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Perspective

White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): Knowledge gaps and opportunities

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Abstract White matter hyperintensities (WMHs) are frequently seen on brain magnetic resonance imaging scans of older people. Usually interpreted clinically as a surrogate for cerebral small vessel disease, WMHs are associated with increased likelihood of cognitive impairment and dementia (including Alzheimer's disease [AD]). WMHs are also seen in cognitively healthy people. In this collaboration of academic, clinical, and pharmaceutical industry perspectives, we identify outstanding questions about WMHs and their relation to cognition, dementia, and AD. What molecular and cellular changes underlie WMHs? What are the neuropathological correlates of WMHs? To what extent are demyelination and inflammation present? Is it helpful to subdivide into periventricular and subcortical WMHs? What do WMHs signify in people diagnosed with AD? What are the risk factors for developing WMHs? What preventive and therapeutic strategies target WMHs? Answering these questions will improve prevention and treatment of WMHs and dementia.
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1. Introduction

1.1. What do we mean by white matter hyperintensities?

White matter hyperintensities (WMHs) of presumed vascular origin are among the most prominent age-related changes observed on brain magnetic resonance imaging (MRI) scans [1]. WMHs are seen as diffuse areas of high signal intensity (hence, "hyperintense") on T2-weighted or fluid-attenuated inversion recovery sequences [1–3] (examples in Fig. 1). WMHs are broadly equivalent to leukoaraiosis seen on computed tomography scans [1]. The variability in WMHs' appearance is hypothesized to reflect differences both in imaging parameters and also in etiology and pathological severity.

1.2. WMHs represent increased water content

WMHs seen on MRI represent changes in white matter composition, indicative of altered water content in hydrophobic white matter fibers and tracts. WMHs can be classified as specific or nonspecific depending on the water content they present [4]. This water disproportion can also vary with the brain area affected [4]. Radiologic insights into WMH etiology can come from relaxometry, where the magnetic resonance signal for water is manipulated using different pulse sequences to derive various images. These images have different contrast characteristics that provide information about various aspects of the brain microstructure. Relaxometry can determine relaxation times (T1R: longitudinal relaxation time, T2*R: effective transversal relaxation time), providing quantitation of the tissue structure and water content [4]. Diffusion tensor imaging provides further information on possible changes of the white matter microstructure and expansion of the WMH penumbra over time [5]. Diffusion tensor imaging data, specifically differences in fractional anisotropy (FA) and mean diffusivity, suggest axonal damage [5]. Differences in water content can also be associated with white matter edema [4].

2. Why are WMHs important?

2.1. Clinical impact of WMHs

In clinical MRI scans of older people, WMHs are typically interpreted as a surrogate of cerebral small vessel disease (SVD) [1,2,6]. Because various pathologies can lead to increased MRI signal intensity in white matter [6,7], WMHs alone are not diagnostically specific. Notably, distinguishing WMHs due to SVD from those of multiple sclerosis and other inflammatory brain diseases or metabolic leukodystrophies can be challenging. Moreover, cortical degeneration common in older persons with degenerative diseases (such as Alzheimer's disease [AD]; see Section 5) can lead to degeneration of fiber tracts and subsequent MRI changes.

Ample evidence supports a cross-sectional association between greater WMH volume and decrements in global or domain-specific cognitive performance [1–3,8]. That said, effect sizes are relatively small. A systematic review concluded that WMHs explain a modest degree of cross-sectional variation in cognition and cognitive decline [3]. WMHs are considered to be particularly correlated with reductions in information-processing speed and executive function, although correlations with other cognitive domains have also been noted [3,9]. Longitudinal studies in diverse populations consistently demonstrate that increasing WMH volume predicts cognitive decline, mild cognitive impairment, incident dementia, stroke, and death [1–3,10].

