DBD[*4] (28)	5.68±0.40	6.58±0.48	0.1480
GDS[*5] (15)	5.13±0.33	4.09±0.31	0.0241
VITL[*6] (10)	8.88±0.15	8.43±0.16	0.0395
ZBI[*7] (88)	21.91±1.54	29.20±1.92	0.0034

＊1；Barthel Index, ＊2；Instrumental ADL, ＊3；Mini Mental State Examination,
＊4；Dementia Behavior Disturbance Scale, ＊5；Geriatric Depression Scale,
＊6；Vitality Index, ＊7；Zarit Burden Interview

認知機能より手段的ADLの変化がより鋭敏な指標として有用な可能性があり、今後、認知症の日常診療で経過観察する上で、健康保険の適用が望まれる。

2　認知症に対するケア（非薬物療法）のエビデンス

（1）　問題行動全般

問題行動全般の改善に関しては、無作為対照試験で有意な成績は得られていないが、Rogers（1999）らは84人の認知症患者に対する25日間の観察研究で行動訓練によって有意な問題行動の減少を報告している。鳥羽らは、6カ月間のグループホームにおける観察研究で、DBDスコアの減少（p=0.14）を示すのを確認した（『効果的医療技術の確立推進研究　2003年度報告書』）。この方法の実施困難性を示すものとして、Matterson（1997）は、施設間比較研究で40%が脱落し、Doyleら（1997）は3週間の行動訓練で、反応者は29～43%であったと報告している。観察研究では看護補助者教育によって、問題行動エピソードの減少が報告されている（Montes、1989）。また、ドアの開放病棟では問題行動数が減少したという報告もある（Namazi、1992）。

（2）　興奮、攻撃性

興奮、攻撃性に関しては非薬物療法の有効性が多く示されている。

①　活動療法、運動療法

活動療法は無作為対照試験により30%以上、対照群より興奮を改善し（Rovner、1996）、運動療法は安眠療法に比べ有意に興奮を改善した（−20%対＋150%）（Alessi、1999）。

観察研究では、散歩によって有意に暴力行為（staff incident reports of aggression）が減少（−30%）している（Holmberg、1997）。

②　リクリエーション療法

8週間のリクリエーション療法で、興奮のエピソードが50%減少（Buettner、1996）し、73%のスタッフがやや有効と判定している（Aronstein、1996）。

〔ケア事例七九〕

969

③　ペット療法

28人に対する１時間のペット療法の観察研究で、定性的ではあるが興奮の改善が示されている（Churchill、1999)。

④　ビデオ、模擬再現療法

興奮に対して有効な成績はなく、無効の成績が示されている（Hall、1997、Cambergl、1999)。

⑤　音楽療法

18週間交差試験（Cross over traia）で65%の興奮の改善（Gerdner、2000）が見られ、観察研究でも、63%の興奮症状の改善が報告されている（Goddaer、1994、Brotons、1996、Clark、1998、Thomas、1997)。音楽療法のタイミング（食事中Goddaer、入浴中Clark、Thomas)、録音か生演奏（Brotons）で特に差はない。また好きな音楽を選択してもらうと効果が47～80%と高いが（Gerdner、1993）十分な統計解析の観察研究もない。

⑥　白色雑音療法

不要な刺激音を遮断するための、広範囲な周波数帯に対する不規則雑音による効果を調べた観察研究で、13人中９人が反応している（Burgio、1996)。

⑦　マッサージ

ハンドマッサージによって有意に（42%）改善したという報告（Kim、1999）があるが多くは無効（Snyder、1995、1996、Brooker、1997）である。

⑧　高輝度光線療法

２～４週の治療で有意に興奮が改善している（Lovell、1995、Thorpe、2000)。

⑨　アロマセラピー

無効（Brooker、1997）の報告のみである。

⑩　環境改善

露天風呂や自然浴で興奮が有意に改善した（Whall、1997)、また特別ケア病棟によって53%改善したという報告がある（Cleary、1988)。

⑪　教育

看護補助者教育によっても20%の興奮が有意に改善した（McCallion、1999)。観察研究では、２カ月の抑制廃止プログラムによって、抑制減少と興奮症状改善（agitation scores）がみられ（Werner、1994)、患者との交わり増加（刺激療法）によって興奮が85%減少した成績もある（Hussian、1988)。

〔ケア事例七九〕

970

暴力行為に関しては無効であるという報告が多い（McCallion、1999）。

（3） 徘徊

有効な報告はほとんどない。

個別対応強化によって50～80%徘徊が減少したという報告があるが、対象症例数が少ない（4人）。環境改善では外出欲求には無効であったという報告（Cohen-Mansfield、1998）、30人に対する15週間の音楽療法は徘徊に無効（Groene、1993）という報告がある。スタッフ教育に関する報告はない。

