadasil. *Eur J Neurol*. 2006;13:187-190

[67] Erkinjuntti T, Benavente O, Eliasziw M, Munoz DG, Sulkava R, Haltia M, Hachinski V. Diffuse vacuolization (spongiosis) and arteriolosclerosis in the frontal white matter occurs in vascular dementia. *Arch Neurol*. 1996;53:325-332

[68] Barkhof F. Enlarged virchow-robin spaces: Do they matter? *J Neurol Neurosurg Psychiatry*. 2004;75:1516-1517

[69] Bots ML, Looman SJ, Koudstaal PJ, Hofman A, Hoes AW, Grobbee DE. Prevalence of stroke in the general population. The rotterdam study. *Stroke*. 1996;27:1499-1501

[70] Mittelmark MB, Psaty BM, Rautaharju PM, Fried LP, Borhani NO, Tracy RP, Gardin JM, O'Leary DH. Prevalence of cardiovascular diseases among older adults. The cardiovascular health study. *Am J Epidemiol*. 1993;137:311-317

[71] Vermeer SE, Den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Incidence and risk factors of silent brain infarcts in the population-based rotterdam scan study. *Stroke*. 2003;34:392-396

[72] Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population-based rotterdam scan study. *Stroke*. 2002;33:21-25

[73] Norrving B. Long-term prognosis after lacunar infarction. *Lancet Neurol*. 2003;2:238-245
[74] Longstreth WT, Jr., Arnold AM, Beauchamp NJ, Jr., Manolio TA, Lefkowitz D, Jungreis C, Hirsch CH, O'Leary DH, Furberg CD. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: The cardiovascular health study. *Stroke*. 2005;36:56-61
[75] Hachinski VC, Potter P, Merskey H. Leuko-araiosis. *Arch Neurol*. 1987;44:21-23
[76] Marshall VG, Bradley WG, Jr., Marshall CE, Bhoopat T, Rhodes RH. Deep white matter infarction: Correlation of mr imaging and histopathologic findings. *Radiology*. 1988;167:517-522
[77] Revesz T, Hawkins CP, du Boulay EP, Barnard RO, McDonald WI. Pathological findings correlated with magnetic resonance imaging in subcortical arteriosclerotic encephalopathy (binswanger's disease). *J Neurol Neurosurg Psychiatry*. 1989;52:1337-1344
[78] Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, Radner H, Lechner H. Pathologic correlates of incidental mri white matter signal hyperintensities. *Neurology*. 1993;43:1683-1689
[79] Fernando MS, O'Brien JT, Perry RH, English P, Forster G, McMeekin W, Slade JY, Golkhar A, Matthews FE, Barber R, Kalaria RN, Ince PG. Comparison of the pathology of cerebral white matter with post-mortem magnetic resonance imaging (mri) in the elderly brain. *Neuropathol Appl Neurobiol*. 2004;30:385-395
[80] Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: Fundamental imaging and clinical features. *AJNR Am J Neuroradiol*. 2008;29:1036-1042
[81] Costello DJ, Eichler AF, Eichler FS. Leukodystrophies: Classification, diagnosis, and treatment. *Neurologist*. 2009;15:319-328
[82] Matthews PM, Tampieri D, Berkovic SF, Andermann F, Silver K, Chityat D, Arnold DL. Magnetic resonance imaging shows specific abnormalities in the melas syndrome. *Neurology*. 1991;41:1043-1046
[83] Fazekas F CJ, Alavi A, Hurtig HI, Zimmerman RA. Mr signal abnormalities at 1.5 t in alzheimer's dementia and normal aging. *AJR Am J Roentgenol*. 1987
[84] Schmidt R, Fazekas F, Kapeller P, Schmidt H, Hartung HP. Mri white matter hyperintensities: Three-year follow-up of the austrian stroke prevention study. *Neurology*. 1999;53:132-139
[85] Scheltens P, Barkhof F, Leys D, Pruvo JP, Nauta JJ, Vermersch P, Steinling M, Valk J. A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *J Neurol Sci*. 1993;114:7-12
[86] Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjogren M, Wallin A, Ader H, Leys D, Pantoni L, Pasquier F, Erkinjuntti T, Scheltens P. A new rating scale for age-related white matter changes applicable to mri and ct. *Stroke*. 2001;32:1318-1322
[87] Kapeller P, Schmidt R, Enzinger C, Ropele S, Fazekas F. Ct and mri rating of white matter changes. *J Neural Transm Suppl*. 2002:41-45
[88] Anbeek P, Vincken KL, van Osch MJ, Bisschops RH, van der Grond J. Probabilistic segmentation of white matter lesions in mr imaging. *Neuroimage*. 2004;21:1037-1044

