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Research Article

Brain Volume and White Matter Lesions Associated with Sarcopenia in Older Patients

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ABSTRACT

Background: Sarcopenia reduces activities of daily living in older individuals and has been attracting attention as a cause of needing nursing care. A relationship between white matter damage and sarcopenia has been suggested, but the details remain unclear. Here, we investigated the relationship between brain volume and sarcopenia in older patients who visited an outpatient memory clinic.

Methods: A total of 218 older patients (Mean age: 80.3 ± 6.6 years) who visited our outpatient memory clinic completed the Mini-Mental State Examination and Geriatric Depression Scale-15. Height, weight, grip strength, muscle strength (measured by bioimpedance), and walking speed were determined. Sarcopenia was assessed using the Asian Working Group on Sarcopenia diagnostic criteria. From magnetic resonance images of the head, Total Brain Volume (TV) and white matter lesion (deep and subcortical white matter hyperintensities and Periventricular Hyperintensities (PVH) volume were determined using Brain Anatomical Analysis using Diffeomorphic deformation voxel-based analysis software. The relationship between the presence of sarcopenia and brain volume was compared.

Results: Of the 218 patients, 111 had and 107 did not have sarcopenia; thus, approximately half of the outpatients with memory loss had sarcopenia. TV, but not white matter lesions, differed significantly between the non-sarcopenia (982 ± 103 ml) and sarcopenia (921 ± 83 ml) groups. After adjusting for the confounding factors of age, sex, body mass index, Mini-Mental State Examination score, and Geriatric Depression Scale-15 score, we found significant differences in TV, PVH, and sarcopenia between the groups.

Conclusion: In this study, we found an association of PVH and TV with sarcopenia. Some of the factors contributing to sarcopenia have been identified and may help in future interventions for sarcopenia.

Keywords: Cerebral ventricle; Leukoaraiosis; Magnetic Resonance Imaging (MRI); Sarcopenia

INTRODUCTION

With the ageing of society, the decline in mobility and function that accompanies ageing has become a major social issue as it is linked to a requirement for medical treatment and nursing care. In this context, the concept of "Sarcopenia" was proposed by Rosenberg in 1989 as a loss of skeletal muscle mass often associated with ageing [1].

Sarcopenia is defined as a physical syndrome characterized by loss of muscle mass, muscle strength, and physical performance. The impact of sarcopenia on older people is far-reaching; it increases immobility, disability, health care costs, and mortality [2]. The mechanism underlying sarcopenia remains to be determined. Previous studies have shown that the physical changes associated with ageing may be the main cause of sarcopenia [3,4]. Genetic predisposition, sex, estrogen, testosterone, and vitamin D levels, protein intake, physical activity, oxidative stress, and many other factors have been considered to play a role. In addition, sarcopenia may be associated with chronic diseases, psychosocial factors, cognitive impairment, and dementia.

Cerebral white matter lesions are primarily ischemic changes affecting the myelin sheath of the central nervous system. Cerebral white matter lesions show up as high-signal lesions in the periventricular white matter and deep and subcortical white matter on T2-weighted images, and as clear high-signal lesions on FLAIR images on head Magnetic Resonance Imaging (MRI). T1-weighted

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images show iso-intense or mildly hypo-intense signals, comparable to those of cerebral grey matter. Cerebral white matter lesions can be divided into Periventricular Hyperintensities (PVH) and Deep and Subcortical White Matter Hyperintensities (DSWMH).

In older people, white matter disorders have been implicated in disabilities, including dementia, depression, motor impairment, and urinary incontinence. In the LADIS study, the authors concluded that severe white matter lesions in older individuals lead to a strong and rapid decline in overall function [5]. Risk factors include diurnal variation in blood pressure, sleep disorders, coagulation abnormalities, oxidative stress, inflammation, and homocysteine.

Although sarcopenia and white matter disorders are related, little research has been conducted on their relationship. By clarifying the relationship between the two, we may be able to reduce the mortality rate, prevent the risk of falls and onset of disability, and ultimately prevent the deterioration of the quality of life of patients and their caregivers.

