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REVIEW ARTICLES

Age-related white matter changes in Asia

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Abstract

Age-related white matter changes are common in the elderly and are considered as manifestation of arteriolosclerotic small vessel disease. Most recent studies have shown that the white matter changes are associated with cognitive impairment and dementia, urinary incontinence, gait disturbances, depression and increased risk of stroke and death. Although the clinical phenotypes of the white matter changes have been extensively studied, to date, only few clinical trials have been conducted in this area. In this review, we discussed the current understanding in the epidemiology, pathogenesis, imaging features, chemical biomarkers, clinical importance, and management of age-related white matter changes, with special emphasis in studies that were conducted among Asians.

INTRODUCTION

Age-related white matter changes (WMC) are common findings among the elderly. WMC are considered to be arteriolosclerotic cerebral small vessel disease and are important substrates for cognitive impairment and functional loss in the elderly.[1] In this article, we aimed to review the epidemiology, pathogenesis, neuroimaging, chemical biomarkers, clinical phenotypes, and treatments of age-related WMC, with special emphasis on studies that were conducted in Asia.

EPIDEMIOLOGY

Few studies among Asians suggested that prevalence of WMC is as common as in Western countries, with prevalence ranging from 28.8% to 77.1%.[2-4] In Chinese lacunar stroke patients, prevalence of WMC was about 80%.[5] Similar to studies from the West, age, hypertension and female gender were found to associate with WMC.[4,6] Overall, associations of diabetes mellitus (DM), hyperlipidemia, and cigarette smoking with WMC are less consistent among studies.

WMC may progress, or even regress over time. Several longitudinal studies have investigated the rate and predictors for progression of WMC.[7-9] In the Austrian Stroke Prevention Study, the median (interquartile range) volume increase over the 6-year period was 0 cm^3 in subjects with no lesions, 0.2 (0.0-1.1) cm^3 in subjects with punctuate lesions, 2.7 (0.5-5.9) cm^3 in subjects with early confluent lesions and 9.3 (7.1-21.0) cm^3 for individuals with confluent WMC at baseline.[8] Perhaps baseline severity of WMC is the most consistent predictor for progression of WMC. Patients with punctate WMC usually have minimal progression of WMC, whereas those with early confluent and confluent WMC at baseline have rapid progression of WMC.[7,8] In a cohort of Chinese patients who were all participants of a clinical trial, similar progression rate was also found.[10] Other factors associated with faster decline in WMC are higher age and elevated BP.[9]

PATHOGENESIS

Pathologically, WMC are characterized by partial loss of myelin, axons, and oligodendroglial cells; mild reactive astrocytic gliosis; and sparsely distributed macrophages as well as stenosis resulting from hyaline fibrosis of arterioles and smaller vessels.[11] The pathophysiology of WMC is complex, and maybe multifactorial. Nowadays, the most accepted opinion is that

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WMC represent incomplete ischemia mainly related to cerebral small vessel arteriolosclerosis.[12] Other mechanisms encompass blood-brain barrier dysfunction[13-15], dysfunction of vasomotor reactivity and autoregulation[16-19], chronic edema[20,21], apoptosis[22] and endothelial dysfunction.[23,24] According to the location of WMC lesions, WMC can be divided into periventricular WMC (PVWMC) and deep WMC (DWMC). Pathological studies have shown that PVWMC were related to disruption of the ependymal lining with subependymal widening of the extracellular space resulting from disruption of the blood brain barrier, whereas the DWMC were mainly related to incomplete ischemic arteriolosclerosis.[25,26]

Although past studies had suggested that WMC are highly heritable[27] and that several polymorphisms in various candidate genes, such as methylenetetrahydrofolate reductase (677 cytosine/thymine polymorphism [C/T]), apolipoprotein E (epsilon 4+/-), and angiotensinogen (Met235Thr), were found to be associated with WMC[2,28,29], a recent meta-analyses failed to show convincing evidence for an association between WMC and the candidate genetic polymorphisms.[30] A study among Chinese lacunar stroke patients showed that WMC was associated with APOE ε4.[31] However, in another Korean study among dementia patients with WMC, the association between APOE ε4 and WMC could not be found.[32]