（4） 支離滅裂言語

個別社会適応訓練（Cohen-Mansfield、1997）や、ビデオによる模擬再現（Woods、1995）が支離滅裂言語減少に有効であるとされている。

（5） 無気力、意欲の低下

① 行動療法

対照群をおいた前向き観察研究で、中等度以上の認知症で、排尿誘導による意欲の向上が認められている（Toba、2002）。認知症症例でデイケアの利用者は在宅単独に比べ、意欲の保持が有意に優れている[5]。

② 音楽療法

音楽療法など感覚刺激療法は、無気力など陰性症状に対し有効な成績は報告されていない。

③ スタッフ教育

看護補助者教育で、陰性症状に対して無効であった（McCallion、1999）。

〔ケア事例七九〕

3 認知症短期集中リハビリテーション

（1） 認知症短期集中リハビリテーション導入までの経緯

認知症リハビリテーションは今に始まったものではなく、全国老人保健施設協会の学術委員会を中心として「認知症高齢者に対する行動療法は認知機能を高める」と確信をもって10年以上前からすでに行っていた取組みである。2006（平成18）年の介護報酬改定で老人保健施設に認知症短期集中リハビリテーション実施加算（理学療法士、作業療法士、または言語聴覚士が1回20分以上の個人療法、1回60点、週3回までで、入所から3カ月以内まで請求できる）が軽症の認知症（MMSE、HDSRが概ね15点以上）に認められ、リハビリ期間が規定されたために、効果の検証研究が容易になった。

971

平成18年度はまず、認知症短期集中リハビリテーションは本当に効果があるかという調査を行った。ここでは、特に情緒的なものを含めてよい結果が出たが、残念ながらＨＤＳＲで測定した認知機能についてはやや改善があったものの、有意差は得られなかった。同時に周辺症状にも改善傾向があったものの、これも有意差は認められなかった。これは解析した対象者が49人、対照群（コントロール）が36人と少なかったことによるものと考えられる。

平成19年度で解析対象者を266人（対象者が203人、対照群が63人）と３倍に増やして、本当に効果がないのかを検証した。この結果、「意欲」についてはっきり効果が出たばかりでなく、中核症状である認知機能に対しても有意な改善が認められ、薬物療法に匹敵する効果が得られた。さらに、症状周辺症状に対しては、非定形精神病薬や漢方薬などの効果は知られているが、ほぼそれに匹敵する非常に強い改善効果が認められた（表３）。しかも、頻度の高い周辺症状のうちの８割くらいに有効であるというインパクトのある成績である[6]。

表３　認知症短期集中リハビリテーション前後の周辺症状の変化（有意差）

	対照群	認知リハ群
物をなくす	ns	p＝0.003
昼間寝てばかり	ns	p＝0.0023
介護拒否	NA	p＝0.0072
何度も同じ話し	ns	p＝0.022
暴言	NA	p＝0.0097
言いがかり	NA	p＝0.0006
場違いな服装	NA	p＝0.0023
ため込み	ns	ns
無関心	ns	p＝0.0072
昼夜逆転	ns	p＝0.0593
常同行動	p＝0.08	ns
散らかし	ns	ns
徘徊	ns	ns

ns：有意差なし、NA：該当なし

（２）　認知症短期集中リハビリテーションの適応拡大

平成19年度の成績のサブ解析において、中等度認知症に対しても効果が認められた

972

ことから、平成21年度から、中等度認知症（ＭＭＳＥ、ＨＤＳＲが５点以上）にも適応拡大され、さらに、老人保健施設入所者だけでなく、デイケア、療養型医療施設へも適応が拡大された。

デイケアなど、在宅型介護施設におけるサービスにも適応が拡大されたのは画期的である。ただしデイケアにおいては週２回までの制限がある。

また、１回60点であった介護報酬も１回240点に引き上げられ、ようやく人件費とのバランスを考えられるレベルになった。

（３） 認知症短期集中リハビリテーションの具体的実施方法と長期効果の検証

今回の解析対象では、回想法、現実見当識訓練、記憶訓練療法、記憶学習療法、音楽療法、運動療法、作業療法、言語コミュニケーション療法が単独または、組み合わせで実施された。主要な方法は、実施例をＤＶＤビデオで作成して、研修会受講者すべてに配付した。

表４ 認知症短期集中リハビリテーションのまとめ[7]

