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Wolf Dieter Heiss*
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Review Article

Imaging in Cerebral Small Vessel Disease

Wolf Dieter Heiss
Max Planck Institute for Metabolism Research, Gleuelerstr, Cologne, Germany
Corresponding Author: **Wolf Dieter Heiss**, Max Planck Institute for Metabolism Research, Gleuelerstr, Germany.
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Introduction

Small vessel disease of the brain denotes a group of diseases with chronic pathological changes in the small vascualture of the brain, most often due to hypertension related atherothrombosis. Other determinants include genetic dispositions, Alzheimer related changes and deposits, chronic lacunes as well as unspecific changes including atrophy and microhemorrhages and in the subcortex of the brain hemispheres. A classification of the different causes of cerebral small vessel disease is given by Banerjee et al [1]. SVD is also associated with geriatric depression (the so called "vascular depression"), likely due to ischemic disruption of the prefrontal cortical subcortical circuits implicated in mood-affect regulation [2, 3]. Recently, consensus diagnostic criteria of subcortical small vessel disease have been published [4] and also the imaging standards for research have been determined [5]. It is important to realize that small vessel disease (SVD) of the brain primarily affects cogntive and emotional domains and usually does not lead to sudden and dramatic motor impairments as is seen in large vessel occlusions of the brain. It is much more frequent than previously thought and a leading cause of cognitive decline and functional loss in the elderly[6]. Because the diagnosis of SVD is largely confirmed by imaging, recent advances in the imaging modalities used for clinical routine as well as for research are reported in this chapter. Other instrumental investigations are emerging as complementary diagnostic tools of cerebral SVD, such as Transcranial Doppler [7] and Transcranial Magnetic Stimulation [8]. Firstly, it is important to differentiate between vascular dementia and vascular cognitive decline. Whereas vascular dementia has been well noted since the 1970s, vascular cognitive decline has not been used as a standard diagnosis until the recent revision of the DSM, which allows determining mild cognitive impairment of vascular cause.

Vascular dementia and small vessel disease

Vascular etiologies are the third most common cause of dementia (~ 8 to 10%), following AD (60 to 70%), and dementia with Lewy bodies (DLB) (10 to 25%) [9], but these numbers vary considerably according to the different criteria used for VaD. Furthermore, it is evident from autopsy studies that many patients have mixed dementias, often vascular disease with other conditions [9]. Old criteria for VaD only included multi infarct dementia [10] or dementia resulting from the cumulative effects of several clinically significant strokes, but the current criteria consider multi infarct dementia as only one of several subtypes of VaD, including single stroke dementia and small vessel disease. The three main neuroimaging patterns in VaD are large vessels strokes (macroangiopathy, arteriosclerosis), small vessel disease (microangiopathy, arteriolosclerosis), and microhemorrhages. Single large territorial strokes, especially in the middle cerebral artery (MCA) territory of the dominant hemisphere, or multiple smaller strokes in bilateral anterior cerebral artery (ACA) or posterior cerebral artery (PCA) territories, cause dementia in ~30% of stroke survivors [9, 11].Single smaller strokes can also cause significant cognitive dysfunction when occurring in particular locations, such as the watershed territories, including the bilateral superior frontal gyrus or bilateral orbitofrontal (ACA/MCA),

Angular gyrus (ACA/MCA/PCA), temporooccipital junction, and inferior temporal gyrus (MCA/PCA) [12].

Cerebral small vessel disease (SVD) is a condition resulting from damage to the cerebral microcirculation; it causes incomplete or complete infarcts in the white matter or in subcortical gray matter nuclei [13, 14], that are usually clinically `silent´. Advanced SVD is characterized by white matter hyperintensities (WMH), enlarged perivascular spaces (PVS), lacunes, microbleeds and cerebral atrophy [15]. These abnormalities are seen in up to 10% of persons in the 7th decade and in above 85% in their 9th decade. Lacunes must be differentiated from perivascular Virchow Robin spaces. Lacunar strokes are small complete infarcts (2 to 15 mm). When located in the caudate head, anterior thalamus, or the mamillothalamic tract [16] lacunae can cause significant cognitive and/or behavioral dysfunction due to the extended functional differentiation of the cortical areas.