NEUROIMAGING ASSESSMENT

WMC are ill-defined hypodensities on CT. On MRI, they appear as hypointensities on T1-weighted imaging, and hyperintensities on T2-weighted imaging and fluid attenuated inversion recovery sequences (FLAIR). (Figure 1)

To assess WMC severity, there are various visual rating scales and automated/semi-automated volumetric measurement. The visual rating scales are simple with less requirement for quality of scans compared with volumetric measurement.[33] However, data is not quantitative and they varied from each other, which may lead to inconsistent findings. To unite the visual rating for WMC, the vascular cognitive impairment harmonization standard recommend the age-related WMC (ARWMC) scale[34] as the preferred visual rating scale.[35] This scale can be applied to both MRI and CT with moderate to excellent reliability. Xiong Y et al had also validated this scale against volumetric measurement and cognitive impairment among Chinese patients.[36] Furthermore, considering that there are many developing countries in Asia where only CT is available, the same group had also operationalized ARWMC scale so as to improve interrater reliability on CT.[37]

TRANSCRANIAL DOPPLER ULTRASOUND

Transcranial Doppler ultrasound (TCD) is a non-invasive, easily administered, and relatively inexpensive test that has traditionally been used to detect intracranial large artery disease. The arterial pulsatility index, which is derived from the flow velocities of large arteries, reflects the downstream vascular resistance. Xiong *et al* study among Chinese stroke patients has found that pulsatility index in TCD was associated with WMC volume in acute stroke patients; thus, TCD may possibly serve as a screening test for WMC. Further study evaluating the clinical utility of TCD in screening for subclinical WMC among community elderly is warranted. Availability of a simple screening tool that can guide selective MRI scanning will promote early detection and management of WMC and also cost effective recruitment into clinical trials for subclinical WMC.[38]

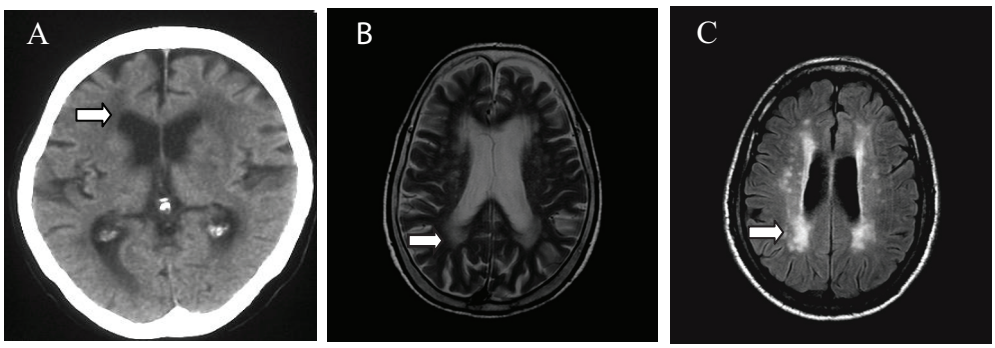

Figure 1: White matter changes on CT and MRI. A: hypodensitity on CT; B and, C: hyperintensity on T2-weighted MRI and FLAIR sequence, respectively.

CHEMICAL BIOMARKERS

Many studies had indicated that hyperhomocysteinemia was an independent predictor for WMC.[39-41] Similar association between hyperchomocysteinemia and severity of WMC was also found in among Chinese stroke patients.[42] Inflammatory biomarkers, such as Intercellular adhesion molecule-1 (ICAM-1)[43,44], high sensitive C-reactive protein (Hs CRP)[45-47], lipoprotein-associated phospholipase A2 (Lp-PLA2) and myeloperoxidase (MPO)[48] were also reported to be associated with WMC load. However, these studies were cross-sectional so that causal relationship cannot be attained. Longitudinal studies are needed to study the relationship between changes of inflammatory factors with progression of WMC.