The aim of this study was to determine whether brain morphological imaging findings are associated with sarcopenia in patients with a chief complaint of forgetfulness. We conducted a comparative study on the relationship between brain volume and the presence of sarcopenia.

METHODOLOGY

Subjects

We recruited patients from the Outpatient Memory Clinic of Tokyo Medical University Hospital who underwent neuroimaging and evaluation with a neuropsychiatric battery for diagnosis and physical assessment. Two-hundred-and-eighteen consecutive older patients (mean age 80.3 ± 6.6 years) who visited the outpatient Memory Clinic of our hospital from October 2017 to July 2018 were included in the study.

Patients with obvious physical functional disabilities, such as inability to walk unaided, inability to undergo imaging and neuropsychological examinations, pacemaker insertion, and severe leg edema, were excluded from the study owing to difficulties or contraindications in performing examinations.

This study was approved by the Ethics Committee of Tokyo Medical University. (T2020-0338). Owing to the retrospective design, written informed consent was not required. However, information about this study was made available to the research subjects, and all subjects had the opportunity to opt-out.

Sarcopenia

Sarcopenia was diagnosed using the Asian Working Group 2014 criteria, [6] as detailed below:

Handgrip strength was measured twice on each side using a Smedley grip strength tester (T.K.K. 5401, Takei Scientific Instruments Co., Ltd., Niigata, Japan); the higher numerical value was used for analysis. The handgrip strength cut-off for sarcopenia diagnosis was <26 kg for males and <18 kg for females.

Walking speed was calculated by measuring the time elapsed when the participant walked at their normal comfortable gait between points separated by a distance of the middle 6 m with acceleration and deceleration portions of 2 m back and forth. For the diagnosis of sarcopenia, a cut-off walking speed of <0.8 m/s was used.

Muscle mass was measured using bioimpedance analysis with an InBody S10 (InBody Co. Ltd., Seoul, Korea) in the supine position. The cut-off for the Skeletal Muscle Mass Index (SMI) was <7.0 kg/m^2 for males and <5.7 kg/m^2 for females.

Patients were considered positive for sarcopenia if they showed a decrease in either walking speed or handgrip strength and a decrease in muscle mass measurement.

Cognitive function

The subject was evaluated by a clinical psychologist using the Mini-Mental State Examination (MMSE) and Geriatric Depression Scale (GDS)-15 as neuropsychological tests.

All subjects underwent general physical, psychiatric, and neurological examinations, extensive laboratory tests, MRI, and single-photon emission tomography to establish a clinical diagnosis. Then, patients were diagnosed by four dementia specialists (S.S., K.H., H.S., and T.S.). Alzheimer's disease (AD) and mild cognitive impairment due to AD were diagnosed according to the National Institute on Aging and Alzheimer's Association (NIA-AA) criteria [6]. Dementia with Lewy bodies (DLB) was diagnosed based on the Consortium on DLB International Workshop Criteria [7].

MRI and volumetric analysis

The subject was evaluated using brain MR images. We used a 1.5-Tesla scanner (Magnetom; Siemens Medical Systems, Erlangen, Germany) with the parameters for T1 gradient echo and FLAIR sequences. FLAIR sequences were taken for quantitative analysis of White Matter Hyperintensity (WMH) volumes, using a slice thickness of 4.0 mm and gap of 0.0 mm.

Brain Anatomical Analysis using Diffeomorphic deformation (h tt p://www.shiga-med.ac.jp/~hqbioph/BAAD/Welcome_to_BAAD.html), a voxel-based morphometry support software based on SPM12, was used to measure WMH, PVH, DSWMH, and Total Brain Volume (TV).

Statistical analysis

Statistical analyses were performed using Student's t-test, Pearson's test, and linear multiple regression analysis. A p-value of <0.05 was considered statistically significant. SPSS v26.0 (IBM Co., Armonk, NY, USA) was used for all statistical analyses.

RESULTS

Of the 218 patients, 111 had and 107 did not have sarcopenia. Table 1 shows the characteristics of the participants. There was no sex difference between the sarcopenia and non-sarcopenia groups, but age, height, weight, Body Mass Index (BMI), MMSE, GDS-15, walking speed, grip strength, and SMI were significantly lower in the sarcopenia group than in the non-sarcopenia group (Table 1).