[89] Sachdev P, Cathcart S, Shnier R, Wen W, Brodaty H. Reliability and validity of ratings of signal hyperintensities on mri by visual inspection and computerised measurement. *Psychiatry Res*. 1999;92:103-115

[90] Gouw AA, van der Flier WM, van Straaten EC, Pantoni L, Bastos-Leite AJ, Inzitari D, Erkinjuntti T, Wahlund LO, Ryberg C, Schmidt R, Fazekas F, Scheltens P, Barkhof F. Reliability and sensitivity of visual scales versus volumetry for evaluating white matter hyperintensity progression. *Cerebrovasc Dis*. 2008;25:247-253

[91] de Groot JC, de Leeuw FE, Oudkerk M, van Gijn J, Hofman A, Jolles J, Breteler MM. Cerebral white matter lesions and cognitive function: The rotterdam scan study. *Ann Neurol*. 2000;47:145-151

[92] van Straaten EC, Fazekas F, Rostrup E, Scheltens P, Schmidt R, Pantoni L, Inzitari D, Waldemar G, Erkinjuntti T, Mantyla R, Wahlund LO, Barkhof F. Impact of white matter hyperintensities scoring method on correlations with clinical data: The ladis study. *Stroke*. 2006;37:836-840

[93] Nebes RD, Meltzer CC, Whyte EM, Scanlon JM, Halligan EM, Saxton JA, Houck PR, Boada FE, Dekosky ST. The relation of white matter hyperintensities to cognitive performance in the normal old: Education matters. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2006;13:326-340

[94] Rovaris M, Iannucci G, Cercignani M, Sormani MP, De Stefano N, Gerevini S, Comi G, Filippi M. Age-related changes in conventional, magnetization transfer, and diffusion-tensor mr imaging findings: Study with whole-brain tissue histogram analysis. *Radiology*. 2003;227:731-738

[95] Benedetti B, Charil A, Rovaris M, Judica E, Valsasina P, Sormani MP, Filippi M. Influence of aging on brain gray and white matter changes assessed by conventional, mt, and dt mri. *Neurology*. 2006;66:535-539

[96] Horsfield MA, Jones DK. Applications of diffusion-weighted and diffusion tensor mri to white matter diseases - a review. *NMR Biomed*. 2002;15:570-577

[97] Mascalchi M, Filippi M, Floris R, Fonda C, Gasparotti R, Villari N. Diffusion-weighted mr of the brain: Methodology and clinical application. *Radiol Med*. 2005;109:155-197

[98] Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed*. 2002;15:435-455

[99] O'Sullivan M, Summers PE, Jones DK, Jarosz JM, Williams SC, Markus HS. Normal-appearing white matter in ischemic leukoaraiosis: A diffusion tensor mri study. *Neurology*. 2001;57:2307-2310

[100] Molko N, Pappata S, Mangin JF, Poupon C, Vahedi K, Jobert A, LeBihan D, Bousser MG, Chabriat H. Diffusion tensor imaging study of subcortical gray matter in cadasil. *Stroke*. 2001;32:2049-2054

[101] Chabriat H, Pappata S, Poupon C, Clark CA, Vahedi K, Poupon F, Mangin JF, Pachot-Clouard M, Jobert A, Le Bihan D, Bousser MG. Clinical severity in cadasil related to ultrastructural damage in white matter: In vivo study with diffusion tensor mri. *Stroke*. 1999;30:2637-2643

[102] Holtmannspotter M, Peters N, Opherk C, Martin D, Herzog J, Bruckmann H, Samann P, Gschwendtner A, Dichgans M. Diffusion magnetic resonance histograms as a

surrogate marker and predictor of disease progression in cadasil: A two-year follow-up study. *Stroke*. 2005;36:2559-2565

[103] Molko N, Pappata S, Mangin JF, Poupon F, LeBihan D, Bousser MG, Chabriat H. Monitoring disease progression in cadasil with diffusion magnetic resonance imaging: A study with whole brain histogram analysis. *Stroke*. 2002;33:2902-2908

