Review of Cerebral Microangiopathy and Alzheimer's Disease: Relation between White Matter Hyperintensities and Microbleeds

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Key Words

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Abstract

Although Alzheimer's disease (AD) is basically considered to be a neurodegenerative disorder, cerebrovascular disease is also involved. The role of vascular risk factors and vascular disease in the progression of AD remains incompletely understood. With the development of brain MRI, it is now possible to detect small-vessel disease, whose prevalence and severity increase with age. The first types of small-vessel disease to be described were white matter hyperintensities (WMHs). More recently, small areas of signal loss on T₂*-weighted images, also called microbleeds (MBs), have been reported. Cerebral MBs are focal deposits of hemosiderin that indicate prior microhemorrhages around small vessels, related to either ruptured atherosclerotic microvessels or amyloid angiopathy. Consequently, using brain MRI for the detection of microangiopathy may prove useful to improve our understanding of the impact of the vascular burden in AD pathology. The relationship between microangiopathy

and the clinical course of AD or the conversion of mild cognitive impairment to AD remains questionable in terms of cognitive or affective symptoms, particularly if we consider MBs.

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The aim of this review was to provide a perspective of brain MRI in the detection of microangiopathy, including both white matter hyperintensities (WMHs) and microbleeds (MBs), and their clinical consequences in the elderly by improving our understanding of the consequences of microangiopathy in Alzheimer's disease (AD), considering both cognitive and noncognitive (affective) symptoms. A better understanding of the role of microangiopathy in AD could contribute to the development of future therapeutic and preventive modalities.

AD is characterized by a progressive decline in memory associated with other cognitive deficits: judgment, abstraction, language, attention and visuoconstructive abilities. The current diagnostic criteria for AD require cognitive decline in memory and at least one other cognitive domain, both of which have been present for 6 months or more and have resulted in a significant impact on the patient's activities of daily living [1]. These cognitive

symptoms are associated with other noncognitive symptoms, particularly behavioral, affective symptoms and personality changes [2]. Behavioral and psychological symptoms have been shown to be associated with a poorer prognosis, to increase caregiver burden [2–5] and to be associated with incident mild cognitive impairment (MCI) and/or AD [6, 7]. Among these symptoms, depression and apathy are associated with an increased risk of developing AD [8–11]. All of these functional losses lead to a significant impairment in the activities of daily living. Recently, clinicians have become increasingly interested in the diagnosis of AD at its prodromal stage, which has also been described as MCI [12–14], in the hope of developing future, disease-modifying therapies.

AD is considered to be an essentially neurodegenerative disorder. However, cerebrovascular disease is involved as well [15, 16]. With the development of brain MRI, we can now detect small-vessel disease: WMHs/leukoaraiosis (LA), and MBs, which are all commonly found on brain MRIs in elderly and AD subjects [17]. The localization and quantification of microangiopathy with MRI are based on normal sequences, and no contrast material is required. The first to be reported were WMHs. WMHs are frequently present and were quickly considered to be markers of brain aging. However, there are increasing data suggesting that WMHs may have consequences in aged-related disabilities and play a role in the clinical course of AD, notably in cognitive and affective symptoms. There has also been increased interest in the role played by MBs due to the development of new brain MRI sequences.

The aim of this paper was to investigate the consequences of microangiopathy on the clinical course of AD by using WMH and, more recently, MB data in elderly patients. Our research selected studies published between 1990 and 2010 from the MEDLINE Database using the search terms: ‘white matter hyperintensities’ or ‘microbleeds and cognition’, ‘affective symptoms’, ‘depression’ and ‘AD’. A better understanding the role of microangiopathy may lead to new therapeutic and preventive modalities in AD patients in the future.

Vascular Factors in AD

Data from epidemiological studies indicate that elderly patients, especially those with vascular risk factors and in particular diabetes, hypertension or hypercholesterolemia, have an increased of developing AD [18–27] and cognitive decline. A history of stroke is also associated with an increased risk of developing AD [28].

