The association of white matter hyperintensities with motoric cognitive risk syndrome

Takehiko Doi [*], Sho Nakakubo, Kota Tsutsumimoto, Satoshi Kurita, Yuto Kiuchi, Kazuhei Nishimoto, Hiroyuki Shimada

Department of Preventive Gerontology, Center for Gerontology and Social Science, Research Institute, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan

A B S T R A C T

Background: The motoric cognitive risk syndrome (MCR) was characterized by slow gait and subjective cognitive complaints. MCR was associated with brain structural changes. However, the association between white matter hyperintensities (WMH) and MCR was unclear and the aim of this study was to examine this association.
Material and methods: The study participants were 1227 older adults (mean age: 72.0 ± 6.0 yrs, women: 52.6%). We collected magnetic resonance imaging (MRI) data to assess WMH. To assess MCR, data on gait speed and subjective cognitive complaints were collected. Demographical and medical data was collected as covariates.
Results: Among participants, the proportion of MCR was 5.0% (n = 61) and severe WMH was 16.8% (n = 206). From logistic regression analysis, severe WMH associated with MCR even when adjusted for covariates (odds ratio 2.18 [95% confidential interval 1.15-4.16], p = 0.017). This association was observed in subgroups stratified by the participants' characteristics: higher age, not having fall history, not obesity, not being physical inactivity and not having depressive symptom.
Conclusions: Our findings revealed that vascular pathophysiological changes in the brain were associated with MCR. The association was pronounced by several factors. Further evaluation was required to clarify pathophysiology of MCR.

1. Introduction

The motoric cognitive risk syndrome (MCR) is characterized by a slow gait and cognitive complaints [1–3]. Prevalence of MCR increases with aging and was estimated at 9.7 % among older adults without dementia and disability in a worldwide study [2]. MCR increases the risk of dementia and cognitive impairment [2]. MCR is also related to prospective adverse health outcomes, such as disability and mortality [4,5]. Although slow gait and cognitive impairment was thought to have common pathophysiological processes [6], biological pathways of MCR remain to be clarified.

Emerging studies examined the neuro pathophysiology of MCR using neuroimaging data. As a potential pathway, MCR was related to the course of dementia, such as Alzheimer's disease (AD) and vascular dementia [1,2,5]. White matter hyperintensities (WMH) with lacunar infarcts and cerebral microbleeds are considered to be the primary pathology in subcortical ischemic vascular dementia [7,8]. WMH is

associated with both slow gait and subjective cognitive complaints. An epidemiological neuroimaging study revealed that brain structural changes of WMH and brain atrophy were associated with slower gait speed [9]. A study using pathway analysis showed that the association between WMH and slow gait was mediated by executive function [10]. As well as gait, subjective cognitive decline was associated with WMH even in late middle-aged adults [11]. However, the association between MCR and WMH was inconsistently presented in various studies. One study revealed that MCR was associated with greater volume of WMH and smaller gray matter volumes in the frontoparietal regions [12]. Conversely, another study showed that MCR was not related to the presence of WMH [13]. Furthermore, lacunar infarcts in the frontal lobe, not WMH, were found to be associated with MCR [14]. Although inconsistencies among studies may be partly due to differences in the characteristics of study participants, this is still unclear. The clarification of the inconsistency may contribute to the understanding of the pathophysiology of MCR and development of therapeutic targets for

* Corresponding author at: Department of Preventive Gerontology, Center for Gerontology and Social Science, Research Institute, National Center for Geriatrics and Gerontology, 7-430, Morioka, Obu, Aichi 474-8511, Japan.
E-mail address: take-d@ncgg.go.jp (T. Doi).

intervention related to prevention or slow progression to dementia. Our hypothesis was that the WMH burden was more prevalent among MCR participants. Thus, the aim of our study is to examine the association between WMH and MCR among community-dwelling elderly adults.

2. Material and methods

2.1. Participants

Study participants were from the National Center for Geriatrics and Gerontology-Study of Geriatric Syndromes (NCGG-SGS) [15], and were recruited by letter invitation. After examination, eligible participants were 1290 elderly adults (60 years or over) who underwent magnetic resonance imaging (MRI) examination. The exclusion criteria were as below: neurological disease (dementia, stroke and Parkinson's disease), independent of basic activity of daily living, severe cognitive impairment (Mini-Mental State Examination [MMSE] scored 17 or lower) and missing values of any variables used in this study. Finally, data for 1227 participants were analyzed. The ethics committee of the National Center for Geriatrics and Gerontology approved this study.