[104] Nitkunan A, Barrick TR, Charlton RA, Clark CA, Markus HS. Multimodal mri in cerebral small vessel disease: Its relationship with cognition and sensitivity to change over time. *Stroke*. 2008;39:1999-2005

[105] Charlton RA, Schiavone F, Barrick TR, Morris RG, Markus HS. Diffusion tensor imaging detects age related white matter change over a 2 year follow-up which is associated with working memory decline. *J Neurol Neurosurg Psychiatry*.81:13-19

[106] Della Nave R, Foresti S, Pratesi A, Ginestroni A, Inzitari M, Salvadori E, Giannelli M, Diciotti S, Inzitari D, Mascalchi M. Whole-brain histogram and voxel-based analyses of diffusion tensor imaging in patients with leukoaraiosis: Correlation with motor and cognitive impairment. *AJNR Am J Neuroradiol*. 2007;28:1313-1319

[107] Offenbacher H, Fazekas F, Schmidt R, Koch M, Fazekas G, Kapeller P. Mr of cerebral abnormalities concomitant with primary intracerebral hematomas. *AJNR Am J Neuroradiol*. 1996;17:573-578

[108] Greenberg SM, Finklestein SP, Schaefer PW. Petechial hemorrhages accompanying lobar hemorrhage: Detection by gradient-echo mri. *Neurology*. 1996;46:1751-1754

[109] Ripoll MA, Siosteen B, Hartman M, Raininko R. Mr detectability and appearance of small experimental intracranial hematomas at 1.5 t and 0.5 t. A 6-7-month follow-up study. *Acta Radiol*. 2003;44:199-205

[110] Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, Hartung HP. Histopathologic analysis of foci of signal loss on gradient-echo t2*-weighted mr images in patients with spontaneous intracerebral hemorrhage: Evidence of microangiopathy-related microbleeds. *AJNR Am J Neuroradiol*. 1999;20:637-642

[111] Tanaka A, Ueno Y, Nakayama Y, Takano K, Takebayashi S. Small chronic hemorrhages and ischemic lesions in association with spontaneous intracerebral hematomas. *Stroke*. 1999;30:1637-1642

[112] Viswanathan A, Chabriat H. Cerebral microhemorrhage. *Stroke*. 2006;37:550-555

[113] Fiehler J. Cerebral microbleeds: Old leaks and new haemorrhages. *Int J Stroke*. 2006;1:122-130

[114] Cordonnier C, Al-Shahi Salman R, Wardlaw J. Spontaneous brain microbleeds: Systematic review, subgroup analyses and standards for study design and reporting. *Brain*. 2007;130:1988-2003

[115] Lee SH, Kwon SJ, Kim KS, Yoon BW, Roh JK. Cerebral microbleeds in patients with hypertensive stroke. Topographical distribution in the supratentorial area. *J Neurol*. 2004;251:1183-1189

[116] Chalela JA, Kang DW, Warach S. Multiple cerebral microbleeds: Mri marker of a diffuse hemorrhage-prone state. *J Neuroimaging*. 2004;14:54-57

[117] Derex L, Nighoghossian N, Hermier M, Adeleine P, Philippeau F, Honnorat J, Yilmaz H, Dardel P, Froment JC, Trouillas P. Thrombolysis for ischemic stroke in patients with old microbleeds on pretreatment mri. *Cerebrovasc Dis*. 2004;17:238-241

[118] Kakuda W, Thijs VN, Lansberg MG, Bammer R, Wechsler L, Kemp S, Moseley ME, Marks MP, Albers GW. Clinical importance of microbleeds in patients receiving iv thrombolysis. *Neurology*. 2005;65:1175-1178

[119] Kidwell CS, Saver JL, Villablanca JP, Duckwiler G, Fredieu A, Gough K, Leary MC, Starkman S, Gobin YP, Jahan R, Vespa P, Liebeskind DS, Alger JR, Vinuela F. Magnetic resonance imaging detection of microbleeds before thrombolysis: An emerging application. *Stroke*. 2002;33:95-98

[120] Nighoghossian N, Hermier M, Adeleine P, Blanc-Lasserre K, Derex L, Honnorat J, Philippeau F, Dugor JF, Froment JC, Trouillas P. Old microbleeds are a potential risk factor for cerebral bleeding after ischemic stroke: A gradient-echo t2*-weighted brain mri study. *Stroke*. 2002;33:735-742