Imaging morphologic substrates of VaD

Neuroimaging provides important information on neuroanatomical substrate of the disorder, plays an important role in the diagnosis and adds to prediction of VaD. Most acute stroke patients undergo computed tomography (CT) brain imaging; thus studies using CT are representative of the whole clinical population. In clinical practice, CT is performed primarily to exclude haemorrhage and some stroke mimics (such as brain tumours), and can often demonstrate early signs of ischaemia (e.g. swelling, hypodensity and hyperdense vessels) and old stroke lesions. Furthermore, the presence and severity of white matter lesions (WMLs) and brain atrophy can also be readily determined from CT brain scans features which may predict subsequent cognitive impairment and dementia. There is very good agreement between brain atrophy and presence of moderate severe white matter lesions on CT and MRI measures [17, 18].

Magnetic resonance imaging (MRI) remains the key neuroimaging modality in VaD (review in [19]. If not contraindicated, MRI, rather than CT, is preferred for research and routine clinical use because it has higher sensitivity and specificity for detecting pathological changes [2]. Standards for neuroimaging with a widely accepted terminology permitting comparison of findings between centers have been recommended (STandards for ReportIng Vascular changes on nEuroimaging, STRIVE) [5]. Numerous studies identified MRI markers of small vessel disease (SVD) (lacunes, white matter hyperintensities, cerebral microbleeds, silent infarcts, white matter changes, global cerebral atrophy, and medial-temporal lobe atrophy) as determinants of VaD. Vascular lesions traditionally attributed to VaD comprise subcortical areas of the brain, especially sub frontal white matter circuits, strategic areas of single infarction such as the dominant thalamus or angular gyrus, deep frontal areas and the left hemisphere, and bilateral brain infarcts or volume driven cortical subcortical infarctions reaching a critical threshold of tissue loss or injury [9].Recently also enlargements of perivascular spaces were identified as MRI markers of Small vessel disease; these are associated with the pathogenesis of vascular related cognitive impairment in older individuals [21].

Small vessel disease identified on MRI in the white matter is called leukoaraiosis [22].

Leukoaraiosis presents as multiple punctuate or confluent lesions, but more often as incomplete infarcts, and is commonly seen in healthy elderly and in subjects with migraine. The markers of small vessel disease white matter hyperintensities, lacunes, dilated vascular spaces, microbleeds, and brain volume are related to decrease in regional cerebral blood flow [23] and must be clearly defined to be reliably used for the diagnosis of this vascular disorder and its progression

[24]. Some studies have suggested that to assess in single cases how much the lesion load affects cognition, a threshold of 10 cm^2 (25) or 25% of total white matter [26] is required before VaD is detectable clinically. On FLAIR images, incomplete infarcts present as hyperintensities, whereas complete infarcts present as lacunae, which are hypointense in relation to the brain and isointense to the cerebrospinal fluid. After stroke, medial temporal lobe atrophy is rather related to cognitive impairment than markers of small vessel disease [27]. When small vessel disease causes subcortical VaD, this is associated with the pathology of Binswanger's disease [28].

Microhemorrhages are the third major neuroimaging aspect of VaD, and in one study they were found in 65% of VaD cases [29]. While macrohemorrhages associated with cognitive impairment (e.g., venous infarcts) can be seen on conventional T1 and T2 weighted spin echo images, microhemorrhages often cannot be seen in these sequences, but can be detected accurately using T2*weighted gradient echo images. In many cases, it is likely that microhemorrhages and white matter ischemic disease are caused by systemic hypertension [30].Molecular imaging in the Diagnosis of Dementia due to Small Vessel Disease.

The diagnosis of vascular cognitive impairment (VCI) is difficult because there is no consensus on clinical criteria. Additionally, cerebral arteriosclerosis frequently is present in elderly patients and even small infarcts or white matter lesions occur in elderly subjects without either cognitive impairment or degenerative dementia. There is a tendency to diagnose VCI on the basis of MRI, which has a high sensitivity for white matter hyperintensities (WMHs), which may be seen in normal elderly as well as those with VCI. Pathological studies reveal a high incidence of both vascular and degenerative pathology of the Alzheimer type. This leads to diagnostic confusion when only the MRI is used, and there is mixed pathologies. PET provides additional information, which increases the diagnostic certainty.

Positron emission tomography can support the clinical diagnosis by visualizing cerebral functions in typically affected brain regions. PET of ^{18}F2 fluoro2 deoxy D glucose (FDG) for measurement of regional cerebral glucose metabolism (rCMRGl) has shown a typical metabolic pattern in patients with probable AD: hypometabolism in temporoparietal and frontal association areas, but relative recessing of primary cortical areas, basal ganglia and cerebellum. In VCI a different pattern is seen [31]. In VCI FDG PET can clearly differentiate scattered areas of focal cortical and subcortical hypometabolism (Fig. 1) that differ from the typical metabolic pattern seen in AD with marked hypometabolism affecting the association areas [32].

