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Neuroimaging in Cerebral Small Vessel Disease

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ABSTRACT

The diagnosis of cerebral small vessel disease (SVD) is difficult because there is no consensus on clinical criteria and therefore, imaging is important for diagnosis. Most patients undergo brain imaging by computed tomography (CT), which is able to detect ischemic strokes, hemorrhages and brain atrophy and may also indicate white matter changes. Magnetic resonance imaging (MRI) remains the key neuroimaging modality and is preferred to CT 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. In SVD multiple punctuate or confluent lesions can be seen in the white matter by MRI and were called leukoaraiosis. Another major neuroimaging finding of small vessel disease in VCI are microhemorrhages. However, while CT and MRI are able to detect morphologic lesions, these modalities cannot determine functional consequences of the underlying pathological changes.

Positron emission tomography (PET) can support the clinical diagnosis by visualizing cerebral functions in typically affected brain regions. In SVD, Fluor-Deoxy-Glucose (FDG)-PET can clearly differentiate scattered areas of focal cortical and subcortical hypometabolism that differ from the typical metabolic pattern seen in Alzheimer Dementia (AD) with marked hypometabolism affecting the association areas. Additional PET tracers can further support the diagnosis of a type of dementia and also yield information on the underlying pathophysiology.

Introduction

Vascular etiologies are among the most common causes of dementia, but the numbers vary considerably according to the different criteria used for vascular cognitive impairment (VCI)[1, 2]. In the Rochester Epidemiology Project of 419 old demented patients, the post mortem diagnosis of AD was established in 51 %, of pure vascular dementia in 13 %, and of mixed vascular-Alzheimer dementia in 12 % of patients, with "other" diagnosis in the remaining patients [3]. According to a controlled neuropathological study, pure vascular dementia (VaD) is responsible for 8–10 %, Alzheimer's disease (AD) for 60–70 %, and dementia with Lewy bodies (DLB) for 10–25 % of dementia cases [4, 5], Furthermore, it is evident from autopsy studies that many patients have mixed dementias [6], often vascular disease with other conditions [5]. Old criteria for VaD only included multi-infarct dementia [7] 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 [5, 8]. 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), temporo-occipital junction, and inferior temporal gyrus (MCA/PCA) [9].

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 [10-13], that are usually clinically `silent´. Advanced SVD is characterized by white matter hyperintensities (WMH), enlarged perivascular spaces (PVS), lacunes, microbleeds and cerebral atrophy [14]. 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) [15, 16]. When located in the caudate head, anterior thalamus, or the mamillothalamic tract [17] lacunae can cause significant cognitive and/or behavioral dysfunction due to the extended functional deafferentation of the cortical areas. Since clinical signs and symptoms are often insufficient to allow for a final diagnosis and usually cannot differentiate among the various etiologies, neuroimaging plays an important role in the management of patients with impaired cognition. Neuroimaging is also relevant for the detection of sporadic SVD [18].

This review will concentrate on the importance of imaging procedures for the diagnosis of SVD as a cause of VCI. Additionally, it will describe the value of molecular and functional imaging for the detection of the relationship of morphological damage and cognitive impairment and of the differentiation between vascular and degenerative causes of dementia.

Imaging morphologic substrates of Small Vessel Disease

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 a very good agreement between brain atrophy and presence of moderate-severe white matter lesions on CT and MRI measures[19, 20].

Magnetic resonance imaging (MRI) remains the key neuroimaging modality in VaD (review in[21, 22]). 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 [23]. 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) [24]. Numerous studies identified MRI markers of small vessel disease (SVD) (lacunes, white matter hyperintensities, cerebral microbleeds, silent infarcts, white matter changes, global cerebral atrophy, medial-temporal lobe atrophy) as determinants of VaD [12, 25-27]. 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 [5, 28]. Recently, 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[29]. The burden of SVD is increased in systemic lupus erythematosus [30] and – as the risk of stroke – in type 2 diabetes [31].