The TV, WMH, PVH, and DSWMH of both groups are shown in Table 2. The TV was significantly higher in the non-sarcopenia group (982 ± 103 ml) than in the sarcopenia group (920 ± 83 ml), as shown by a t-test ($p<0.01$) (Table 2).

After adjusting for the confounding factors of age, sex, BMI, MMSE, and GDS-15, we found significant associations of TV ($R2=0.400$, $p=0.003$) and PVH ($R2=0.229$, $p=0.026$) with sarcopenia (Table 3).

Table 1: Characteristics of the subjects.

	Non-Sarcopenia	Sarcopenia	*p*
No. of patients	107	111	<0.01
Age (years)	78.5 ± 7.1	82.0 ± 5.5	0.144
Sex (men/women)	49/58	40/71	<0.01
Height (cm)	156.7 ± 7.8	151.1 ± 8.2	<0.01
Weight (Kg)	58.9 ± 10.6	48.5 ± 8.5	<0.01
Body Mass Index (BMI) (kg/m^2)	23.9 ± 3.4	21.2 ± 2.9	<0.01
Mini-Mental State Examination (MMSE)	23.2 ± 5.0	21.2 ± 4.3	<0.01
Geriatric Depression Scale-15 (GDS-15)	4.0 ± 3.1	5.7 ± 3.9	<0.01
Walking Speed (m/sec)	1.09 ± 0.22	0.94 ± 0.21	<0.01
Grip Strength (kg)	21.8 ± 6.5	15.5 ± 4.9	<0.01
Skeletal Muscle Mass Index (SMI) (kg/m^2)	6.64 ± 0.97	5.46 ± 0.83	<0.01
Alzheimer's Disease (AD)	47	76	
Dementia with Lewy Bodies (DLB)	2	9	
Mild Cognitive Impairment (MCI)	29	11	
normal	8	3	
other	21	12	

Note: (BMI) Body Mass Index; (MMSE) Mini-Mental State Examination; (GDS-15) Geriatric Depression Scale-15; (SMI), Skeletal Muscle Mass Index; (AD) Alzheimer's disease; (DLB) Dementia with Lewy Bodies; (MCI) Mild Cognitive Impairment.

Table 2: Brain imaging findings in the sarcopenia and non-sarcopenia groups.

	Non-Sarcopenia	Sarcopenia	*p*
Total Brain Volume (TV) (ml)	982 ± 103	921 ± 83	<0.01
White Matter Lesion (WM) (ml)	32.8 ± 22.0	35.2 ± 19.0	0.388
Deep and Subcortical White Matter Hyperintensity	19.4 ± 15.6	20.8 ± 12.6	0.478
Periventricular Hyperintensity (PVH) (ml)	8.78 ± 3.99	9.41 ± 4.06	0.249
WM/TV (%)	3.44 ± 2.44 (x 10-2)	3.88 ± 2.14 (x10-2)	0.158
DSWMH/TV (%)	2.04 ± 1.72 (x10-2)	2.30 ± 1.43 (x10-2)	0.239
PVH/TV (%)	0.92 ± 0.47 (x10-2)	1.04 ± 0.47 (x10-2)	0.067

Note: (TV) Total Brain Volume; (WMH) White Matter Hyperintensity; (DSWMH) Deep and Subcortical White Matter Hyperintensity; (PVH) Periventricular Hyperintensity.

Table 3: Factors associated with sarcopenia.

	B	SD	β	95% CI		*p*	Adj R^2
Total Brain Volume (TV)	-36.71	12.31	-0.191	-61	-12.43	0.003	0.4
White Matter (WM)	4.327	2.869	0.104	-1.331	9.986	0.133	0.299
Deep and Subcortical White Matter Hyperintensities (DSWMH)	2.53	2.001	0.088	-1.415	6.476	0.207	0.29
Periventricular Hyperintensities (PVH)	1.322	0.587	0.163	0.163	2.48	0.026	0.229
WM/TV	0.578	0.326	0.124	-0.065	1.221	0.078	0.278
DSWMH/TV	0.338	0.225	0.106	-0.106	0.781	0.135	0.274
PVH/TV	0.172	0.07	0.182	0.034	0.31	0.015	0.197
Adjustment variable: Age, sex, BMI, MMSE, GDS-15.							