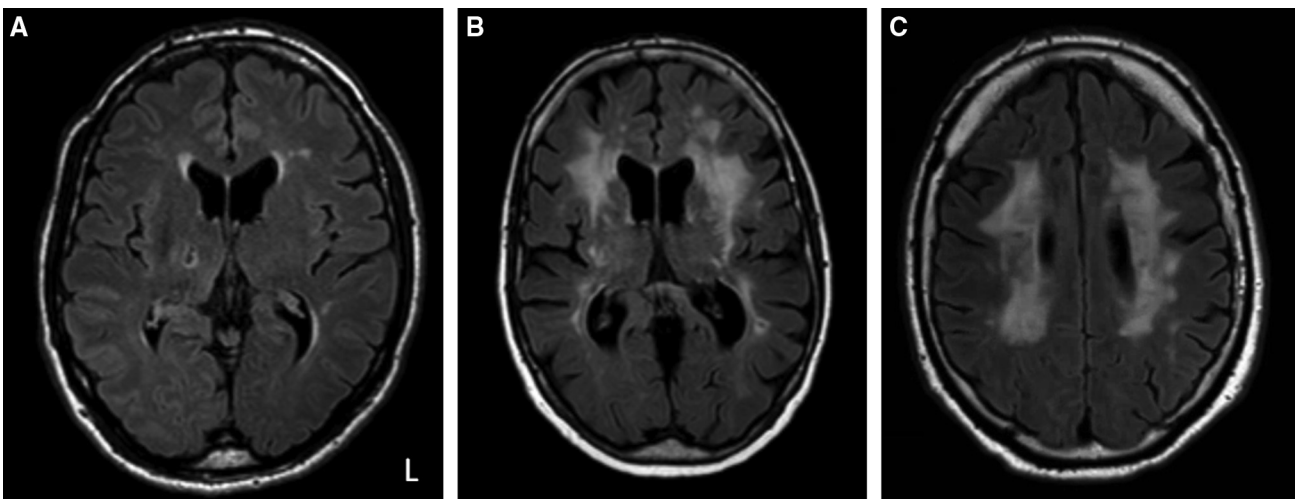

Fig. 1. MRI scans showing typical examples of WMHs of presumed vascular origin. (A) Punctate deep subcortical WMH in the left hemisphere and periventricular caps. This scan is Fazekas grade 1, on the Fazekas scale of WMH severity (range: 0-3). In the right thalamus, a lacune can be seen. (B, C) Two examples of severe confluent WMH. Note that borders between periventricular and deep subcortical WMHs become difficult to define. Scans B and C are Fazekas grade 3. Scans A-C are FLAIR sequences. Figure provided by GJ Biessels. Abbreviations: MRI, magnetic resonance imaging; WMHs, white matter hyperintensities; FLAIR, fluid-attenuated inversion recovery.

Box 1. Vascular contributions to cognitive impairment and dementia

- The concept of vascular contributions to cognitive impairment and dementia (VCID) encompasses the spectrum of vascular disease processes that impact cognitive function [13,16]. Brain vascular pathology is an important comorbidity in the multietiology view of common sporadic dementias of aging [14]. Mechanism-oriented VCID research can be described as the aging brain vasculature failing to cope with biological insults because of vascular disease, proteinopathies, metabolic disease, and immune affront. In 2016, a National Institutes of Health-sponsored summit defined research priorities in Alzheimer's and related dementias [13]. One output is the MarkVCID consortium, which is designed for multisite development and validation of small vessel VCID candidate biomarkers to the point of readiness for large-scale clinical trials (see https://markvcid.partners.org/).

WMHs are also associated with decline in gait and related aspects of physical performance [11,12]. Nevertheless, a given individual may have extensive WMHs but minimal cognitive impairment. WMH location, individual resilience factors, and cognitive reserve likely determine clinical impact.

WMHs play a key role in lowering the threshold for the clinical expression of dementia in the presence of neurodegenerative lesions [13,14], specifically, AD-related pathology [15] (see Box 1). Although there is the possibility that WMHs promote or interact with AD-related pathologies, current data support an additive role for vascular pathologies rather than a synergistic interaction with AD-related pathological lesions [17].