認知機能短期集中リハビリテーションの前後で対照群を設け、効果を比較した。

1．開始時の両群間に、差はなかった。

2．臨床的認知症重症度（ＮＭ）はリハビリ群で有意に（$p<0.0001$）改善した。
下位項目では、記銘力、関心・意欲・見当識が改善した。

3．認知機能（ＨＤＳＲ）はリハビリ群で有意に（$p=0.001$）改善した。

4．周辺症状（ＤＢＤ）はリハビリ群で有意に（$p=0.0064$）改善した。
下位項目では、出現頻度の高い「同じ話を繰り返す」「物をなくす」「無関心」「昼間寝てばかり」といった症状と、「暴言」などの陽性症状にも改善がみられた。常同行動、徘徊は不変であった。

5．意欲（Vitality Index）はリハビリ群で有意に改善した（$p=0.0004$）。

6．ＡＤＬはリハビリ群で有意に（$p=0.0009$）改善した。

7．活動はリハビリ群で有意に（$p=0.0207$）改善した。

8．抑鬱は両群とも不変であった。

認知症短期集中リハビリテーション終了後の維持ができるかどうかを集団療法を行った群と行わなかった群で比較すると、３カ月後の維持は集団療法で引き継いだ群が優れていたが、３カ月以降は個別療法の効果には及ばなかった。認知症短期集中リハビリテーションをどの程度の間隔で行えば効果が持続するかは、今後の検討課題である。また今後、デイケアでの本リハビリテーションの普及によって、在宅期間の延

〔ケア事例七九〕

973

長、介護負担の軽減などの直接効果の検証がなされるべきと考えられる。

（鳥羽　研二）

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〔ケア事例七九〕

974（～1004）

Geriatrics Gerontology INTERNATIONAL Medline Indexed

Validation of a simple and reliable visual rating scale of white matter hyperintensity comparable with computer-based volumetric analysis

Dear Editor,

White matter hyperintensity (WMH), which is detected as hyperintense signals on T2-weighted images of brain magnetic resonance imaging (MRI), is a common finding in the aging brain. WMH is associated with various geriatric conditions,[1] and regional WMH has specific effects on cognitive impairment, gait and lower urinary tract symptoms.[2–4] To measure WMH, visual rating and volumetric analysis using a computer program have been used. Volumetric measurement of WMH is more sensitive and accurate than visual rating, although the former requires specific laboratory instruments to analyze WMH. Visual rating is time-consuming, and the results often vary among raters. Because physicians have to evaluate longitudinal changes in WMH in patients during a limited consultation time, an easier and more reliable method of visual assessment is required. WMH can be divided into two parts; periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH). Previous studies suggested that PVH and DWMH largely share common pathological characteristics.[5] Automatic segmentation of WMH mostly recognized DWMH in continuity with PVH, and therefore the volume of DWMH is much smaller.[4] Thus, we hypothesized that semiquantitative analysis of PVH could predict total WMH volume. The purpose of the present study was to validate the accuracy of our newly developed visual rating scale for global and regional analysis of WMH. Comparison with conventional methods was carried out by referencing computational volumetric analysis.

The participants were 460 patients (318 women) aged 65–85 years; 69 diagnosed with amnestic mild cognitive impairment and 391 with Alzheimer's disease. Clinical data were obtained from the Biobank of National Center for Geriatrics and Gerontology, which collects clinical data for research. All participants underwent brain MRI. The protocol of brain MRI is described elsewhere.[4] WMH on brain MRI was evaluated by both visual and computational volumetric analysis. For visual rating, we used the Fazekas scale,[6] a scale used in the Rotterdam scan study (Rotterdam scale)[7] and our new scale, which is a modified version of the Rotterdam scale (modified Rotterdam scale).[2,3] The Fazekas scale is a simple classification of PVH (grade 0–3), whereas the Rotterdam scale and modified Rotterdam scale are semiquantitative methods. PVH in the Rotterdam scale is visually rated into four grades at frontal caps, bands and occipital caps. The total score was calculated by adding the three region-specific scores.[7] In contrast, the modified Rotterdam scale rates PVH as five grades with definitive ranges of WMH dimension from the edge of ventricles at the identical regions of PVH, but separately in the left and right hemisphere. The degree of PVH was calculated by adding up the scores of six separate regions.[2,3] Details of each scale are described in the supplemental information. Automatic segmentation of WMH was carried out using Software for Neuro-Image Processing in Experimental Research (SNIPER).[8] SNIPER was used to determine the intracranial volume (IC) and WMH volume in each brain lobe (frontal, parietal, temporal and occipital lobes). WMH volume divided by IC (WMH/IC), to adjust for brain size, was used as an index of WMH. All analyses were carried out using the Japanese version of SPSS for Windows version 22.0 (IBM Corporation, Armonk, NY, USA). Pearson's correlation analysis was used to analyze the association between visual scales and WMH/IC.