However, the role of vascular disease in the progression of AD or the conversion of CI to AD remains unknown. Some authors have failed to find any association between vascular risk factors and the rate of cognitive decline in AD subjects during follow-up periods of 1 year [29], 18 months [30], 2 years [31] or even 3 years [32].

In contrast, other authors have reported a faster cognitive decline in AD patients with hypertension, angina or atrial fibrillation than in AD patients without these disorders, during a 3-year follow-up [33, 34]. Moreover, the cognitive decline is faster in subjects who have a history of stroke [32]. Another argument in favor of the role of vascular risk factors in the clinical course of AD was reported by Deschaintre et al. [35]. They described a slower decline in MMSE scores in AD patients who had no cerebrovascular disease as opposed to subjects under treatment for vascular risk factors. The role played by cerebrovascular disease in cognitive impairment has not been completely elucidated [26]. In fact, other factors, like asymptomatic stroke, genetic factors particularly ApoE4 genotype (ApoE ϵ 4) [36] and microangiopathy, may be involved.

White Matter Hyperintensities on Brain MRI: Not New but Still Debated

Progress in brain imaging, particularly in CT and MRI scans, led to the description of changes in white matter in elderly subjects. Their prevalence varies from 10 to 94% [37]. The term leukoaraiosis was proposed by Hachinski et al. [38] to describe the radiological rarefaction of white matter. It refers to white matter abnormalities such as large hypodensities on CT scans and WMHs on T₂-weighted MRI images (fig. 1), whose prevalence and severity increase with age [38–41].

Different methods can be used to measure the extent of WMHs and include visual rating to fully computerized techniques. Visual rating of WMHs is easy, and several scales, such as the scales of Fazekas et al. [42], Scheltens et al. [43] and the Age-Related White Matter Changes (ARWMC) scale [44], are available with good reproducibility. For example, the ARWMC scale, a modified version of the visual scale of Fazekas et al. [42], classifies periventricular and deep WMHs into three categories (low, moderate and severe) in six regions (frontal, parietal, occipital, temporal, basal ganglia/thalamus and infratentorial). Most volumetric studies use supervised semi-automated techniques that may provide more information on location and size, as well as continuous data,

Fig. 1. LA. Axial T₂ FLAIR-weighted MR image showing white matter intensities mainly around the ventral and occipital horns of the lateral ventricles.

Fig. 2. Lacune. Axial T₂ FLAIR-weighted MR image showing a lacuna in the right corona radiata: nodular hyposignal surrounded by a hyperintense rim (arrow).

but they are time-consuming [45, 46]. Both methods have been used to correlate WMHs with clinical data and have had varying results. Volumetry may be more sensitive for detecting small group differences [47, 48]. Van Straaten et al. [47] found good correlations between all three visual rating scales and WMH volume, but this study also showed an important variability in WMH volume in the patient groups with high visual scores. Subject groups with higher visual scores contain individuals with different degrees of WMH burden, leading to a decreased correlation with clinical data. When the progression of WMHs is measured, this ceiling effect could be even greater.

A strong association between LA, vascular risk factors and vascular disorders has been reported [49]. The anatomopathological significance of white matter changes is incompletely elucidated and is probably heterogeneous [50]. These hyperintense lesions on MRI may correspond to areas characterized by loss of myelin, axons and oligodendroglial cells, astrogliosis, dilatation of perivascular spaces, activated macrophages and fibrohyalinotic vessel changes. This range of tissue changes resembles incomplete infarcts [37, 51, 52]. Given the anatomopathological picture, in MRI studies, the term 'lacuna' is generally used for a lacunar infarct even when a lacuna corresponds to small infarcts, dilated perivascular spaces or old small hemorrhages. Lacunas are small cavities with diameters of 3–10 mm and signal intensities comparable to cerebrospinal fluid (CSF) on T₂-weighted MRI images. They consist in focal CSF-filled cavities, often surrounded by a