2.2. WMHs in terms of clinical diagnostic criteria

The heterogeneity of WMH etiology and clinical manifestations present diagnostic challenges [18,19]. Even in patients with dementia and significant WMHs, the vascular contribution to the clinical phenotype may be missed if neuroimaging is not performed. The National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria, a popular diagnostic framework for clinical definition of vascular dementia, require clinical dementia with a temporal relationship to a preceding stroke with relevant imaging. In clinical practice, this may not be straightforward, and most patients who exhibit WMHs have no stroke history. It remains challenging to attribute cognitive deficits to WMHs at an individual patient level. Three examples of possible "vascular" clinical courses to symptomatic cognitive impairment are illustrated in Fig. 2. These archetypes rarely present in isolation, nevertheless they illustrate the heterogeneity of vascular cognitive impairment. Refined diagnostic criteria taking account of the clinical course of WMHs are likely to be beneficial [18,19].

2.2.1. Biochemical biomarkers for clinical use

Fluid biomarkers relevant to WMHs will be clinically beneficial, reviewed elsewhere [20]. The low molecular weight neurofilament marker (NF-L), extracellular metalloproteinase matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1, the matrix metalloproteinase-2 index, and the albumin brain-plasma ratio are all increased in people with clinical diagnosis of SVD. Peripheral blood markers for WMHs, alongside fluid biomarkers related to AD pathology, will help to subtype patients according to their degree of AD pathology and brain vascular burden [13,20,21].

3. Epidemiology of WMHs

3.1. Prevalence and progression of WMHs

3.1.1. Prevalence of WMHs

Most individuals older than 60 years have some degree of WMH, and prevalence increases with age. In the Rotterdam Scan Study, prevalence of subcortical WMHs increased by 0.2% per year of age, whereas periventricular WMHs increased by 0.4% [22] (See Box 2). For participants aged 60-70 years, 87% had subcortical and 68% had periventricular WMHs. For participants aged 80-90 years, 100% had subcortical and 95% had periventricular WMHs [22]. This age gradient of WMHs has been confirmed in a wider age range (ages 20-90 years, Study of Health in Pomerania cohort) [25]. In addition, many cognitively healthy younger adults show some degree of WMH on MRI.

3.1.2. Progression of WMHs

Longitudinal studies of community-dwelling, healthy older adults show increasing WMH severity or WMH volume over time [26]. Rates of progression are variable, likely due to study-specific definitions of progression or duration of follow-up. For example, in the Cardiovascular Health Study, 28% of participants had a worsening WMH grade (by at least 1 grade on a 0-9 visual rating scale) over five years [27], whereas in the Rotterdam Scan Study, 39% had progression of WMH volume over 3.4 years [28]. In the Leukoaraiosis and Disability in the Elderly study, 74% exhibited worsening over 3.1 years [29], and 84% had progression of WMH volume over 9.1 years in the Oregon Brain Aging Study [12]. Overall, longitudinal studies show annual increases in WMH volume ranging from 4.4% to 37.2% [26]. In some cohorts, decrease in WMH volume has been reported, although effect sizes were small [30].

