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# Vascular neuropathology and cognitive decline

## *Neuropathologie vasculaire et déclin cognitif*

**V. Deramecourt**

*Centre mémoire de ressources et de recherche, CNR maladie d'Alzheimer du sujet jeune, département d'histologie, EA1046, laboratoire d'excellence DISTALZ, université Lille-Nord-de-France, centre hospitalier régional universitaire de Lille, hôpital Roger-Salengro, rue Emile-Laine, 59037 Lille, France*

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ABSTRACT

Cerebrovascular disease is an important cause of cognitive decline and dementia. Despite numerous epidemiological, clinical, neuroimaging and neuropathological studies, the link between cerebrovascular lesions and their impact on cognition and behavior is still a matter of debate. Cerebrovascular lesions are heterogeneous and most descriptive studies distinguish vessel wall modifications, perivascular space modifications, white matter changes, and infarcts as the main features of vascular dementia. However, to date there is still no consensual criteria for the neuropathological diagnosis of vascular or mixed dementia. The diagnosis of these conditions still relies on both clinical and neuropathological expertise.


RÉSUMÉ

Les pathologies cérébrovasculaires sont une cause importante de déclin cognitif et de démence. Malgré de nombreux travaux épidémiologiques, cliniques, neuroradiologiques et neuropathologiques, les liens entre les lésions cérébrovasculaires et leurs conséquences cognitives et comportementales sont encore débattus. L'éventail lésionnel est large depuis les modifications des parois vasculaires elles-mêmes, les modifications des espaces périvasculaires, les lésions de substance blanche, jusqu'aux infarctus tissulaires constitués. En l'absence de critères neuropathologiques consensuels de démence vasculaire, ce diagnostic, comme celui de démence mixte, doit absolument reposer sur une expertise clinicopathologique.


Cerebrovascular lesions and their causal links with the emergence of cognitive decline probably constitute one of the most complex subjects in the neuropathology of dementia (Ferrer, 2010). There are three levels of explanation for this complexity. Firstly, the cerebrovascular lesions and the underlying disease mechanisms are very heterogeneous and range from vessel wall changes to tissue damage itself. Secondly, there is still much debate over the causal relationships that drive cerebrovascular lesions and their harmful effects on cognitive function. Lastly, there is not yet any consensus on the most relevant way of assessing and quantifying cerebrovascular lesions, which therefore prevents

E-mail address: vincent.deramecourt@chru-lille.fr.
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the large-scale harmonization of clinical and pathological studies.

## 1. A historical overview

The 17th century physician Thomas Willis was probably the first person to describe post-stroke cognitive impairment. In the early 20th century, the famous neuropsychiatrists and pathologists Aloïs Alzheimer and Otto Binswanger drew a distinction between cerebrovascular lesions and syphilitic dementia. Kraepelin considered that the most frequent cause of senile dementia was arteriosclerosis, inducing a progressive narrowing of the vessels, a reduction in cerebral blood flow and neuron loss. In 1970, Tomlinson et al. published the first large study on ''arteriosclerotic dementia'' and showed that cerebrovascular lesions constituted a major cause of cognitive decline in about a third of elderly demented patients and, indeed, the only cause in about a sixth of these patients (Tomlinson et al., 1970). Tomlinson et al.'s observations were mainly based on the presence of brain infarcts: they suggested that a volume threshold of 100 mL of infarcted tissue was associated with a high risk of dementia. Hachinski completed this viewpoint by introducing the concept of multi-infarct dementia in 1974 (Hachinski et al., 1974). However, it then became clear that lesions other than infarcts could also contribute to cognitive decline. Hence, ''multi-infarct dementia'' was replaced first by the more general concept of ''vascular dementia'' (Roman et al., 1993) and then by the term ''vascular cognitive impairment'' (Gorelick et al., 2011; O'Brien et al., 2003).

## 2. Cerebrovascular lesions of interest

### 2.1. *Vessel wall changes*

The vessel wall changes most frequently linked to vascular dementia are cerebral arteriosclerosis, cerebral arteriolosclerosis and cerebral amyloid angiopathy (CAA). The frequency and the severity of these changes increase with age.