Figure 1a shows the distribution of the three rating scales and WMH/IC with box and whisker plots. The three visual rating scales strongly correlated with SNIPER value (WMH/IC; %). The correlation coefficient was 0.820 for all three scales; however, deviation increased with WMH progression, although it was smaller with the modified Rotterdam scale than with the other scales. As the correlation of visual rating and WMH/IC did not seem to be linear, the association of WMH with cubed values of the visual rating scales was examined (Fig. 1b). With cubed values, we were able to find a clear linear association between visual ratings and WMH/IC, with a correlation coefficient of 0.862 and 0.879 for the Rotterdam scale and modified Rotterdam scale, respectively. Finally, the correlation between the visual rating of PVH at frontal caps and frontal WMH/IC was tested. As a result, the cubed score of frontal caps was strongly correlated with WMH/IC in the frontal lobe ($r = 0.827$; Fig. 1c).

The present study found that cubed values of our modified Rotterdam scale showed a good correlation with WMH/IC, with smaller deviation. In addition, the visual rating of PVH at frontal caps correlated with frontal WMH/IC. Several strengths and limitations of the modified Rotterdam scale should be mentioned. First, it requires PVH evaluation only, which is simple and not time-consuming. Therefore, it is easily

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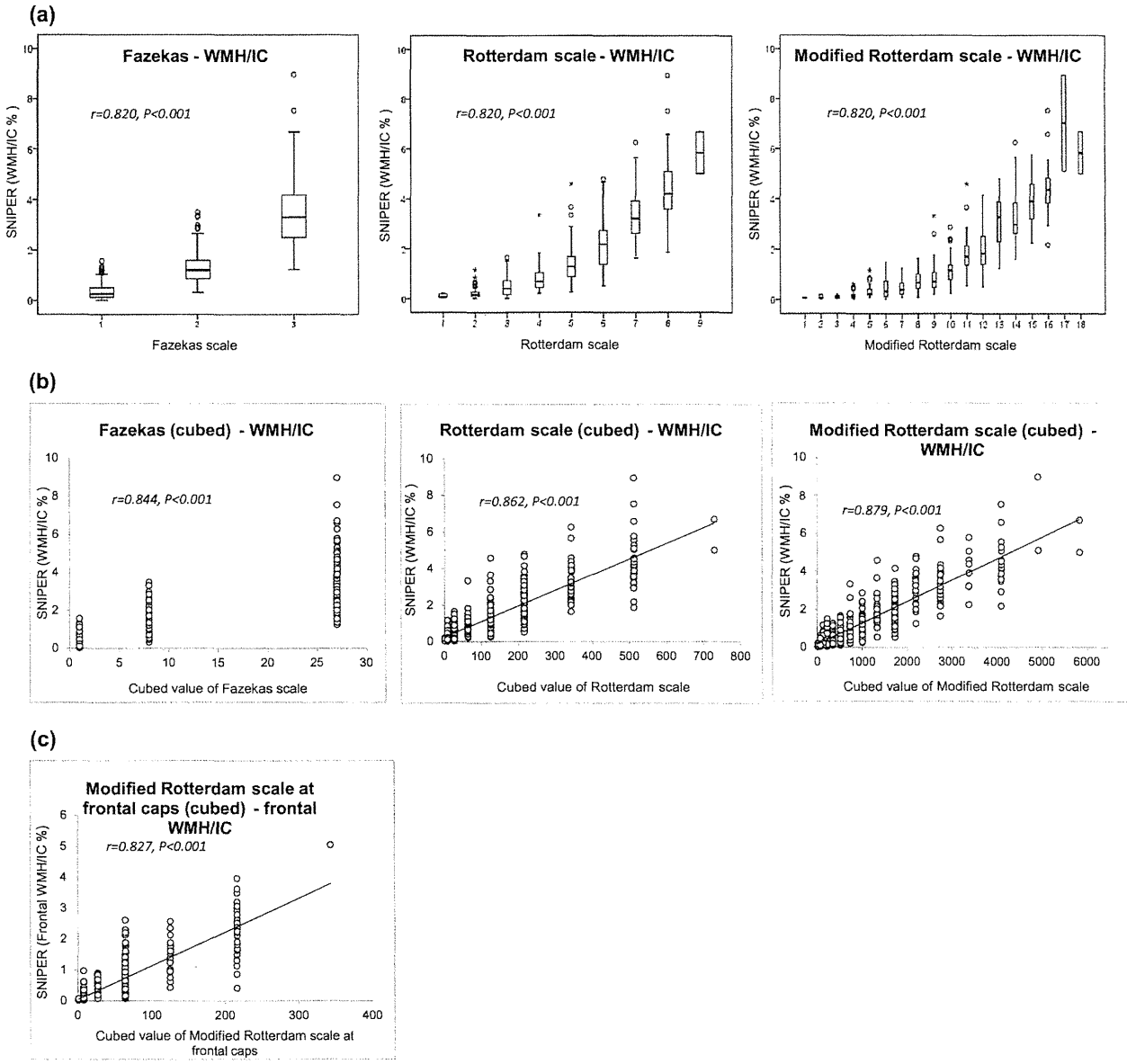