Small vessel disease identified on MRI in the white matter is called leukoaraiosis [32]. Leukoaraiosis presents as multiple punctuate or confluent lesions, but more often as incomplete infarcts, and is commonly seen in healthy elderly [33] 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 [34] and must be clearly defined to be reliably used for the diagnosis of this vascular disorder and its progression [25]. Some studies have suggested that to assess in single cases how much the lesion load affects cognition, a threshold of 10 cm^2 [35] or 25% of total white matter [36] 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. Diffusion-weighted MRI is best suited

to reveal surrogate markers of SVD progression [37]. After stroke, medial temporal lobe atrophy is rather related to cognitive impairment than markers of small vessel disease [38]. When small vessel disease causes subcortical VaD, this is associated with the pathology of Binswanger's disease [39].

Microhemorrhages are the third major neuroimaging aspect of VaD, and in one study they were found in 65% of VaD cases [40]. 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 [41].

Morphologic imaging indicates the extent and severity of SVD, but the observed changes are not directly related to functional or cognitive impairment and prognosis. In one study [42] several MRI findings together with older age and lower gait speed were identified as risk factors associated with mortality. Functional effects of SVD can only be detected by combining morphological imaging with more complex technologies , e.g. magnetic resonance spectroscopy for showing biochemical changes [43] and functional MRI for analysis of cortical dysfunction [44]. Advanced imaging techniques including molecular imaging by positron emission tomography (PET) will help to understand the mechanisms by which SVD causes VCI and will improve diagnostic accuracy; they might reflect disease progression and in the future might be useful for development of therapies [45].

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}F-2-fluoro-2-deoxy-D-glucose (FDG) for measurement of regional cerebral glucose metabolism (rCMRGl) has shown a typical metabolic pattern in patients with probable Alzheimer Disease (AD): hypometabolism in temporoparietal and frontal association areas, but relative recessing of primary cortical areas, basal ganglia and cerebellum [46, 47]. In VCI a different pattern is seen [48]: In VCI FDG PET can clearly differentiate scattered areas of focal cortical and subcortical hypometabolism (Figure 1) that differ from the typical metabolic pattern seen in AD with marked hypometabolism affecting the association areas [49].

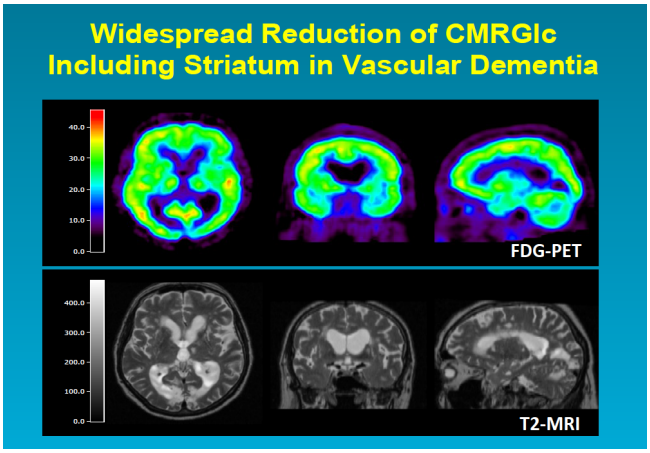

Figure 1: Co-registered T2-weighted MRI and PET orthogonal slices through the brain of a patient with vascular cognitive impairment: T2-MRI shows typical periventricular and multiple small white matter lesions, the PET images reveal the widespread effect of these lesions on the glucose metabolism of the whole cortex and the basal ganglia (Copyright W.-D. Heiss, MPI Cologne).

In VaD patients [50] 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 in VCI [51]. 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 (Figure 2). Subcortical ischemic vascular disease (SIVD) can be distinguished from clinically probable AD by a more diffuse