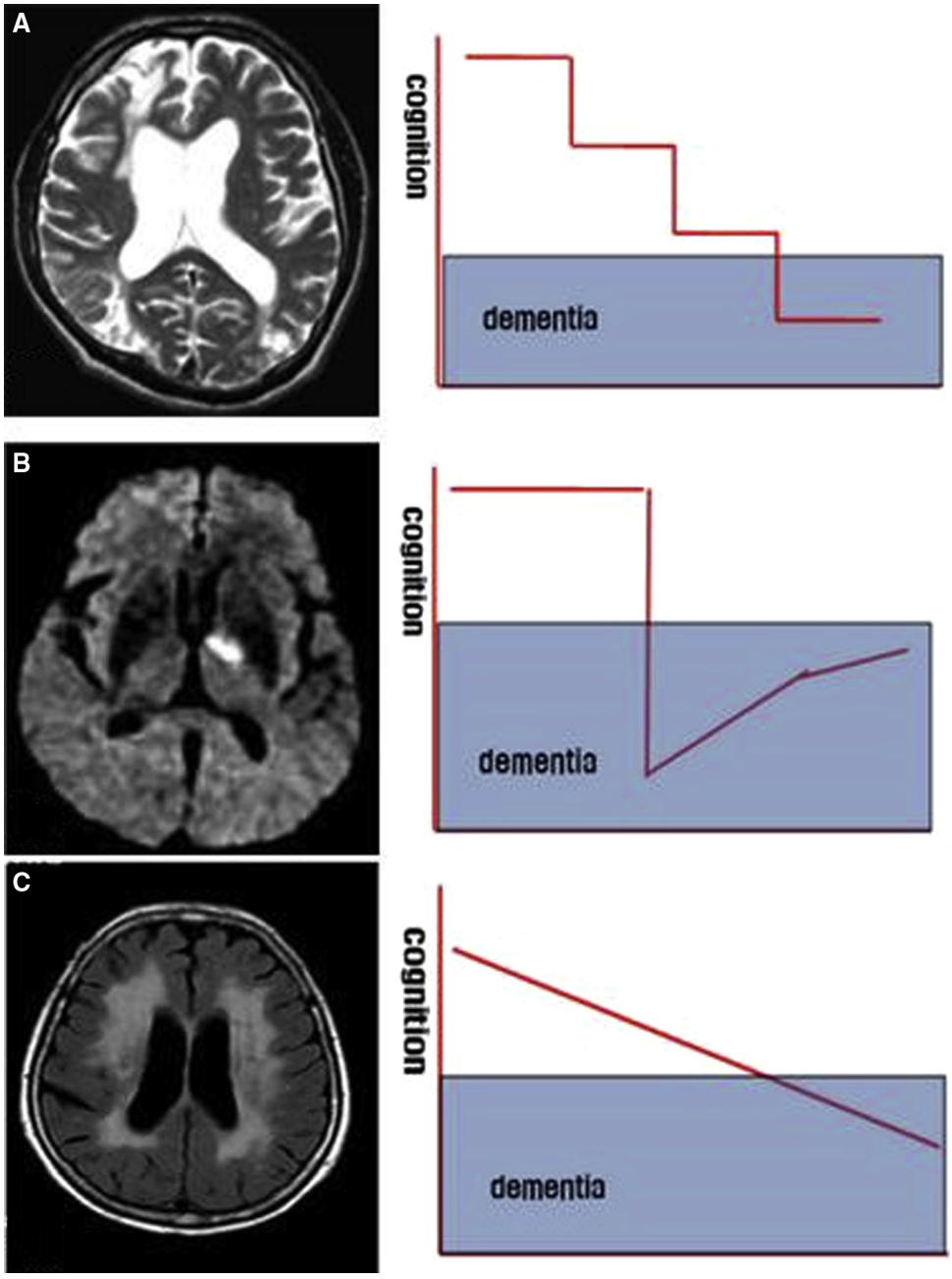

Fig. 2. Conceptual clinical courses leading to vascular dementia. (A) Multi-infarct dementia, stepwise pattern of cognitive decline. (B) Strategic vascular dementia due to a focal lesion in a clinically eloquent site. One-step pattern, with some recovery. (C) WMH-associated subcortical vascular dementia. Slow progression without stepwise pattern. Figure provided by J Kwon. Abbreviation: WMH, white matter hyperintensity.

3.2. Risk factors for WMHs

3.2.1. Nonmodifiable risk factors

WMHs are more prevalent at older ages, and some studies support faster progression with advanced age (see a recent review by Jorgensen et al) [26]. Black race, female sex, and *apolipoprotein E ε4* allele presence have all been associated with greater cross-sectional WMH burden or WMH progression, although results have been mixed [26,31].

3.2.2. Modifiable risk factors

Identified risk factors for WMH severity and progression are primarily vascular, cardiometabolic, and nutritional [26]. Among these, associations are strongest for blood pressure–related measures. In cross-sectional analyses, elevated blood pressure is unequivocally associated with the presence or severity of WMHs. Studies considering high blood pressure earlier in life generally report an association with subsequent WMHs. In the Rotterdam Scan Study, elevated blood pressure was associated with increased WMH risk 5 and 20 years later.