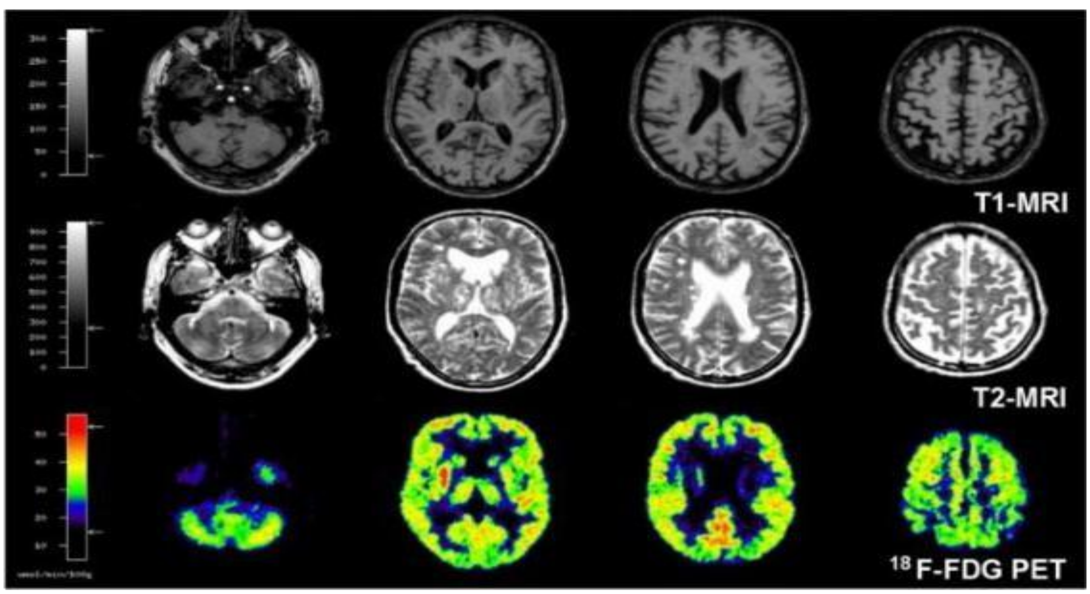

Figure 1: Typical changes of small vessels disease in the white matter as demonstrated in CT and MRI causing reduction in cortical glucose metabolism detected by FDG-PET.

In VCI patients [33] a significant reduction of rCMRglc in comparison to normal patients was observed in widespread cerebral regions (middle frontal cortex, temporoparietal cortex, basal ganglia, cerebellum and brainstem). In subcortical areas and primary sensorimotor cortex this hypometabolism was more marked than in AD while the association areas were less affected than in AD. A metabolic ratio (rCMRglc of association areas divided by rCMRglc of primary areas, basal ganglia, cerebellum and brainstem) mainly reflecting the contrast between association areas and subcortical regions was significantly lower in AD than that in VCI. Whereas it was not possible to identify a single region that could discriminate between VCI and AD, the composite pattern, as expressed in the metabolic ratio, was significantly different. Considering that the VCI patients in that study had mainly WMHs and small subcortical infarcts, it suggests furthermore that even small infarcts in combination with WMHs may contribute to cognitive decline. Rather than the total volume of infarction, the volume of functional tissue loss is more important, since it also includes the effects of incompletely infarcted tissue and morphologically intact but deafferented cortex. Subcortical ischemic vascular disease (SIVD) can be distinguished from clinically probable AD by a more diffuse pattern of hypometabolism involving also the primary cortices, basal ganglia, thalamus and cerebellum.

Alzheimer's disease (AD) is characterized by regional impairment of cerebral glucose metabolism in neocortical association areas, whereas the primary visual and sensorimotor cortex, basal ganglia, and cerebellum are relatively well preserved [34]. In a multicentre study comprising 10 PET centers that employed an automated voxel---based analysis of FDG PET images, the distinction between controls and AD patients had 93% sensitivity and 93% specificity [35]. Significantly abnormal metabolism in mild cognitive impairment (MCI) indicates a high risk to develop dementia within the next two years. Reduced neocortical glucose metabolism can probably be detected with FDG PET in AD on average one year before onset of subjective cognitive impairment.