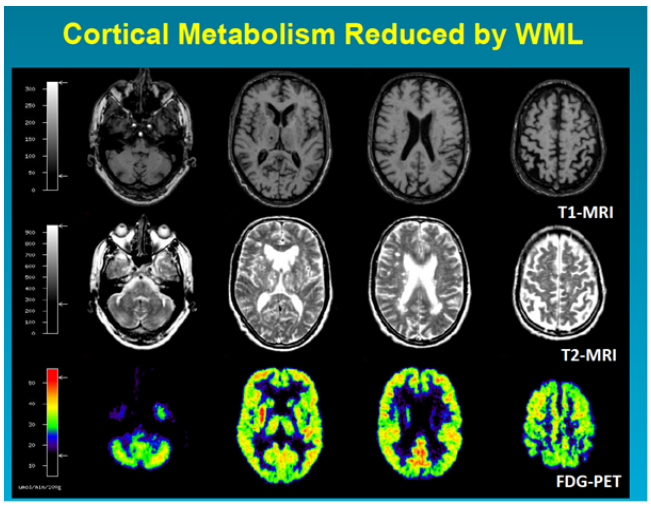

Figure 2: T1 and T2-weighted MRI and PET images in VCI caused by multiple small infarcts, lacunes and widespread white matter changes. The PET images show diffuse impairment of metabolism in both hemispheres and also in basal ganglia, thalamus and cerebellum (Copyright W.-D. Heiss, MPI Cologne).

pattern of hypometabolism involving also the primary cortices, basal ganglia, thalamus and cerebellum.

Differential diagnosis of dementias with FDG-PET

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 [52]. 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 [53]. 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 [54, 55].

Characteristic patterns of regional hypometabolism are also seen in other degenerative dementias [56-60]. 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) [61], 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 [62], the caudate nucleus in Huntington's chorea [63], the frontal cortex and midbrain in progressive supranuclear palsy [64], pons and cerebellum in olivopontocerebellar atrophy [65]. 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 [66] - or the dopaminergic system in LBD [67] and the detection of pathogenetic depositions, e.g. amyloid and tau in AD [68] 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) [69] or by several newer 18F labeled tracers [70]. Whereas only small amounts of amyloid can be detected in the white matter in normal aging [71], accumulation is visible in the frontal and temporo-parietal cortex in AD and MCI [72]. However, also in 20-30% of aged persons without relevant cognitive impairment an increased accumulation of amyloid can be detected [73], and the grade of amyloid deposition as detected by PET is not related to the severity of cognitive impairment [74]. That means that amyloid might be deposited in the brain eventually long before cognitive impairment is recognized. Amyloid deposition in combination with neuroinflammation as expressed in microglia activation might play a role in the development of post-stroke dementia [75].

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 [76] and the amount of tau detected in the cortex by selective PET-tracers is related to the severity of cognitive impairment [77]. These PET-tracers also detect the primary pathological substrate in other degenerative dementias (e.g. tau in FTD) [78] and permit the differentiation between AD and VCI and other degenerative dementias [79-82].

The unique potentials of PET in localizing and quantifying metabolic changes in gray matter structures responsible for functional/cognitive disturbances and caused by SVD mainly affecting the white matter makes this technique the preferred tool for studying patients with VCI; the additional ability of PET to detect pathologic proteins (amyloid and

tau), to image synaptic transmission and receptor activity is of special value for the differential diagnosis of different types of dementia. All together PET studies may shed light into the pathophysiological mechanisms responsible for the disease in a single patient, repeated investigations in the course may reflect progression and may help to demonstrate efficiency in the develpment of new treatment strategies. However, due to the scarcity of complete PET installations including cyclotron and radiochemistry, PET is mainly restricted to applications in research. With the installation of more clinical PET cameras as satellites to a central FDG producing unit - a concept, which is already successful for imaging in oncology - more patients with mild cognitive impairment could benefit from improved diagnostic imaging.

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. The diagnosis of SVD is difficult because there is no consensus on clinical criteria. Clinical manifestations include cognitive impairment and emotional disturbances. The initially observed mild neurocognitive disorder 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 in neuroimaging.

In acute cerebrovascular disease, computed tomography is the first imaging procedure, as it can detect ischemic strokes, hemorrhages and brain atrophy and may also indicate white matter changes. MRI remains the key neuroimaging modality in chronic vascular cognitive impairment (VCI) because it has higher sensitivity and specificity for detecting pathological changes. It permits to detect vascular lesions traditionally attributed to SVD in subcortical areas of the brain, lacunes in strategic areas (thalamus or angular gyrus). Multiple punctuates or confluent lesions can be seen in the white matter by MRI and are called leukoaraiosis. 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, which can be detected and quantitatively assessed by PET. 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 by PET may play an important role in the differentiation of vascular and degenerative cognitive impairment.

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