Box 2. Is it helpful to classify WMHs into subcortical and periventricular?

- Subcortical WMHs are defined as isolated foci appearing in the superficial white matter, which in most cases are not contiguous with periventricular WMHs. The neuropathological substrates differ between the localizations [23,24] (see Section 4), which can also have different risk factors and effects on cognition [1]. It has been proposed that cognitive impairments associated with periventricular WMHs reflect disruption of cholinergic projections from the basal forebrain to the cortex.
- Elevated levels of activated microglia in periventricular WMH indicate that these may particularly involve neuroinflammatory responses following disruption of the blood-brain barrier (BBB), see Box 4. This response is not seen in subcortical WMH [23]. In contrast, subcortical (but not periventricular) WMH volume was associated with lipid peroxidation in blood, which mediated the effect of hypertension, adding biological validity to a vascular etiology for subcortical WMH [21]. There may be further valid subdivisions within subcortical WMH. Nevertheless, it may be premature to discriminate periventricular from subcortical WMH clinically.

Similarly, both midlife and late-life blood pressure were associated with increased WMH risk in the Cardiovascular Risk Factors, Aging and Incidence of Dementia Study [32], and elevated midlife blood pressure was related to late-life WMH volume in the National Heart Lung, and Blood Institute Twin Study [33]. There is mixed evidence for dyslipidemia as a risk factor for WMHs. Omega-3 polyunsaturated fatty acids have been associated with lower WMH burden. Neither diabetes mellitus nor insulin resistance is strongly related to WMHs, whereas fasting glucose has been related to WMH progression. Greater visceral fat accumulation is more strongly associated with WMHs than body mass index. Tobacco smoking, higher blood levels of inflammatory markers (C-reactive protein, interleukin-6), low levels of vitamin B12, and hyperhomocysteinemia have all been associated with WMHs (see Box 4). These studies of risk factors are discussed in a recent review by Jorgensen et al [26].

Elevated levels of activated microglia in periventricular WMHs indicate that these may particularly involve neuroinflammatory responses after disruption of the blood-brain barrier (BBB) (see Box 4). This response is not seen in subcortical WMHs [23]. In contrast, subcortical (but not periventricular) WMH volume was associated with lipid peroxidation in blood, which mediated the effect of hypertension, adding biological validity to a vascular etiology for subcortical WMHs [21]. There may be further valid subdivisions within subcortical WMHs. Nevertheless, it may be premature to discriminate periventricular from subcortical WMHs clinically.

4. Neuropathological changes that underlie WMHs

4.1. Types of underlying tissue damage in WMHs

The pathophysiology of SVD-associated white matter histological lesions has been attributed to multiple mechanisms, including hypoperfusion, defective cerebrovascular reactivity, and BBB dysfunction [5,6,37–39]. The white matter microvascular network likely contributes to WMH pathogenesis, with vascular changes including arteriolar tortuosity, loss of blood vessel density, and venous collagenosis. Other possible mechanisms include dysfunction of oligodendrocyte precursor cells [40] or impaired perivascular ("glymphatic") clearance. Different presentations of WMHs indicate differences in underlying pathological changes. For example, punctate WMHs (considered to represent mild tissue changes) are associated with myelin damage, gliosis, and enlarged perivascular spaces, whereas extensive, confluent WMHs are considered