2.2. MCR definition

The original concept of MCR was previously described elsewhere [1–3]. MCR was defined as having subjective memory complaints and slow gait. The subjective memory complaints were judged from a question of the 15-item Geriatric Depression Scale (GDS):"Do you feel you have more problems with memory than most?" [16]. This question was used to define MCR in the other cohorts, parts of the worldwide MCR prevalence study [3]. Slow gait was defined as gait speed at normal pace that was 1.0 standard deviations or below age- and sex-appropriate mean values established in the NCGG-SGS database. Gait speed was assessed by the walking time measured over the middle 2.4-meter section. Participants were instructed to walk with their normal speed over a 6.4 m level course in a well-lit area and 2 m at either end of the course was not included in the measurement to account initial acceleration and terminal deceleration.

2.3. MRI

Detailed protocol to acquire MRI was described in the previous study [17]. MRI was performed on a 3-T system (TIM Trio, Siemens, Germany) and 3-D volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (1.1mm slice thickness). Then axial T2-weighted SE images (5mm slice thickness) and axial FLAIR images (5mm slice thickness) were obtained. WMH was assessed by medical specialists regarding periventricular hyperintensity and deep and subcortical white matter hyperintensity, and participants were classified into severe groups who matched severe in periventricular hyperintensity or white matter hyperintensity [18,19] Severe WMH was defined according to a score graded 3 or 4 in the modified Fazekas scale [18,19], equal to grade 3 score in the original Fazekas scale [18,19].

2.4. Other covariates

As demographic data, age, sex, body mass index, and educational history were recorded. Information on medical and related conditions was collected in the interview: history of disease (hypertension, diabetes mellitus, cardiovascular disease, osteoporosis), obesity (BMI ≥25), depressive symptom (GDS ≥6), history of fall and medication numbers. In addition, as lifestyle, data on physical inactivity (not having a regular physical activity) was collected.

2.5. Statistical analysis

Participants' characteristics according to MCR status was compared using an unpaired t-test for continuous variables or a chi-square test for categorical variables. A comparison between the characteristics of participants in the severe WMH and not severe WMH groups was also conducted. To examine the association between MCR and WMH, a logistic regression analysis was conducted. MCR status was set as objective variable and WMH was set as explanatory variable. Analyses were conducted in the crude and adjusted models with covariates (age, sex, obesity, educational history, hypertension, diabetes mellitus, hyperlipidemia, depressive symptom, fall, medication numbers, physical inactivity and MMSE). As it was unclear whether the association between MCR and WMH was different among specific characteristics, to explore the association between them among subgroups, logistic regression analyses were conducted in stratified sub groups, which were set by age (<75 yrs; ≥75 yrs), sex, fall, obesity, physical inactivity and depressive symptom. Odds ratio (OR) and 95% confidential intervals (CI) were calculated. All analyses were performed using SPSS statistics software, Version 26 (IBM Corporation, Chicago, IL). Finally, in all the analyses, statistical significance was set as p < 0.05.

3. Results

In total, data of 1227 participants were analyzed (mean age: 72.0 ± 6.0 yrs, women: 52.6%). Among participants, the prevalence of MCR was 5.0% (n = 61) and severe WMH was 16.8% (n = 206). Participants' characteristics of MCR was summarized and compared to no MCR (Table 1). Participants with MCR had higher proportion of fall, physical inactivity, and depressive symptoms. Prevalence of severe WMH was also higher among MCR participants (31.1%) compared to no MCR participants (16.0%). Compared to not severe WMH groups, severe WMH groups had higher age (severe WMH: 76.2 ± 6.0 yrs, not severe WMH: 71.1 ± 5.7 yrs, p < .001), higher proportion of hypertension (severe WMH: 61.2 %, not severe WMH: 43.8 %, p < .001), higher numbers of medication (severe WMH: 3.0 ± 2.6, not severe WMH: 2.5 ± 2.4, p = .010) and higher proportion of depressive symptom (severe WMH: 14.1 %, not severe WMH: 8.0 %, p = .006). The other characteristics were not different between severe WMH and not severe WMH groups.