CLINICAL PHENOTYPES

Cognitive impairment and decline

Lines of evidence show that WMC are associated with executive dysfunction[49,50], impaired mental processing speed[51,52] and global cognition[53,54], as well as cognitive decline.[55] Study by Wen *et al* among Chinese lacunar stroke patients found that severity of WMC was associated mainly with executive dysfunction.[5] However, in some studies when brain atrophy was added into the predicting models, WMC severity became insignificant whereas global and/or regional atrophy (i.e. medial temporal lobe atrophy, cortical gray matter [cGM] and hippocampus atrophy) independently predicted cognitive decline.[56-58] A Chinese study by Mok *et al* also study found that in those who already had confluent WMC, baseline cGM atrophy and frontal atrophy, rather than severity of WMC, predicted cognitive decline. Yet in this study, cGM atrophy was associated with WMC volume.[59] It was thus proposed that cognitive decline in patients with WMC was mediated by brain atrophy.[59]

Gait disturbance

WMC were associated with gait disturbance (i.e. slow walking speed, deficiency in balance and short-stepped gait) and falls.[60,61] Tasmanian Study of Cognition and Gait study showed that the risk of incident falls was doubled in people with WMC volumes in the highest quintile of its distribution than the lowest (adjusted relative risk 2.32, 95% confidence interval [CI]:1.28–4.14).[62] Accumulating evidence suggests that the disruptions in motor network may account for gait disturbance in WMC.[63,64]

Urinary incontinence

Some studies had shown that WMC were associated with urgency urinary incontinence.[65-69] A community study found that among 100 residents, 64% of them had urinary incontinence.[66] The presence of WMC in right inferior frontal regions and specific pathways (anterior thalamic radiation and superior longitudinal fasciculus) might affect continence control.[66,70]

Depression

Lines of evidence suggested that WMC are associated with late life depression.[71-79] In post-stroke Chinese patients, severe deep WMC predicted post-stroke depression.[80] In another study among Chinese stroke subjects who already had confluent WMC, concurrent atrophy of left inferior frontal gyrus was associated with depressive symptoms.[81] The vascular depression hypothesis proposes that WMC cause depression by disrupting fiber tracts within frontostriatal circuits.[77]

Stroke and death

The WMC increased the risk for stroke[82-85] and death.[85-88] A recent meta-analysis revealed that stroke yielded a significant association of WMC with incident stroke (Hazard ratio 3.5, 95% CI: 2.5-4.9, P<0.001) and increased risk of death (Hazard ratio 2.0, 95% CI: 1.6-2.7, P<0.001).[55] Severe WMC also increase the risk for hemorrhagic stroke. In patients treated with thrombolysis for acute stroke, the rate of symptomatic intracerebral hemorrhage increased by 10% in patients with severe WMC and multiple lacunes.[89] A recent Korean study found that severe WMC predict mortality (relative risk 2.61, 95% CI: 1.79-3.82) after intracerebral hemorrhage.[90]

WMC are actual predictors for poor clinical and functional outcomes. Overall, studies in Asia on WMC have focused mainly on cognition, depression and stroke, while studies concerning other clinical phenotypes are very few. Therefore, more studies are needed to study the clinical significance of WMC in Asia.

MANAGEMENT

Albeit WMC are clinically important, to date, very few clinical studies had been conducted to

evaluate treatments for WMC or for preventing its progression.

Blood pressure lowing therapy

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) MRI substudy[91] was a longitudinal randomized placebo-controlled trail investigating the BP lowing therapy using perindopril or perindopril plus indapamide on WMC progression in 192 participants with followed up duration of 36 months. The blood pressure reduction in the active arm compared with the placebo arm was 11.2 mm Hg for systolic blood pressure and 4.3 mm Hg for diastolic blood pressure. The mean total volume of new WMC was significantly lower in the active treatment group compared with the placebo group, and the difference was greatest for patients with severe WMC at entry.[91] Albeit a positive finding, it is important to note that this study was a post-hoc analysis and the result may be hypothesis driven. Although hypertension is a risk factor for WMC, low blood pressure is also harmful for WMC.[92] Nocturnal blood pressure dipping was associated with WMC as well.[93] Therefore, randomized placebo-controlled trails dedicated to examine the effects of blood pressure lowering therapy upon progression of WMC and to identify the best blood pressure control are needed.