hyperintense rim on fluid attenuation inversion recovery (FLAIR) images (fig. 2). On histological examination, MRI lacunas were found to correspond to irregular cavitation with scattered fat-laden macrophages, which can be accompanied by surrounding reactive gliosis and myelin and axonal loss. The most frequently reported cause of lacunas is acute arteriolar occlusion by arteriosclerosis/thrombosis. Other possible mechanisms include thromboembolism, generalized hypoxia or tissue damage caused by extravasated toxic serum proteins due to blood-brain barrier leakage [53].

WMHs and Age-Related Disabilities

In elderly subjects, WMHs may be considered as a normal aging phenomenon. However, from the clinical point of view, WMHs have been associated with *cognitive, motor and neuropsychiatric symptoms*.

In cross-sectional studies, white matter changes are associated with (1) cognitive impairment: impaired recall and speed processing, a dysexecutive syndrome [54–57] and difficulties in working memory [55, 58–61]; (2) age-related motor deficits: gait apraxia, impaired balance in walking, increased risk of falls [57, 62–68], severe urinary incontinence [56], or (3) global functioning [39, 56, 69]. They have also been associated with neuropsychiatric symptoms, particularly depressive symptoms [68, 70, 71].

In elderly subjects, white matter changes are also associated with an increased risk of dementia [72–74]. Prospective studies have confirmed these results. The multicenter Leukoaraiosis and Disability Study (LADIS) is

a prospective multinational European project investigating the impact of white matter changes on the transition to disability in the elderly [75]. This study began in 2000 and included subjects aged 65–84 years, who were independent in activities of daily living at the time of enrollment in the study. On MRI, they had different degrees of severity in white matter lesions (1.5 T) measured with the scale of Fazekas et al. [42]. The subjects were evaluated at baseline and yearly for a period of 3 years, with repeated clinical assessment and a final MRI. The rate of functional decline was different according to the severity of the white matter lesion at 1 and 3 years follow-up: there was a 2-fold increase in the risk of transition to disability or death in the severe group compared with the mild group following adjustment for confounding factors [39, 76]. In a recent study from the LADIS, age-related white matter changes and vascular risk factors were predictive of cognitive decline [77]. In elderly subjects living independently, white matter changes and diabetes at baseline were independent predictors of cognitive decline (dementia and no dementia) after controlling for medial temporal atrophy, age and educational level.

The 3-C study is another multicenter cohort study conducted in three French cities aimed at estimating cognitive impairment and the risk of dementia attributable to vascular factors. A total of 9,294 subjects were enrolled between 1996 and 2001. The MRI studies evaluated the relationship between brain MRI markers (white matter lesions, silent brain infarct and hippocampal volume) and longitudinal changes in cognition during the 4-year follow-up period. The risk of dementia and the rate of cognitive decline significantly increased in subjects with more voluminous white matter lesions and smaller hippocampal volumes, suggesting a cumulative effect [78].

The white matter changes also have consequences on neuropsychiatric symptoms. Depression in individuals older than 65 years is strongly associated with a vascular component leading to the concept of vascular depression [79–84]. The hypothesis is that cerebrovascular disease, especially white matter lesions, may contribute to the pathogenesis of depression, predisposing or precipitating depressive symptoms in elderly people, by disrupting neural circuits or fiber tracts connecting frontal and subcortical regions [81, 85, 86]. According to the cross-sectional analysis by Godin et al. [68], subjects with late-onset major depression have more voluminous white matter lesions than subjects with smaller lesions.

In the LADIS study [87, 88], the baseline severity of white matter changes independently predicted the development of depressive symptoms at 2 and 3 years of follow-

up and incident depression. In addition, WMHs are predictive of the progression of depressive symptoms [89]. The study by Godin et al. [68] was the first longitudinal study to investigate the relationship between white matter lesion volumes, white matter volume changes, and depression in the elderly. The progression of white matter lesions during the 4-year follow-up period was faster in subjects with late major depression at baseline. In addition, more voluminous baseline white matter lesions were associated with an increased risk of developing depression during life in subjects who were free of depression. In contrast, in a 3-year longitudinal study, Versluis et al. [90] did not find any relationship between WMHs and depressive symptoms in elderly subjects.