#### 2.1.1. *Arteriosclerosis*

Arteriosclerosis affects the large and medium-sized arteries of the brain and results in thickening of the tunica intima, with the accumulation of lipids (mainly cholesterol) and proteins within the vessel wall (Fig. 1B). This process is followed by the calcification of atheromatous plaques and fibrosis of the vessel wall. Plaque rupture frequently induces local thrombosis and complication of the latter by a large infarct. Embolization of the atherogenic thrombus creates an infarct of variable size.

#### 2.1.2. *Arteriolosclerosis/lipohyalinosis*

Arteriolosclerosis affects arteries with a diameter of between 40 and 150 μm and manifests itself as concentric, hyalinised thickening of the arteriolar wall, loss of smooth muscle cells and disorganisation of the tunica media (Fig. 1C) (Pantoni, 2010). Lipohyalinosis has a fairly similar appearance, although the hyalinosis and fibrosis are asymmetrically distributed and there may be fibrinoid necrosis of the arteriolar wall. Arteriolosclerosis and lipohyalinosis are complicated by lacunar infarcts, micro-infarcts, microbleeds and/or large haemorrhages. They appear early in the course of the disease in the arterioles of the basal ganglia and then extend to the white matter, the leptomeningeal arterioles and (in severe cases) the arterioles of the cerebellum and the brain stem (Thal et al., 2003). In general, the cortical arterioles are not affected.

#### 2.1.3. *Cerebral amyloid angiopathy*

Sporadic CAA is characterized by the deposition of Aβ peptides within the vessel wall. Whereas the intraparenchymatous amyloid plaques in Alzheimer's disease (AD) are mainly constituted of Aβ-42 peptide, vascular deposits (and particularly those in the leptomeningeal vessels) are mainly constituted of Aβ-40 and form concentric layers that replace the smooth muscle cells. The amyloid deposits in arterioles and small cortical arteries are constituted of a mixture of Aβ-40 and Aβ-42, whereas those affecting the capillaries are mainly composed of Aβ-42 (Thal et al., 2008). In severe forms, the vessel wall is totally remodelled and weakened, with shrinkage of the lumen and the development of microaneurysms and fibrinoid necrosis (Fig. 1D). A neuropathological examination also reveals haemorrhagic complications (microbleeds and perivascular and leptomeningeal haemosiderin deposits) and ischaemic complications (cortical micro-infarcts and myelin loss). It has been suggested that two types of sporadic CAA exist: CAA type 1 is characterized by Aβ deposits in cortical capillaries (in the presence or absence of damage to the other types of vessels), whereas in CAA type 2, deposits are limited to the leptomeningeal and cortical arteries and arterioles and (more rarely) venules (Thal et al., 2002). The ε4 and ε2 genotypes of *APOE* are associated with CAA types 1 and 2, respectively. The occipital lobe is the most frequently affected area, followed by the frontal, temporal and parietal lobes. The cerebellum may be damaged in late-stage disease, whereas the basal ganglia, the white matter and the brain stem are not usually affected (Thal et al., 2008). The prevalence of CAA in autopsy cohorts varies between 20 and 40% in non-demented cases and between 50 and 60% in demented cases (Keage et al., 2009). CAA is strongly associated with increasing age. CAA is almost always present in AD cases, but only 25% of them exhibit severe forms of the disease (Ellis et al., 1996). There is no etiological link between CAA and the classical vascular risk factors, despite arterial hypertension may aggravate its hemorrhagic complications. The only known genetic risk factors of CAA are E4 and E2 genotypes of *APOE* gene. CAA probably represents a cause of cognitive decline by itself since the association between CAA and dementia persists after adjustment for age and the severity of associated neuritic plaques (Neuropathology group of the MRC-CFAS, 2001). Thus, CAA is to be considered as a pathophysiological process located at the crossroad between microvascular and neurodegenerative pathologies.

#### 2.1.4. *Hereditary microangiopathies*

These conditions, mostly represented by the cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), are usually characterized by

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