Figure 1 Associations of three visual rating scales with computer-based volumetric analysis. (a) The distribution of the three rating scales and white matter hyperintensity (WMH)/intracranial volume (IC) with box and whisker plots. The *x*-axes are original values of the three visual rating scales. The visual rating scales were strongly correlated with WMH/IC, but the deviation increased with WMH progression. We transformed each WMH/IC (%) value to a z-score for standardization. As a reference, we used the Fazekas scale (grade 1–3), and the Rotterdam scale and modified Rotterdam scale were classified into the three corresponding grades. Then, we compared the difference of deviation of z-score in each Fazekas grade. In the highest Fazekas group (grade 3), a standard deviation of standardized WMH/IC (%) was 0.95. Standard deviation of the Rotterdam scale and modified Rotterdam scale was 0.78 and 0.73, respectively. We analyzed significant difference using the *F*-test, which showed that modified the Rotterdam scale had the smallest deviation ($P = 0.001$). (b) The association between cubed values of the three visual scales and Software for Neuro-Image Processing in Experimental Research (SNIPER; WMH/IC). The *x*-axes denote cubed values of the three visual rating scales. A linear association of WMH/IC with the Rotterdam scale and modified Rotterdam scale is observed. (c) The correlation between cubed values of the modified Rotterdam scale at frontal caps and SNIPER (frontal WMH/IC). The cubed score of PVH at frontal caps was strongly correlated with WMH/IC in the frontal lobe.

applicable in clinical practice. Second, the cubed PVH scale was strongly correlated with total and regional WMH/IC in a linear manner, which enables us to follow longitudinal changes in WMH. In contrast, our scale might not be useful in patients with extensive DWMH lesions. In this connection, automatic segmentation of WMH mostly recognized DWMH in continuity with PVH. Visual differentiation of PVH and DWMH in each MRI slice might be difficult unless 3-D continuity of WMH is apparent. It is suggested that classification of

PVH and DWMH is arbitrary, and causal factors for PVH and DWMH are merely a reflection of total WMH volume.[5] Recently, specific impacts of frontal WMH have been reported.[3,4] Not only the overall presence of WMH in the brain, but also the size and local distribution of WMH might directly cause several clinical symptoms. The modified Rotterdam scale showed the strongest association with frontal WMH/IC, which implies it is a more useful index than the other visual rating scales. Because WMH in bands and occipital caps are mixed in the temporal, parietal and occipital lobes, it was difficult to distinguish an association with regional WMH. WMH increases with age, and is involved in the development of several geriatric conditions.[4] The cubed score of PVH using the modified Rotterdam scale might facilitate evaluation of WMH progression in daily clinical practice.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site: http://onlinelibrary.wiley.com/doi/10.1111/ggi.12664/suppinfo

Appendix S1 Details of the three visual rating scales.

Geriatrics Gerontology INTERNATIONAL Medline Indexed

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LETTERS TO THE EDITOR
RESEARCH STUDIES

Left ventricular diastolic dysfunction is directly associated with cerebral white matter lesions in elderly patients

Dear Editor,

Cerebral white matter lesions (WML) have been established to increase with age, and are associated with heightened risks of stroke,[1] cognitive decline[2] and depressive disorder.[3] We previously reported that the severity of left ventricular (LV) diastolic dysfunction is associated with the volume of cerebral WML.[4] However, the analysis could not be carried out by removing the effect of the common or specific risk factors that are known to be involved in the progression of LV diastolic dysfunction and/or cerebral WML, such as age, hypertension, diabetes mellitus, hyperlipidemia, smoking, obesity and so on. Consequently, whether LV diastolic dysfunction is directly associated with cerebral WML remained unclear. Therefore, to clarify this, we carried out a cross-sectional study by conducting further in-depth examination of these risk factors and also by increasing the study population.

