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# Vascular cognitive impairment — An ill-defined concept with the need to define its vascular component

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ABSTRACT

New guidelines for the diagnosis of vascular cognitive impairment (VCI) represent an important step in the definition of this clinical entity. These guidelines still remain vague in the definition of "vascular" brain lesions causing cognitive decline, because longitudinal correlative imaging studies are still scarce. In this review we explore which abnormalities are likely to contribute to VCI based on a proven vascular etiology, fast progression and their incidence or progression being related to cognitive decline. Among focal changes visible on standard MRI these features apply for coalescent white matter changes. The evidence for lacunes and microbleeds is much less convincing. Microstructural alterations in normal appearing brain tissue which can be detected by new MRI techniques such as magnetization transfer imaging (MTI), diffusion tensor imaging (DTI) and high resolution MR appear to better correlate with cognitive decline, but the etiology of these changes and their histopathological correlates is still incompletely understood as is their evolution over time. New multimodal image processing such as voxel-based lesion-symptom mapping (VLSM) or combinations of DTI and voxel-based analysis will allow to allocate the lesion patterns that show the greatest covariance with clinical outcome. Such data and more longitudinal correlative data on lacunes and microbleeds will increase our pathophysiologic understanding of VCI including the interplay with primary degenerative processes and will lead to refinement of current VCI criteria.



## 1. Introduction

The term "vascular cognitive impairment" (VCI) has been proposed to account for the contribution of vascular pathology to cognitive decline irrespective of co-existing primary degenerative disease [1]. It refers to all cerebrovascular disease that can lead to cognitive impairment including vascular risk per se. Moreover, impairment encompasses all levels of cognitive decline, from the earliest deficits to severe and broad dementia-like cognitive syndromes [2]. Structured diagnostic VCI criteria have been only recently proposed [3]. Accordingly, the core cognitive symptoms should, but not necessarily resemble a "vascular pattern", there is no requirement regarding the onset or course of cognitive impairment, and vascular brain lesions can be heterogeneous including a plethora of vascular abnormalities as well as presence of CADASIL-like diffuse, subcortical cerebrovascular disease.

Introduction of a diagnostic guideline for VCI is obviously an important step to define VCI, yet the criteria remain vague as to the specification of the type, extent and location of vascular abnormalities leading to VCI. Such data can only be obtained by longitudinal imaging, which allows to study the timely association between lesion evolution and cognitive deterioration. We here review recent longitudinal MRI data on different vascular lesion types (Fig. 1) and explore which abnormalities are likely to contribute to VCI based on a proven vascular etiology, fast progression and their incidence or progression paralleling cognitive decline.

## 2. Focal abnormalities visible on standard MRI

### 2.1. White matter lesions (WMLs)

Histopathological studies assessing the pathological correlates of different white matter lesion types are scarce and their findings are summarized in Table 1. Periventricular changes appear to be of non-vascular origin. The histopathological correlates of deep and subcortical white matter changes are also non-uniform. It is important to distinguish between the punctate lesion type, and more widespread early confluent and confluent changes. Punctate hyperintensities are commonly also non-ischemic. Their most common correlate is widening of periarteriolar spaces [4–7] accompanied by reduced myelination with atrophy of the neuropil around fibrohyalinotic arteries. Early confluent and confluent white matter hyperintensities are true ischemic lesions and represent a continuum of increasing tissue damage including widespread perivascular rarefaction of myelin, mild to moderate fiber loss, and varying extents of gliosis. Confluent changes

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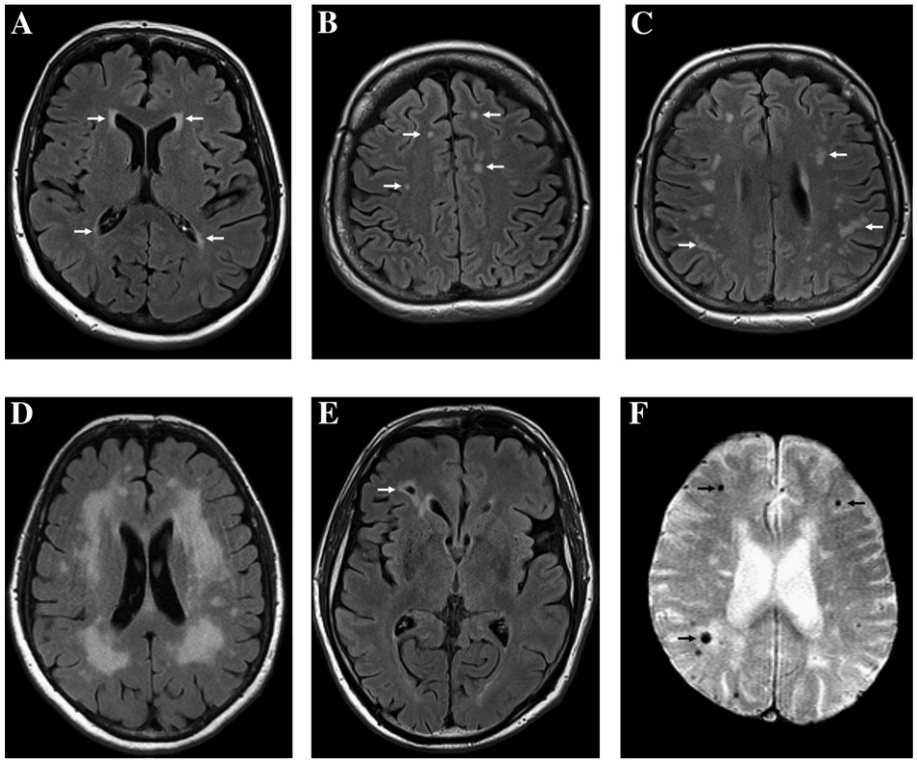