Box 3. White matter pathology and cognitive impairment in experimental primates

- The rhesus monkey has a brain structure similar to humans and similar age-related decline in cognitive function [34]. The monkey adult life span is up to 40 years, and cognitive impairments appear from around 13 years and accelerate from 20 years, with deficits in executive function, working memory, and recognition memory (resembling clinical criteria for subcortical SVD). There is considerable variability between subjects, with the majority exhibiting severe impairments while some are only mildly impaired. Markers of AD pathology (amyloid plaques, hyperphosphorylated tau) are variable or absent and correlate poorly with cognitive impairment. Neuronal loss is not detectable, and gray matter is well preserved [34]. MRI shows age-related loss of forebrain white matter volume and decrease of FA in subcortical white matter tracts, both correlated with cognitive decline. Electron microscopy shows accumulating myelin defects, including splitting and ballooning of myelin sheaths, as well as complete degeneration of axons and their myelin. Age-related myelin histopathology correlates well with FA reduction and with diminution in the corpus callosal compound action potential. Possible mechanisms for age-related white matter damage in monkeys include oxidative stress and inflammation, worsened by age-related reductions in microglial activity and myelin repair [34,35]. These observations point to white matter pathology, independent of neurodegeneration, as the source of age-related VCID in primates.

Box 4. Is inflammation a feature in WMHs?

- An explicit inflammatory process, in the manner of multiple sclerosis, does not apply to WMHs of presumed vascular origin. Nevertheless, participation of some inflammation-related molecules and cells appears likely and merits deeper understanding. In some large studies, circulating peripheral proinflammatory markers (e.g., C-reactive protein and interleukin-6) have been associated with WMHs, indicating possible involvement of inflammatory pathways in WMHs. Other peripheral proinflammatory and anti-inflammatory cytokines (e.g., interleukin-8) are found elevated specifically in people with a clinical AD diagnosis who also have extensive WMHs [36].

to represent more progressive pathological changes, including some degree of myelin loss, axonal disruption, and astrogliosis [6,7]. Pathological differences in WMHs also occur based on anatomical location, for example, when evaluating periventricular versus subcortical WMHs (see Box 2) or watershed versus nonwatershed regions. Minor pathological changes associated with WMHs (at the caps/rims of periventricular regions; Fig. 1) are most consistent with disturbed cerebrospinal fluid transport and periventricular edema, both of which accompany aging.

Watershed zones are bordered by the distal territories of the anterior, middle, and posterior cerebral arteries. In an event of hemodynamic compromise, watershed regions are more susceptible to hypoperfusion and thus more likely to develop ischemic (or oligemic) lesions. There are differences in the arteries supplying to the periventricular and subcortical white matter. While long perforating branches supply to the periventricular white matter, shorter branches supply to the subcortical white matter.

WMH severity has been associated with microinfarcts and diffuse amyloid plaque load in brains of people diagnosed with AD [41]. In the context of AD pathology, especially in late stages of the disease, it is conceivable that some white matter lesions occur secondary to Wallerian degeneration, triggered by cortical neurodegenerative pathology [42]. More likely, AD pathology (common in older people) and WMHs of vascular origin (even more common in older people) frequently copresent as has been noted in multiple autopsy-based studies on mixed pathologies [14].

4.2. Demyelination in WMHs

Early imaging studies indicated that severe WMHs are related to cell death and myelin loss, see the studies by Gouw et al and Schmidt et al [6,7], with early confluent WMHs presenting more marked demyelination than focal/punctate WMHs. Compared with subcortical WMHs, periventricular WMHs show increased axonal loss, astrocytosis, microglial density, and loss of oligodendrocytes. There may also be lobar variability. Early myelin changes may involve the frontal lobe, with subsequent gradual involvement of the parietal, temporal, and occipital lobes [43].

Demyelination is not a universal feature of WMHs. In addition to demyelination, myelin "pallor" has been confirmed as a histological substrate of WMHs. With aging, the ability of the oligodendrocytes to regenerate myelin sheaths decreases [40]. To what degree pallor represents loss of myelin sheaths or loss of myelin secondary to axonal loss remains unresolved [44]. In aged primates, cognitive impairment exacerbated by hypertension is associated with myelin damage and microglial changes within the white matter (Box 3).

4.3. Insights from MRI-histopathology correlative studies of WMHs

Several studies have examined the underlying pathology of WMHs using ex vivo MRI combined with histopathology [6,37–39]. Early MRI-neuropathology correlative studies reported ischemic changes, with evidence of plasma extravasation (indicative of BBB dysfunction), rarefaction, or loss of parenchymal tissue structure [45]. More advanced lesions showed reduced myelin density [45]. These data are broadly confirmed by more recent molecular studies [38,39].