Note: (TV) Total Brain Volume; (WM) White Matter; (DSWMH) Deep and Subcortical White Matter Hyperintensities; (PVH) Periventricular Hyperintensities.

DISCUSSION

In the present study, we found that approximately half of the patients who visited the outpatient Memory Clinic had sarcopenia. Multiple regression analysis showed significant associations of TV and PVH with sarcopenia.

The prevalence of sarcopenia varies from 1% to 77% among studies [8-10]; in large-scale studies, it is reported to be 6%-12%, [10-12] whereas in institutionalised patients, it is reported to be 14%-33% [9]. Thus, the prevalence of sarcopenia was relatively high in the subjects of this study.

The relationship between white matter damage and sarcopenia remains to be clarified, with some reports showing an association, whereas another study showed no association, between these conditions [13-15]. Our report was in agreement with the former studies. Differences between these studies may be owing to differences in the prevalence and influence of various causes of sarcopenia (e.g., vitamin deficiency, energy intake, and physical activity), white matter damage, and brain atrophy.

It has been reported that the periventricular area contains not only functionally important cholinergic neuronal circuits but also monoaminergic circuits [16,17]. This could explain some of the consequences of age-associated white matter lesions, such as depression, increased risk of falling, and executive tasks involving the frontal lobe.

In patients with PD and diabetes mellitus, an association between white matter damage in the frontal lobe and sarcopenia has been reported previously [18,19]. Moreover, the LADIS Study and Three-City Study both large cohort studies, found a strong association between the severity and volume of white matter changes and motor impairments, such as walking difficulties [20,21]. However, a study of patients with cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leukoencephalopathy has reported that other factors, such as ageing, have a stronger influence on walking motion than cerebrovascular disease [22].

Brain pathology may contribute to a change in body composition by disrupting the control of energy metabolism and food intake by the central nervous system [23]. This may be related to sarcopenia. Moreover, vitamin D deficiency has been pointed out as a cause of sarcopenia, and it has also been reported that white matter damage is caused by nutritional deficiencies, such as vitamin B1, B12, and D deficiencies, and inflammation [24,25]. However, in this study, we did not evaluate blood samples. Furthermore, there may be a relationship between brain volume and sarcopenia in agreement with the findings of the present report [26].

High levels of physical activity and total energy expenditure have been reported to be significant predictors of the progression of frontal lobe atrophy suggesting that a decline in motor function induces sarcopenia and is associated with brain atrophy. It is also possible that white matter damage is itself associated with brain atrophy [27]. In a systematic review, WMH and asymptomatic cerebral infarction were identified as causes of cerebral atrophy [28]. However, a previous report has shown that brain atrophy is not related to nutritional deficiencies of vitamins B1 and B12,24 which have been thought to cause white matter damage in other studies. Moreover, in another report, brain atrophy was observed in patients with metabolic disorders without microvascular disorders [29]. Therefore, it is possible that atrophy is not caused by white matter damage alone but by a combination of factors.

CONCLUSION

Sarcopenia is associated with brain volume and white matter damage, and particularly with periventricular lesions. Some of the factors contributing to sarcopenia have been identified and may help in future interventions for sarcopenia. A correlation between Total Brain Volume (TV), Periventricular Hyperintensities (PVH), and sarcopenia was found in this study. Recognizing some of the factors that contribute to sarcopenia may be helpful for developing future treatments for the condition.

LIMITATIONS

The first limitation of this study is that it was cross-sectional. Thus, it is unclear whether sarcopenia was caused by white matter damage or brain volume loss. There is a need to clarify this in longitudinal studies. Secondly, the subjects were outpatients with memory loss, and it is unclear whether brain atrophy and white matter lesions are reactions to memory loss without conducting a study on general subjects. In addition, we cannot deny the possibility that cognitive conditions, such as AD, may have affected brain atrophy. Thirdly, as the study was conducted within a single institution, multi-institutional and community-based studies will be necessary to verify the results.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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