However, the physiopathological and anatomical correlates of late-onset depression is complex [91] even if the role of white matter lesions has been reported. Recent clinicopathological studies comparing elderly nondemented subjects with late-onset depression with healthy controls, using a semiquantitative assessment of microangiopathy (white matter lesions, microinfarcts and gliosis) reported that the frequency of all the lesions did not differ between late-onset depression and controls [92, 93]. Moreover, clinicopathological correlates of late-onset depression, Alzheimer-type pathology and microangiopathy are questionable, and need more neuropathological studies and clinical longitudinal studies using biomarkers of amyloid load: molecular PET imaging and CSF concentration of A β peptide (A β 42), total tau (T-tau) and phosphorylated tau (p-Tau).

WMHs: What Are Their Consequences for the Clinical Course of AD?

At autopsy, deep white matter changes are found in more than 60% of patients with AD [94]. WMHs are also common in MCI [95–97]. We know that white matter changes are associated with cognitive decline, but the clinical significance of microangiopathy in AD is more complex, especially considering its role in the clinical course of the disease.

A few longitudinal studies have examined the role of microangiopathy in the risk of progression from MCI to AD, but the results have been contradictory [26, 54, 96, 98, 99]. Some researchers failed to find any association between white matter changes and the risk of progression from MCI to AD [26, 54, 100], whereas others did in fact find a relationship between white matter changes and progression to AD in MCI patients [96, 98]. Some characteristics of WMHs need to be studied further: white matter volumes, localization (periventricular or total)

and rate of progression. Progression in total and periventricular WMH volumes predicts an increase in persistent cognitive impairment when compared to the baseline WMH burden [101]. In the longitudinal DESCRIPTA study (European Multicenter Clinic-Based Memory), Jacobs et al. [102] studied the influence of the location of WMHs on the executive functions in MCI during a 3-year period and found that parietal WMHs were associated with a decline in executive functions in MCI. In the ADNI study (Alzheimer Disease Neuroimaging Initiative) [103], a greater WMH volume at baseline and 1-year follow-up was associated with greater cognitive impairment at baseline and at follow-up.

Data investigating the consequences of WMHs on the clinical course of the affective symptoms of AD are lacking. Staekenborg et al. [5] studied the differences in the prevalence of behavioral and psychological symptoms in AD according to the prevalence of WMHs and found no difference in prevalence according to white matter lesions. In a cross-sectional study, Kumar et al. [104] investigated structural brain MRI correlates of depressive symptoms in MCI subjects. They failed to find any correlation between depression severity and MRI measures (WMH load and hippocampal volume), but the lack of association may be due to the relatively young age of the patients in the MCI group (60–64 years). Recent data in AD suggest that vascular disease could affect cognition through effects on subcortical connections and white matter changes but may also exacerbate cortical atrophy, suggesting a potential synergistic effect [105]. Further prospective clinicopathological studies are required to elucidate the relationship between microangiopathy, cognition and affective symptoms.

MBs: New Protagonists in the Microangiopathy Debate

Appropriate magnetic resonance T_2^* -weighted gradient-echo can detect hemorrhagic manifestations of microangiopathy (MBs) [106, 107]. MBs are small, round, hypointense foci on T_2^* (or gradient echo)-weighted MRI scans (fig. 3). These small areas of signal loss on T_2^* -weighted images correspond to hemosiderin deposits surrounding small vessels. Histopathological studies have confirmed that MBs are linked to either disrupted atherosclerotic microvessels [108–110] or amyloid angiopathy [111–113].