The study registration period was from April 2010 to October 2013. Participants comprised 133 outpatients between aged 65 and 75 years with normal LV contraction (ejection fraction >50%) and no signs or history of symptomatic heart failure, ischemic heart diseases, atrial fibrillation, stroke, or cognitive dysfunction. We also excluded those patients with ≥50% stenosis in the carotid arteries on ultrasonography with 2-D and Doppler analysis. The volume of cerebral WML was quantified on brain magnetic resonance imaging using a fully automatic segmentation program[5] developed in the Department of Radiology at Leiden University Medical Center (Leiden, the Netherlands), and early diastolic mitral inflow and early diastolic mitral annular tissue velocity (E/E') ratio, a parameter that indicates the severity of LV diastolic dysfunction, was measured by tissue Doppler echocardiography.[6] A total of 20 4-h systolic and diastolic blood pressure were obtained by ambulatory blood pressure monitoring. In addition, LV ejection fraction, body mass index, estimated glomerular filtration rate, carotid intimal media thickness, and levels of plasma B-type natriuretic peptide, hemoglobin A1c and low density lipoprotein cholesterol were also determined. Values are shown as mean ± standard deviation unless otherwise stated. Data were analyzed using SPSS version 17.0 software (SPSS, Chicago, IL, USA). The study protocol was approved by the ethics/conflict of interest committee at the National Center for Geriatrics and Gerontology. Written informed consent was obtained from all participants before participation.

Table A shows the patient characteristics. The results of linear regression analysis between cerebral WML volume and estimated factors are shown in Table B. These results showed that four factors (age, systolic blood pressure, plasma B-type natriuretic peptide and E/E') had a significant correlation ($P < 0.05$) with cerebral WML volume. Based on the results, multivariate analysis was carried out in order to clarify the principal factors involved in the increase of the cerebral WML. As a result, E/E' and age had been shown to be significantly correlated with cerebral WML volume ($P < 0.01$), with the correlation greater for E/E' ($P = 0.003$) than for age ($P = 0.03$; Table C).

The present study clarified the direct association between the severity of LV diastolic dysfunction and the volume of WML in elderly patients even after removing the effects of risk factors that were involved in the progression of LV diastolic dysfunction and/or cerebral WML. The results can be interpreted in two ways. The first interpretation is that a common, but unknown, factor exacerbates both cerebral WML and LV diastolic dysfunction, with this complicating factor being profoundly involved in the onset and progression of both diseases. The second interpretation involves chronic low cardiac output and chronic cerebral ischemia. Some reports in recent years have suggested that cerebral perfusion is impaired in patients with chronic low cardiac output.[7–9] Thus, considering that cardiac output decreases with the decrease in blood flow into the LV from the left atrium as a result of the progression in LV diastolic dysfunction, and also considering that a chronic decrease in cerebral blood flow is thought to be the primary mechanism underlying cerebral WML formation, the present results can also be interpreted as suggesting that decreased cardiac output elicits chronic cerebral ischemia.[10] Further investigation is necessary to clarify these points.

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Table A Patients characteristics

	Total	Mean ± SD
n	133	
Men (*n*)	64	
Smoking episode (*n*)	42	
Age (years)		69.7 ± 3.2
BMI (kg/m^2)		23.6 ± 3.5
Echocardiographic data		
EF (%)		65.9 ± 4.8
E/E'		12.0 ± 3.7
SBP (mmHg)		129.0 ± 11.5
DBP (mmHg)		75.6 ± 7.2
IMT (mm)		0.7 ± 0.1
HbA1c (%)		5.9 ± 0.6
LDL-C (mg/dL)		109.6 ± 23.5
eGFR (mL/min/1.73 m^2)		69.0 ± 12.5
BNP (pg/mL)		27.0 ± 28.0
WML (mL)		6.5 ± 7.2
PVL (mL)		5.7 ± 6.3
DWML (mL)		0.8 ± 1.4

Table B Results of linear regression analysis

	β-coefficient	*r*-value	*p*-value
Sex	0.350	0.240	0.781
Smoking episode	2.368	0.144	0.098
Age	0.579	0.258	0.003*
BMI (kg/m^2)	0.038	0.017	0.834
Echocardiographic data			
EF (%)	0.023	0.014	0.890
E/E'	0.793	0.381	<0.001*
SBP (mmHg)	0.171	0.272	0.001*
DBP (mmHg)	0.083	0.082	0.345
IMT (mm)	8.995	0.141	0.104
HbA1c (%)	1.628	0.131	0.133
LDL-C (mg/dL)	0.020	0.063	0.469
eGFR (mL/min/1.73 m^2)	-0.007	0.010	0.897
BNP (pg/mL)	0.065	0.253	0.003*