Statins

Statins are considered to lower lipid level, and reduce cardiovascular events and ischemic stroke among patients with coronary heart disease.[94] Whether statins retard progression of WMC is still controversial. The PROSPER (Prospective Study of Pravastatin in Elderly at Risk) Study failed to demonstrate an overall beneficial effect of statins upon WMC progression using pravastatin 40 mg daily in 270 placebo-treated subjects and 265 active subjects within a period of 33 months. The Cardiovascular Health Study found that patients treated with statins had slightly less cognitive decline than untreated subjects, however, the improvement of cognition was due to reduced progression in cerebral infarcts and progression of WMC was not statistically different between treated and untreated subjects.[95] The ROCAS (Regression of Cerebral Artery Stenosis) study in Hong Kong is a randomized, double-blind, placebo-controlled study evaluating simvastatin on WMC progression in patients with asymptomatic middle cerebral artery stenosis.[10] Two hundreds and eight randomized subjects were assigned to either placebo (n = 102) or simvastatin 20 mg daily (n = 106) for 2 years. Simvastatin group did not slow the overall progression of WMC volume compared with the placebo group. However, in those with severe WMC at baseline, the median volume increase in the simvastatin group (1.9 cm^3) was less than that in the placebo group (3.0 cm^3; P = 0.047). However, stains probably prevented WMC progression among those with severe WMC at baseline was based only on subgroup analysis upon a small subset of subjects. Moreover, all subjects of this study had concurrent MCA stenosis. Hence, the findings may not be applicable to patients with less vascular burden or to those with WMC but without concurrent MCA stenosis. On the other hand, a recent cross-sectional study found that low cholesterol had more severe WMC in acute stroke patients.[96] Other studies showed that low cholesterol was associated with intracerebral hemorrhage and high mortality in these patients.[97,98] Therefore, effects of stains and cholesterol control upon WMC progression are still uncertain and randomized clinical trails are needed to investigate this issue.

Symptomatic treatments with acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists

Currently, patients with dementia that are associated with severe WMC are labeled as having subcortical vascular dementia. Meta-analyses of clinical trials in vascular dementia using acetylcholinesterase inhibitors and memantine have found only a modest cognitive benefit of these drugs. Post-hoc analyses suggested that acetylcholinesterase inhibitors induced even a lesser improvement in cognition in those with subcortical vascular dementia compared with that in cortical vascular dementia.[99] By contrast, cognitive benefits in the memantine trials appeared to be more pronounced for patients with subcortical vascular dementia over those with cortical vascular dementia.[99,100]

In Asia, effectiveness of acetylcholinesterase inhibitor was also explored in a randomized double-blind placebo-controlled 26-week trial using rivastigmine among Chinese patients with subcortical vascular dementia.[101] Forty subjects were randomized to either placebo (n = 20) or 6 mg daily of rivastigmine (n = 20). The study found no statistical significant benefit could be observed in the active group in mini-mental state examination, frontal assessment battery, neuropsychiatric inventory, instrumental activities of daily living

and clinical dementia rating scale. Types of common adverse effects (e.g., nausea, vomiting, loss of appetite, leg cramp) were typical to that seen with rivastigmine.[101] This study is limited by its small sample size, short follow-up duration and insensitive neuropsychological tests. A recent 24-week randomized double-blinded placebo-controlled trail in Singapore also investigated the safety and efficacy of rivastigmine in cognition, particularly executive function in ischemic stroke patients with cognitive impairment no dementia (CIND).[102] Fifty patients were randomized into 9 mg daily of rivastigmine (n = 25) and placebo (n = 25) arms. The study found that patients in the active group had statistically significant improvement on the animal subtask of the verbal fluency measure compared with placebo. There was also a trend towards improvement in Color Trails II. It demonstrated that rivastigmine was well tolerated in ischemic stroke patients with CIND and may potentially improve executive function.[102]

SUMMARY

Similar to Western countries, WMC are common in elderly Asians and are also associated with poor clinical outcomes. Although WMC are related to age and various vascular risk factors, the exact underlying mechanisms explaining the development and progression of WMC are still uncertain. Furthermore, it is unclear if treating vascular risk factors will prevent or delay WMC progression. Current data on the management of WMC progression was derived mainly from post-hoc analyses and definitive treatment for treatment of WMC is still not available. Therefore, randomized studies dedicated in evaluating treatments for preventing WMC progression are urgently needed both in the Western and Asian countries.

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