In the literature, authors varied in their classifications of the distribution of MBs; they also varied in their de-

Fig. 3. Microbleeds. Axial T_2^* MR image showing numerous cortical hyposignal foci in the left parietal area (arrows).

scription of either the presence or the mean number of MBs per location and used different grading systems [114, 115]. None of these classifications of MB distribution has been validated. In most studies, their number and location are analyzed visually and distinguished by their number into four groups [112, 116, 117]: no MBs, 1–5 MBs, 6–10 MBs and more than 11 MBs.

MBs are frequently associated with ischemic cerebral changes, such as lacunar lesions and white matter changes [106]. The prevalence of MBs in apparently healthy subjects is estimated to be 5%, but MBs can be present in 34% of patients who have had ischemic strokes and in 60% of individuals who have had nontraumatic intracerebral hemorrhages [109]. The prevalence increases with age, reaching 13% in subjects older than 75 years [107] and 17% in a large cohort of patients followed in a memory clinic [109]. MBs are associated with hypertension and diabetes [109]. When they are associated with hypertension, the most frequent locations are the basal ganglia, thalamus, brainstem and cerebellum [111], and lobar (mainly in the occipital lobe) when they are associated with amyloid angiopathy [118].

The potential cognitive effects of MBs in elderly subjects remain relatively unexplored. In the general population, studies on the cognitive consequences of MBs are lacking and the few results published have been conflicting. Cordonnier et al. [114], in a hospital-based study of 772 subjects followed in a memory clinic, found no rela-

tionship between MBs and MMSE scores. In contrast, Yakushiji et al. [110] reported that MBs are associated with global cognitive dysfunction (lower scores on the MMSE), independently of coexisting vascular risk factors. The consequences of MBs for selected cognitive domains have received little attention, and the published studies mainly looked at executive functions [119, 120]. A correlation between cognitive decline and the burden of MBs in patients with intracerebral hemorrhages has been demonstrated [121]. MBs are particularly frequent in subjects with subcortical vascular dementia and mainly concern all the cognitive domains with the exception of the language functions [120, 122]. Few data are available on the effects of cerebral MBs on psychiatric symptoms and are restricted to poststroke subjects. Tang et al. [123] reported that lobar MBs were associated with a higher risk of poststroke depression, emotional lability [124] and that MBs contribute to the severity of poststroke depression [125].

The relationship between MBs and neuropsychological testing in AD patients has received but little attention as well. Pettersen et al. [118] failed to demonstrate any association with neuropsychological performances, but most of the AD patients they studied had only one or a few MBs. The available data on MBs suggest that we need to take into account whether or not they are present and the number of MBs when they are. Goos et al. [115] in a retrospective study on 63 AD subjects investigated the association between MBs and neuropsychological data and CSF biomarkers. They compared two groups of AD subjects according to the number of MBs they had: AD patients with multiple MBs (more than 8) and AD patients without MBs. The AD group with multiple MBs had lower MMSE scores than those without MBs and lower performance on animal (verbal) fluency, visual-associated test object naming and digit span (forward and backward) than the group without multiple MBs. They also had more severe WMHs and lower A β 42 CSF levels than patients without MBs and no more atrophy. In MCI subjects, MBs are predictive of cognitive decline [126, 127] and have been found to be a risk factor for progression from MCI (without any clinical data on the subtype) to non-Alzheimer dementia [100].

Unfortunately, there are no data on the relationship between MBs and affective symptoms in AD or MCI patients. Moreover, many questions remain unresolved: should we consider MBs to be a new marker for aging? Do they have any clinical consequences? We probably need to consider not only the presence of MBs but equally their number. The detection of MBs could have practical con-

sequences for the diagnosis of AD and perhaps for understanding the physiopathology of the disease and, consequently, new therapeutic modalities.