Characteristic patterns of regional hypometabolism are also seen in other degenerative dementias [36]. Frontotemporal dementia (FTD) clinically characterized by changes in personality and behavior, semantic deficits and progressive aphasia can be identified by distinct frontal or frontotemporal metabolic impairments that are typically quite asymmetrically centered in the frontolateral cortex and the anterior pole of the temporal lobe. Dementia with Lewy bodies (LBD), combining fluctuating consciousness, Parkinsonian symptoms and impairment of visual perception including hallucinations, shows reduction of glucose metabolism in primary visual cortex in addition to that in posterior association areas. Other degenerative disorders show typical hypometabolism in the specifically affected brain structures: the putamen and cortex in corticobasal degeneration, the caudate nucleus in Huntington's chorea, the frontal cortex and midbrain in progressive supranuclear palsy and pons and cerebellum in olivopontocerebellar atrophy. It is also important to note that depressive disorders may mimic cognitive impairment; in these cases glucose metabolism does not show regional abnormalities.

Imaging synaptic transmission and accumulation of pathologic proteins

Additional PET tracers can further support the diagnosis of a type of dementia and also yield information on the underlying pathophysiology: Tracers permit the study of selectively affected transmitter / receptor systems, e.g. the cholinergic system in AD --- significant reduction of cholinergic activity in the cortex of AD patients and those with MCI and early conversion to AD [37] or the dopaminergic system in LBD [38] and the detection of pathogenetic depositions, e.g. amyloid and tau in AD [39] or inflammatory reactions with microglia activations as in VCI. Especially the imaging of accumulation of pathologic proteins is a recent strategy to differentiate degenerative dementias: Amyloid is a pathogenetic product in the development of AD and its accumulation is a key finding in this disease. Its accumulation can be imaged by 11C labeled Pittsburgh Compound B (PiB) [40] or by several newer 18F labeled tracers [41].

Whereas only small amounts of amyloid can be detected in the white matter in normal aging [42], accumulation is visible in the frontal and temporo parietal cortex in AD and MCI. However, also in 20-30% of aged persons without relevant cognitive impairment an increased accumulation of amyloid can be detected [43], and the grade of amyloid deposition as detected by PET is not related to the severity of cognitive impairment [44]. That means that amyloid might be deposited in the brain eventually long before cognitive impairment is recognized. Amyloid deposition in combination with neuro inflammation as expressed in microglia activation might play a role in the development of post stroke dementia [45].

A more specific pathologic protein produced in AD is tau, and its deposition in the mesial temporal lobe is an early marker of AD or MCI [46] and the amount of tau detected in the cortex by selective PET tracers is related to the severity of cognitive impairment [47]. These PET tracers also detect the primary pathological substrate in other degenerative dementias (e.g. tau in FTD) [48] and permit the differentiation between AD and VCI and other degenerative dementias [49, 50].

Conclusion

Small vessel disease (SVD) denotes a group of diseases that affect the small vessels of the brain, mostly due to chronic hypertensive damage to small arteries and arterioles. Clinical manifestations include cognitive impairment and emotional disturbances. It is called mild neurocognitive disorder and usually is progressive and affects other domains such as sensorimotor functions, coordination, language and memory. Over time it can result in vascular dementia. SVD is more frequent than previously thought and can now be better detected due to progress of neuroimaging.

Imaging is critical in diagnosis and treatment of dementias, particularly in VaD because of the ability to visualize ischemic and hemorrhagic injury to the grey and white matter. Most patients undergo brain imaging by computed tomography, which is able to detect ischemic strokes, hemorrhages and brain atrophy and may also indicate white matter changes. Magnetic resonance imaging remains the key neuroimaging modality and is preferred to CT for research and routine clinical use in vascular cognitive impairment (VCI) because it has higher sensitivity and specificity for detecting pathological changes. These modalities for imaging morphology permit to detect vascular lesions traditionally attributed to VCI in subcortical areas of the brain, single infarction or lacunes in strategic areas (thalamus or angular gyrus), or large cortical subcortical lesions reaching a critical threshold of tissue loss.

Multiple punctuate or confluent lesions can be seen in the white matter by MRI and were called leukoaraiosis, which is often seen in healthy elderly and in subjects with migraine. Another major neuroimaging finding of small vessel disease in VCI are microhemorrhages. However, while computed tomography and magnetic resonance imaging are able to detect morphologic lesions, these modalities cannot determine functional consequences of the underlying pathological changes. Additionally, pathological studies reveal a high incidence of mixed dementias with both vascular and degenerative pathology of the Alzheimer type. This leads to diagnostic confusion when only MRI is used. That means that molecular imaging may play an important role in the differentiation between vascular and degenerative cognitive impairment. Imaging guided techniques described in this paper can aid the development and efficacy of innovative disease modifying therapy in post stroke or in vascular cognitive impairment.

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