5. Are WMHs related to Alzheimer's disease?

We acknowledge a distinction between AD as a syndromal diagnosis in living people and AD as a neuropathological description or molecular etiology [15]. With regard to clinical diagnosis, most people with AD diagnosis above the age of 70 years have some degree of WMHs. This may reflect associated vascular pathology, consistent with autopsy studies showing a high prevalence of mixed AD and vascular pathologies [14]. To what extent AD neuropathology causes WMHs (of vascular or nonvascular origin) is still debated. Most amyloid PET studies found no association between β-amyloid (Aβ) tracer uptake and WMH burden [17,46]. Nevertheless, a recent study in the Alzheimer's Disease Neuroimaging Initiative cohort (using florbetapir instead of Pittsburgh compound-B as the amyloid tracer) observed a correlation between elevated brain Aβ and WMHs [47]. Furthermore, in people carrying dominant AD mutations, WMH volume remains elevated up to 20 years in advance of cognitive symptoms, concomitant with altered levels of Aβ and tau in cerebrospinal fluid [48]. Because vascular disease is uncommon in these younger mutation-bearing persons, these data suggest that AD pathology may be related to vascular and/or nonvascular processes resulting in WMHs.

Cerebral amyloid angiopathy (CAA) is a common age-related SVD, characterized by the accumulation of Aβ in the walls of cortical arterioles and leptomeningeal vessels [46,49]. Some degree of histological CAA is present in most (but not all) brains that contain AD neuropathological hallmarks. CAA may contribute to the

microvascular processes underlying WMHs (impaired perivascular clearance, plasma extravasation, inflammation, hypoperfusion, endothelial dysfunction) [46]. Whether or not AD is concomitant, CAA plays a distinct role in the spectrum of dementia [17,49].

6. Implications for treatment interventions

6.1. Nonpharmacological interventions

6.1.1. Physical activity and diet

A meta-analysis of cross-sectional observational studies demonstrated that physical fitness and activity were associated with lower global WMH volume but had mixed results when local WMHs (periventricular and subcortical) were examined separately [50]. In relation to WMHs, few randomized-controlled trials of physical activity have been carried out. These studies have been restricted to prevention of WMH progression as opposed to primary prevention. In older women, twice weekly resistance training reduced WMH volume progression, relative to balance and toning control [24].

Observational cohort studies of diet and nutrition suggest that the consumption of tuna/nonfried fish and the Mediterranean diet is associated with less WMH load [51,52]. Higher plasma omega-3 polyunsaturated fatty acids (abundant in both diets) are associated with less WMH-mediated executive function decline in aging, and these findings have led to a randomized-controlled trial of omega-3 fatty acids for the prevention of WMH accumulation (n-3 PUFA for Vascular Cognitive Aging, NCT01953705).

6.1.2. Multidomain interventions

The Look AHEAD study tested a 10-year physical activity and dietary modification intervention in older adults who are overweight and obese with type 2 diabetes mellitus. Although there was no effect of the intervention on cognition in the MRI substudy, the intervention group had significantly lower WMH volume than the control group [53]. Similarly, in the Evaluation of Vascular care in Alzheimer's disease study, participants with clinical AD diagnoses and MRI evidence of SVD (WMHs, lacunar or cortical infarcts) were randomized to either a multidomain approach (dietary and physical activity counseling, smoking cessation, and pharmacologic treatment of cardiovascular risk factors) or standard care. Those randomized to the composite intervention had reduced progression of WMH (but not global atrophy or new infarcts) [54].