Discussion and Future Directions for Study

MRI evidence of small-vessel disease (or microangiopathy) is commonly found on the brain MRIs of elderly subjects and has rapidly been considered a brain marker of aging. However, there are increasing data suggesting that microangiopathy has consequences for aged-related disabilities and that it potentially plays a role in the clinical progression of the cognitive and affective symptoms of AD subjects. MBs, lacunar lesions and WMHs/LA are frequently associated and may be considered to predict the severity of cerebral microangiopathy [106], lacunas representing the final pathway in the spectrum of small-vessel disease [57].

The influence of microangiopathy on the clinical course can be seen from two main perspectives: on the one hand, the severity of microangiopathy, and on the other hand, the neuropathological correlates underlying microangiopathy [128]. In fact, some recent reports have shown that neuroinflammation may be involved [37, 129–131]. Postmortem studies of AD brains demonstrated the presence of acute-phase inflammatory reactions in senile plaques and neurofibrillary tangles and their implication in neuronal death [132–135]. This inflammatory response is mainly orchestrated by resident cells, such as activated microglia, surrounding the senile plaques. Various human and animal studies demonstrated the implication of neuroinflammation in amyloidogenic processing [136, 137]. Moreover, the relationship between microangiopathy and amyloid burden remains unresolved and could possibly be elucidated with molecular PET imaging. In fact, neuro-inflammation may be assessed in vivo by PET imaging using TSPO (translocator protein)-specific ligands which were formerly known as the peripheral benzodiazepine receptor. Molecular imaging of neuro-inflammation should contribute to our understanding of the physiopathology of white matter lesions and their clinical correlations [138, 139]. Some AD subjects seem to have just one or only a few MBs, without measurable clinical effects, contrasting with other AD subjects with a more severe MB burden. But we do not know whether or not MBs reflect a distinct pathological subgroup of AD subjects.

The development of diagnostic biomarkers in AD may help to understand the neuropathological correlates of

WML/MBs and AD pathology in vivo [14]: amyloid burden by PET using [^{11}C]-Pittsburgh compound B ([^{11}C]-PIB) or other radioligands, such as [^{18}F]-AV45 [140], CSF concentration of A β 42, total Tau (T Tau) and phosphorylated Tau (p Tau), hippocampal volume (MRI), metabolic changes with PET using 2-deoxy-2-[^{18}F] fluoro-D-glucose ([^{18}F]-FDG).

No studies have addressed WMH and amyloid load using [^{11}C]-PIB. The association between WML and CSF levels of A β 1–42, Tau and P Tau levels were studied in cerebral autosomal dominant arteriopathy with subcortical infarcts leukoencephalopathy (CADASIL), a model of pure subcortical dementia [141]. CSF A β 1–42 levels were significantly lower in CADASIL subjects than in controls whereas CSF T Tau and P Tau levels did not differ between the two groups. An additional study [142] evaluated the relationship between WML and CSF A β 1–42 in 127 consecutive subjects with subjective memory impairment (mean MMS score 24 with no more details about cognition) and reported a link between WML and low CSF A β . In contrast, in nondemented elderly subjects with WML (from the LADIS study), Jonsson et al. [143] reported no association between WML and AD biomarkers (P Tau and A β 1–42).

The relationship between MBs and β -amyloid deposition, studied using PIB, was evaluated in cerebral amyloid angiopathy [144]. PIB retention was increased at the sites of cerebral amyloid angiopathy-related MBs and declined with increasing distance from the MBs. In a retrospective study, Goos et al. [115] investigated the relationship between MBs and CSF biomarkers in AD and showed that AD with multiple MBs (≥ 8 MBs) had lower CSF amyloid β 1–42 levels than patients without MBs, even after adjustment for white matter lesions. The relationship between cerebral glucose metabolism using PET with [^{18}F]-FDG and WML was only studied in cognitively intact elderly subjects. The severity of WML (particularly periventricular WML) was associated with a decline in global and regional cerebral glucose metabolism [145, 146].