[121] Enzinger C, Fazekas F, Matthews PM, Ropele S, Schmidt H, Smith S, Schmidt R. Risk factors for progression of brain atrophy in aging: Six-year follow-up of normal subjects. *Neurology*. 2005;64:1704-1711

[122] Karas GB, Scheltens P, Rombouts SA, Visser PJ, van Schijndel RA, Fox NC, Barkhof F. Global and local gray matter loss in mild cognitive impairment and alzheimer's disease. *Neuroimage*. 2004;23:708-716

[123] Zivadinov R, Sepcic J, Nasuelli D, De Masi R, Bragadin LM, Tommasi MA, Zambito-Marsala S, Moretti R, Bratina A, Ukmar M, Pozzi-Mucelli RS, Grop A, Cazzato G, Zorzon M. A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2001;70:773-780

[124] Kraemer M, Schormann T, Hagemann G, Qi B, Witte OW, Seitz RJ. Delayed shrinkage of the brain after ischemic stroke: Preliminary observations with voxel-guided morphometry. *J Neuroimaging*. 2004;14:265-272

[125] Schmidt R, Ropele S, Enzinger C, Petrovic K, Smith S, Schmidt H, Matthews PM, Fazekas F. White matter lesion progression, brain atrophy, and cognitive decline: The austrian stroke prevention study. *Ann Neurol*. 2005;58:610-616

[126] Preul C, Lohmann G, Hund-Georgiadis M, Guthke T, von Cramon DY. Morphometry demonstrates loss of cortical thickness in cerebral microangiopathy. *J Neurol*. 2005;252:441-447

[127] Seshadri S, Wolf PA, Beiser A, Elias MF, Au R, Kase CS, D'Agostino RB, DeCarli C. Stroke risk profile, brain volume, and cognitive function: The framingham offspring study. *Neurology*. 2004;63:1591-1599

[128] Viswanathan A, Godin O, Jouvent E, O'Sullivan M, Gschwendtner A, Peters N, Duering M, Guichard JP, Holtmannspotter M, Dufouil C, Pachai C, Bousser MG, Dichgans M, Chabriat H. Impact of mri markers in subcortical vascular dementia: A multi-modal analysis in cadasil. *Neurobiol Aging*.31:1629-1636

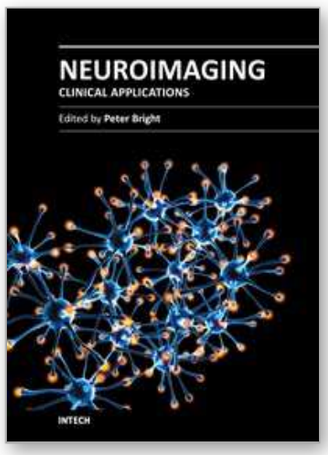
[129] Fein G, Di Sclafani V, Tanabe J, Cardenas V, Weiner MW, Jagust WJ, Reed BR, Norman D, Schuff N, Kusdra L, Greenfield T, Chui H. Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. *Neurology*. 2000;55:1626-1635

[130] Jouvent E, Mangin JF, Porcher R, Viswanathan A, O'Sullivan M, Guichard JP, Dichgans M, Bousser MG, Chabriat H. Cortical changes in cerebral small vessel diseases: A 3d mri study of cortical morphology in cadasil. *Brain*. 2008;131:2201-2208

[131] Viswanathan A, Gray F, Bousser MG, Baudrimont M, Chabriat H. Cortical neuronal apoptosis in cadasil. *Stroke*. 2006;37:2690-2695

[132] Rao DG, Lyons PR. Wallerian degeneration of the pyramidal tract after a thrombotic stroke. *J Neurol Neurosurg Psychiatry*. 1998;65:944

[133] Jouvent E, Viswanathan A, Chabriat H. Cerebral atrophy in cerebrovascular disorders. *J Neuroimaging*.20:213-218



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Modern neuroimaging tools allow unprecedented opportunities for understanding brain neuroanatomy and function in health and disease. Each available technique carries with it a particular balance of strengths and limitations, such that converging evidence based on multiple methods provides the most powerful approach for advancing our knowledge in the fields of clinical and cognitive neuroscience. The scope of this book is not to provide a comprehensive overview of methods and their clinical applications but to provide a "snapshot" of current approaches using well established and newly emerging techniques.

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