6.2. Pharmacological interventions

6.2.1. Blood pressure medications

Randomized clinical trial subanalyses indicate that effective antihypertensive therapy reduces WMH incidence. Treatment with an angiotensin-converting enzyme (ACE) inhibitor over 36 months reduced the WMH number and total WMH volume in the Perindopril Protection Against Recurrent Stroke Study trial [55]. An observational cohort study suggested that treatment with an angiotensin receptor blocker, versus an ACE inhibitor, was associated with smaller WMH volumes in people with a clinical AD diagnosis [56]. An MRI substudy of the Prevention of dementia by intensive vascular care trial suggested a beneficial effect in the sub-group with large baseline WMH volume, but found no overall impact of intensive vascular management on WMH progression [57]. A trial of intensive versus standard blood pressure control (based on ambulatory blood pressure) is ongoing in individuals who are either normal or mildly impaired on cognition and mobility, with WMH progression as a secondary outcome [58]. The results of the Systolic Blood Pressure Intervention Trial (SPRINT-MIND) of intensive versus standard blood pressure control on WMH were presented at Alzheimer's Association International Conference 2018. This trial demonstrated reduced mild cognitive impairment in the intensive treatment arm (though this was not a primary endpoint of the trial) [59]. The effect of two years of treatment with either ACE inhibitor or angiotensin II receptor blockers on an outcome of SVD progression, including WMHs and silent brain infarcts, is currently being tested [60].

6.2.2. Statins

Nearly three years of treatment with 40 mg of pravastatin daily in the Pravastatin in elderly individuals at risk of vascular disease (PROSPER) study did not reduce WMH progression over the placebo group in individuals with increased vascular risk [61].

6.2.3. Antithrombotic agents

The ASPirin in Reducing Events in the Elderly (ASPREE-NEURO) study is evaluating 100 mg of aspirin daily versus placebo over one year, with a secondary outcome of WMH volume change [62].

7. Concluding comments

Converging data from clinical, neuropathological, and experimental studies has begun to unravel WMH mechanisms. We are optimistic that the next ten years will see substantial advances in molecular understanding and clinical management of WMHs and VCID. Deeper molecular understanding of the various etiologies and pathologies that lead to WMHs will improve diagnostic specificity. It will also enable more refined medicinal chemistry for generating improved biomarkers (both imaging and biochemical) and novel therapeutic agents. Better structural and molecular biomarkers will serve as endpoints in clinical trials of targeted treatments, based on pathological understanding. How the WMH profile of a given dementia patient should guide treatment, while minimizing adverse clinical outcomes, remains a fertile field for clinical research.

Currently, treatment of WMHs of presumed vascular origin is limited to lifestyle modifications and risk factor management. Given the associations between WMHs and vascular risk factors, it is imperative to target vascular health throughout the life course as a prevention strategy. At a societal level, there are enormous opportunities for policy makers to combat the 21st century obesogenic environment, which contributes significantly to poor vascular and metabolic health. Effective regulations on the content of foods (e.g., sugar in food and drinks), clear labeling of food products, and food marketing (to children in particular) will likely have more health-care impact than any drug.

Scientific progress is needed in the following areas: (1) application of emerging diagnostic criteria to identify different subtypes of WMHs, possibly with differing etiology, outcomes, and clinical significance; (2) robust differential biomarkers to discriminate different pathologies (SVD, CAA, and AD), their possible interactions, and their relation to VCID; (3) consensus on segregation algorithms (e.g., definitions of regional WMH boundaries); (4) animal models relevant to WMHs of different pathological origin; (5) further detailed MRI-histopathology correlative studies to encompass the range of WMH-related lesion characteristics; (6) hypothesis-driven, randomized-controlled trials of drugs and other interventions targeting WMHs.

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RESEARCH IN CONTEXT

1. Systematic review: This perspective came from a multidisciplinary author team, across a range of seniority from graduate students to emeritus professors. Citations provided come from the authors' expertise and from PubMed. We did not attempt a formal systematic review.
2. Interpretation: We aimed i) to summarise the knowledge base on WMHs and their relation to cognitive impairment, ii) to identify perceived knowledge gaps related to WMHs, particularly those relevant to accelerating dementia therapies.
3. Future directions: Molecular studies in human tissue and bio-fluid samples will yield biological understanding of the processes that underlie WMHs, hence better biomarkers (both imaging and biochemical) and molecular targets for drug treatment.

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