A few studies have assessed the relationships between the MR biomarkers of small-vessel disease (WMHs, MBs) and the MR biomarker of AD (hippocampal atrophy) [100, 115, 147–149]. Firstly, it is important to note that white matter lesions, cortical MBs and hippocampal atrophy are associated with each other and with age, and that these changes are affected by the aging process independently of any cerebrovascular risk factor [150]. Van der Flier et al. [147] showed that after adjustment for age, a combination of hippocampal atrophy and severe WMH

was associated with a more than fourfold increase in the frequency of MCI in a large group of nondisabled elderly subjects. In contrast, MCIs were not more frequent in the groups of patients with a single MRI abnormality (either medial temporal atrophy or severe WMHs). These results suggest the combined involvement of both an Alzheimer-type disorder and vascular pathology in the earliest stages of cognitive decline. Microvascular dysfunction caused by cerebral amyloid angiopathy could lead to both hippocampal atrophy and white matter lesions in AD [148]. Because amyloid angiopathy is also one of the major features of normal aging [151], it suggests that simultaneous progression of hippocampal atrophy and white matter lesions may reflect the progression of amyloid angiopathy in elderly persons without major cerebrovascular risk factors.

The presence of cortical infarctions also increased the risk of dementia in patients with hippocampal atrophy, demonstrating that patients with MCI progress to dementia faster if they have cortical infarctions along with findings associated with AD on MRI [149].

In a cohort of AD patients with multiple (≥ 8) MBs on T $_2^*$ -weighted MRI and matched for age, atrophy (medial temporal lobe or global cortical) was not related to the presence of MBs [115], but an interaction between MBs and cortical atrophy was found to result in a 6-fold increased risk of death for patients with severe cortical atrophy and multiple MBs in comparison to subjects without cortical atrophy and MBs.

Consequently, biomarkers contribute to our understanding of the pathophysiology of WML/MBs. In contrast to WML, cerebral MBs seem to share features with amyloid angiopathy.

A better understanding of the pathological basis of MRI changes and their consequences on the clinical course of dementia is important from a nosological point of view. In fact, vascular dementia and AD have generally been considered to be separate disease entities. However, they share common features (like vascular risk factors) and vascular risk factors are also risk factors for white matter changes [77]. Microangiopathy is present in both AD and vascular dementia, and WMHs are associated with an increased risk of AD [152] and MCI [54]. Vascular and degenerative processes have complex interactions. Therefore, a better understanding of the role of microangiopathy could suggest that there is in fact a spectrum ranging from pure vascular dementia to pure AD and including a majority of patients with contributions from both Alzheimer and vascular pathologies [23]. The topography of brain MBs (a corticosubcortical or a

deep location) could allow us to predict whether dementia is vascular or AD [153].

Thanks to the development of brain MRI, we are now capable of obtaining a more precise description of microangiopathy lesions. However, microangiopathy, ranging from WMHs to MBs, is perhaps only the tip of the iceberg. In fact, cortical microinfarcts and mild tissue changes in normal-appearing white matter on T₂-weighted images are other expressions of small-vessel disease revealed by postmortem studies, which are not detectable by conventional MRI. These abnormalities could also play an important role in the clinical symptomatology. Future research directions should include the use of newer MR techniques, especially diffusion tensor imaging, magnetization transfer imaging or relaxation time mapping that could help detect white matter injuries at an earlier time point [127, 154–156] and to investigate tissue damage that is not visible by conventional structural MRI T₂ relaxation time measurements [37].

Many questions concerning MBs have not been answered yet: what is their significance? Do they have sig-

nificant clinical consequences for elderly subjects and AD? What is the relationship between microangiopathy and neurodegenerative lesions in AD? Additional information on their physiopathology may lead to efficient therapeutic modalities and help us define specific subgroups of patients with specific disease processes and a different clinical course, who would benefit from a specific type of management. In the future, neuroimaging using both MRI and molecular imaging should be a major tool to assess the efficacy of preventive and therapeutic measures in the treatment of microangiopathy.

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