Table C Results of multivariate analysis

	p-value
Age	0.030*
E/E'	0.003*
SBP (mmHg)	0.089
BNP (pg/mL)	0.611

*$p < 0.05$. BMI, body mass index; EF, ejection fraction; E/E', ratio of early diastolic mitral inflow (E) to early diastolic mitral annular tissue velocity (E'); SBP, systolic blood pressure; DBP, diastolic blood pressure; IMT, carotid intimal media thickness; HbA1c, hemoglobin A1c; LDL-C, low density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; BNP, plasma B-type natriuretic peptide; WML, white matter lesions; PVL, periventricular white matter lesions; DWML, deep subcortical white matter lesions.

Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Impact of night-time blood pressure on cerebral white matter hyperintensity in elderly hypertensive patients

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Aim: Cerebral white matter hyperintensity (WMH) is highly prevalent in the elderly population, and increases the risk of dementia and stroke. We investigated the relationship between ambulatory blood pressure monitoring levels and quantitatively measured WMH volumes among elderly hypertensive patients with well-controlled blood pressure (BP) to re-evaluated effective hypertension management methods to prevent the progression of WMH.

Methods: Participants comprised 84 hypertensive patients aged between 65 and 75 years without symptomatic heart failure, ischemic heart disease, atrial fibrillation, stroke or cognitive dysfunction.

Results: Linear regression analysis showed that office BP was not associated with WMH volume increases. Raised night-time systolic BP ($P = 0.013$) were associated with greater WMH volumes during ambulatory blood pressure monitoring. To clarify the effect of asleep systolic BP on WML volume, we then classified patients into two systolic BP groups as follows: <125 mmHg ($n = 47$) and ≥125 mmHg ($n = 37$). Baseline characteristics were almost similar in both groups, except the dipper type of circadian BP variation was significantly common in the group with night-time systolic BP <125 mmHg. However, WMH volume was greater in the group with night-time systolic BP ≥125 mmHg than that in the <125 mmHg group (9.0 ± 8.4 mL *vs* 4.1 ± 4.3 mL, $P = 0.015$).

Conclusion: Higher night-time systolic BP levels were observed to contribute greater WMH volumes in elderly hypertensive patients. To prevent the progression of WMH, controlling BP on the basis of ambulatory blood pressure monitoring is important. **Geriatr Gerontol Int 2015; 15 (Suppl. 1): 59–65.**

Keywords: ambulatory blood pressure monitoring, cerebral white matter hyperintensity, circadian blood pressure variation, night-time blood pressure, office blood pressure.

Introduction

Cerebral white matter hyperintensity (WMH) on brain magnetic resonance imaging (MRI) is highly prevalent in the elderly population, and increases the risk of stroke,[1,2] and cognitive[3,4] and mobility impairment.[5–7] Although believed to be vascular in origin, the exact etiology of WMH remains unknown.

Populations with hypertension, diabetes, metabolic syndrome, chronic kidney disease, high serum total homocysteine levels, a history of smoking and vitamin D deficiency have been reported as high-risk groups for WMH developing and becoming severe.[8–12] Furthermore, our group has clarified that left ventricular diastolic dysfunction is associated with WMH in elderly patients without ischemic heart disease and stroke.[13] Of the aforementioned risk factors, hypertension is considered the greatest risk factor for the progression of WMH. It has been reported that in patients with hypertension, the WMH grade is significantly worse in non-treated groups compared with that in the treated groups.[14] Other reports have shown that the WMH grade has a positive correlation with systolic and diastolic blood pressure (BP) of the arm,[15] as well as central arterial systolic BP,[16] and that WMH strongly correlates with a high 24-h mean BP, particularly high nocturnal BP and non-dipper type hypertension.[17,18] Therefore, it is considered that early aggressive BP management is important to prevent the progression of WMH. Studies carried out to date have primarily targeted patients aged in their 50s to 60s, and there is still limited information

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on the older population. Furthermore, the severity of WMH has been determined using grade classification on the basis of visual observation.

A method of quantifying WMH volume by processing images obtained by MRI, which enables quantitative evaluation, has recently been established. Geriatric syndromes, such as cognitive impairment, can develop at approximately 75–80 years-of-age, and from a prophylactic perspective, studies should be carried out that focus on elderly individuals before this stage. Therefore, we quantitatively measured WMH volume in elderly patients with hypertension, examined the relationship between clinical data, such as blood pressure, and re-evaluated effective management methods for hypertension to prevent the progression of WMH.