Results of a logistic regression analysis are summarized in Table 2. WMH was found to be associated with MCR even in an adjusted model set with covariates (OR 2.18 [1.15-4.16]). Then, a logistic regression analysis, stratified by participants' characteristics, was conducted (Fig.1.). MCR was not associated with WMH (OR 1.68 [0.69-4.08])

Table 1

Characteristics in no MCR and MCR participants.

Variables	No MCR(n = 1166)	MCR(n = 61)	p
Age, yrs	71.9 (6.0)	73.0 (7.4)	.165
Sex (women), %	52.6	52.5	.986
Education, yrs	11.4 (2.5)	11.5 (2.8)	.758
Hypertension, %	46.8	44.3	.696
Diabetes, %	13.1	13.1	.999
Hyperlipidemia, %	36.4	36.1	.952
Fall, %	16.3	29.5	.007
Medication, number	2.5 (2.4)	2.9 (2.3)	.230
Obesity, %	26.8	32.8	.302
Physical inactivity, %	21.9	32.8	.046
Depressive symptom, %	8.0	29.5	< .001
Mini-Mental State Examination, score	27.1 (2.1)	26.7 (2.0)	.160
Severe WMH, %	16.0	31.1	.002

Values are Mean (SD) or proportion. MCR: motoric cognitive risk syndrome WMH: white matter lesions.

The comparison between groups was by t test or chi-square test.

Table 2
Results of logistic regression analysis to examine the association with motoric cognitive risk syndrome.

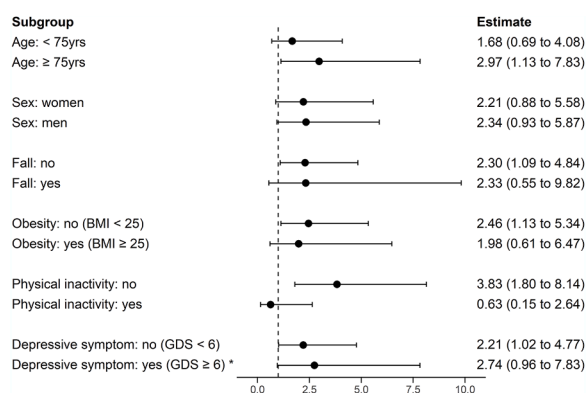| Variables	Odds ratio (95%CI)	p
WMH (ref: not severe)	2.18 (1.15-4.16)	.017
Age	0.99 (0.94-1.05)	.811
Sex (ref: women)	0.89 (0.51-1.57)	.700
Education	1.06 (0.95-1.19)	.269
Hypertension (ref: no)	0.74 (0.42-1.30)	.292
Diabetes (ref: no)	0.87 (0.39-1.97)	.744
Hyperlipidemia (ref: no)	0.93 (0.52-1.65)	.796
Medication	1.03 (0.93-1.15)	.557
Fall (ref: no)	1.86 (1.03-3.37)	.040
Obesity (ref: no)	1.37 (0.77-2.46)	.289
Physical inactivity (ref: no)	1.52 (0.84-2.73)	.165
Depressive symptom (ref: no)	4.19 (2.24-7.82)	< .001
Mini-Mental State Examination	0.95 (0.83-1.08)	.408

WMH: white matter lesions.

Fig. 1. Odds ratios of white matter lesions for MCR in subgroups.
Subgroups were stratified by age, sex, fall, obesity, physical inactivity, and depressive symptoms. Odds ratios were calculated by adjusting for other covariates than the variable used stratification. Odds ratios and 95% CIs were estimated and shown.
BMI: body mass index, GDS: 15-item Geriatric Depression Scale.
* After stratification, due to few events against the outcome among explanatory variables, crude odds ratio was shown.

among young older adults, while MCR was associated with WMH (OR 2.97 [1.13-7.83]) among old older adults. The association was not found among women (OR 2.21 [0.88-5.58]) and men (OR 2.34 [0.93-5.87]). MCR was associated with WMH among elderly adults with no fall (OR 2.30 [1.09-4.84]), no obesity (OR 2.46 [1.13-5.34]), and without physical inactivity (OR 3.83 [1.80-8.14]). In addition, MCR was associated with WMH among those without depressive symptom (OR 2.21 [1.02-4.77]).