**Fig. 1.** Different types of focal brain changes commonly seen in elderly individuals with and without cognitive impairment (arrows): A. Periventricular white matter hyperintensities (PVWMH); B–D. Deep/subcortical white matter hyperintensities (DWMH). B. Punctate; C. Early confluent; D. Confluent; E. Lacune in the frontal white matter; F. Microbleeds in subcortical location.

are irregular, mostly relatively well demarcated areas of incomplete parenchymal destruction with focal transitions to true infarcts. In line with these findings punctate white matter lesions show low rates of progression while early confluent and confluent white matter abnormalities progress fast [8].

**Table 1**
Studies on histopathological findings concerning white matter lesions (WMLs).

| Study | Sample | Findings |
|---|---|---|
| Fazekas et al. [5] | 6 patients with white matter hyperintensities | Reduced myelination, neuropil atrophy around fibrohyalinotic arteries, perivenous damage. |
| Chimowitz et al. [4] | 7 consecutive patients with neurologic disease | PVR: subependymal gliosis, loss of ependymal lining<br>Caps: myelin pallor, arteriosclerosis.<br>Punctate lesions: dilated perivascular spaces/gliosis. |
| Fazekas et al. [6] | 11 elderly patients | Punctate, early confluent and confluent WMLs relate to increasing severity of ischemic tissue damage.<br>Caps/periventricular halo: nonischemic; demyelination, gliosis. |
| Munoz et al. [7] | Unselected series of 15 autopsies | Extensive WMH: diffuse vacuolation, reduction in density of glial cells.<br>Non-extensive WMH (<10 mm): probably dilated Virchow–Robin spaces. |
| Fernando et al. [40] | 207 patients from MRC-CFAS | Periventricular WMLs: loss of ventricular ependyma.<br>Deep WMLs: arteriolar sclerosis, perivascular enlargement<br>Support of a hypoxic environment within WMLs |

PVR = periventricular rim, WMH = white matter hyperintensities.

WMLs are strongly associated with cognitive decline (Table 2), dementia [9,10] and progression from mild cognitive impairment (MCI) to AD [11].

Early confluent and confluent white matter changes have been proposed as surrogate markers in VCI trials. A sample size calculation based on the Austrian Stroke Prevention Study showed that only 227 patients with early confluent and confluent combined or 87 patients with confluent WML are needed per treatment to detect treatment effects in the range of 30%. The complex interaction between WML and brain atrophy on cognitive functioning needs further exploration.

### 2.2. Lacunes

Lacunes are of vascular origin, most likely caused by ischemia in the territory of a small perforating artery [12]. Incidence rates of lacunes in MRI studies are shown in Table 3.

Results from the LADIS study showed that lacunes in the thalamus were associated with poorer MMSE, speed, motor control and executive functions scores, independent of WMH burden [13]. Incident lacunes on MRI seem to parallel a steeper rate of decline in executive functions and psychomotor speed and determine longitudinal cognitive impairment [14].

Importantly, newer imaging processing techniques such as voxel-based lesion-symptom mapping (VLSM) [15] will allow to further determine the strategic locations of incident lacunes alone or in combination with other lesions that are crucial for the occurrence of cognitive decline. A recent study by Duering et al. [16] used this technique and demonstrated a significant association between lacunes in the anterior part of the thalamus, the anterior limb of the internal capsule, in the left genu of corpus callosum and in the left anterior corona radiata and processing speed. The authors found that the tracts involved were the anterior thalamic radiation and the forceps minor unilaterally [16].