4. Discussion

Our study revealed that WMH is associated with MCR in older adults. The proportion of WMH is higher among older adults with MCR compared to those without MCR. The association between MCR and WMH was not well documented and there is scope for argument. Gomez et al examined the difference between MCR and mild cognitive impairment (MCI) using neuroimaging data from Atherosclerosis Risk in Communities Study (ARCS) [12]. Both MCR and MCI associated with increased volume of WMH and MCR associated increase in WMH volume was more than double that associated with MCI [12]. On the contrary, other studies with similar purpose to examine the association between MCR and WMH had different results [13,14]. The differences among studies can be partly attributed to the differences in participants' characteristics, sample size, prevalence of MCR, and methodology of

WMH assessment. Our study and ARCS revealed the association between MCR and WMH. Both studies were community based and the prevalence of MCR was relatively low (our study: 5.0%, ARCS: 4.1%). On the contrary, other studies, which revealed no association, were clinic-based studies and the prevalence of MCR was high (20.7% [14], 27.3% [13]). The difference of prevalence may be linked with population characteristics (community vs clinic). Further studies are required to examine the effects of participants' characteristics on the association between MCR and WMH.

The pathophysiological hypothesis of MCR was thought to be related to a course of dementia. The association between WMH and MCR supported the course of vascular dementia. The ARCS examined the association of MCR with not only WMH but also amyloid deposition. Amyloid deposition related to AD was higher in MCI compared to no MCI, while MCR was not associated with amyloid deposition [12]. These results also supported that the association between WMH and MCR related to vascular dementia, not AD. However, pathology of vascular dementia associated with AD and discrimination between pathology of vascular dementia and AD was difficult. In fact, vascular markers represented cerebral small vessel disease caused to vascular dementia and amyloid positivity represented AD pathology were commonly overlapped among older adults. WMH associated with AD markers: brain atrophy [20], reduced cerebrospinal fluid levels of Aβ [21] and Aβ positivity in brain [22]. These pathophysiological changes had synergistic effects on cognitive decline [23]. Furthermore, the association between WMH and Aβ positivity was more pronounced in the earlier stages of dementia such as subjective cognitive decline participants compared to dementia [22]. Thus, MCR participants would have mixed pathology that make it difficult to clarify pathophysiological background of MCR. To investigate the pathophysiology, further studies using multimodal neuroimaging and other markers such as blood biomarkers were required.

The association between WMH and MCR was pronounced among subgroups; higher age, not having fall history, not obese, no physical inactivity and not having depressive symptoms. These characteristics among modifiable factors would help to develop intervention for MCR. A vascular care intervention included physical exercise and medication delayed progression of WMH among AD participants [24], while long-term effects of physical exercise on WMH was not clarified in older adults at risk of cognitive decline [25]. Although evident conclusion had not been established, the development to cope with WMH would contribute to intervention for MCR. Our study conducted relatively large samples with neuroimaging data as strong points, although study design was cross-sectional. In addition, our study also had limitations. The assessment of WMH was qualitative according to the Fazekas scale [18], while a quantitative assessment has also used among studies [10,26]. Quantitative assessments may enhance the understanding of findings in this study. Then, to clarify pathophysiology of MCR, not only vascular marker but biomarkers of other pathophysiological types of dementia, e. g., AD, need to be examined simultaneously. Furthermore, biomarkers other than neuroimaging studies such as blood biomarker or genetic information should also be used.

5. Conclusion

The presence of WMH is associated with MCR and this association was pronounced by several modifiable factors. The association supported that vascular pathophysiological changes associated with MCR. The study to clarify pathophysiology in MCR is further required.

Authors' contributions

TD substantially contributed to the conception of the methods used, participants recruitment, analysis and writing the manuscript. HS, KT and SN made substantial contributions to conception and design, participants recruitment, data acquisition and writing the manuscript. SK,

KN and YK were involved in the analysis, interpretation of data and writing the manuscript. TS made substantial contributions to conception and design and writing the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

None.

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