Methods

Participants

Hypertensive outpatients aged 65–75 years treated with regular antihypertensive agents by the Department of Cardiology at the National Center for Geriatrics and Gerontology, Obu, Japan, were recruited. Among these, patients with symptomatic heart failure, ischemic heart disease, valvular heart disease, atrial fibrillation, stroke, neurodegenerative disorder or clinically diagnosed dementia were excluded.

Age, sex, height, bodyweight and office BP were recorded. Thereafter, biochemical blood tests and other tests including 24-h ambulatory blood pressure monitoring (ABPM), carotid duplex ultrasound for measurement of intima media thickness, brachial-ankle pulse wave velocity and ankle brachial index were examined, and the relationships with WMH volume were analyzed.

The study protocol was approved by the ethics/conflict of interest committee at the National Center for Geriatrics and Gerontology. Written informed consent was obtained from all participants before participation.

Neuroimaging studies

WMH volume was measured according to the following procedure using MRI.

A standard series of axial T1-weighted (repetition time [TR], 485 ms; echo time [TE], 11 ms; matrix, 256 × 256), T2-weighted (TR, 3800 ms; TE, 93 ms; matrix, 352 × 352) and fluid-attenuated inversion recovery (FLAIR; TR, 8000 ms; TE, 101 ms; inversion time, 2500 ms; matrix, 256 × 256) MRI sequences were carried out using a 1.5-T MR system (Siemens Avanto, Muenchen, Germany). Scans were carried out parallel with the anterior commissure-posterior commissure line, with 6-mm thick slices and an interslice gap of 1.2 mm. MRI data were processed to measure total volumes of the intracranial space, parenchyma, ventricles and WMH using a fully automatic segmentation program (Software for Neuro-Image Processing in Experimental Research) developed in the Department of Radiology at Leiden University Medical Center (Leiden, the Netherlands). WMH were defined as hyperintense lesions on both FLAIR images and T2-weighted images. WMH connected to the lateral ventricles were labeled as periventricular hyperintensity (PVH). WMH not connected to the lateral ventricles were labeled as deep WMH. Detailed procedures for MRI post-processing using Software for Neuro-Image Processing in Experimental Research have been described elsewhere.[19]

ABPM

A validated ambulatory recorder (TM-2431; A&D, Tokyo, Japan) and cuff on the non-dominant arm were used to carry out ABPM. BP was measured at 30-min intervals for day (06.00–21.59 hours) and 1-h intervals for night (22.00–05.59 night). Night-time was defined as the period in bed given in the sleep diary entries. BP measured <10 times during daytime or <5 times during night-time, as the result of errors, were excluded from analysis. BP and heart rate, including 24-h mean value, mean daytime value and mean night-time value, were calculated from recorded measurements and used in data analyses. Non-dipper was defined as <10% fall in night-time systolic BP relative to daytime systolic BP.

Statistical analysis

Values are shown as mean ± standard deviation unless otherwise stated. The correlation between WMH and each clinical item was found by linear regression analysis. Differences among the two groups were analyzed using the χ^2-test or Fisher's exact test, Student's t-test and Welch's test. Values of $P < 0.05$ were considered significant. Data were analyzed using SPSS version 17.0 software (SPSS, Chicago, IL, USA).

Results

Patient characteristics

A total of 84 patients with hypertension were enrolled in the present cross-sectional study (mean age 69.7 ± 3.6 years), including 40 male patients (47.6%; Table 1). The mean body mass index was 23.4 ± 3.4, with no severe obesity or leanness observed. Antihypertensive therapy including calcium antagonists, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, diuretics, and beta-blockers were given to 46 patients (54.8%), 48 patients (57.1%), four patients (4.8%), 10 patients (11.9%) and 21 patients (25.0%), respectively. The number of antihypertensive agents administered included monotherapy in 33 patients (39.2%) and dual

Table 1 Patients' characteristics

Parameters	$n = 84$
Age (years)	69.7 ± 3.6
Male (%)	40 (47.6%)
Height (cm)	157.8 ± 8.3
Bodyweight (kg)	58.8 ± 10.4
BMI (kg/m^2)	23.4 ± 3.4
Diabetes	14 (16.7%)
Dyslipidemia	31 (36.9%)
Antihypertensive therapy	
Ca-antagonist	51 (60.7%)
ARB	54 (64.3%)
ACE-I	4 (4.8%)
Diuretics	13(15.5%)
βblocker	22 (26.1%)
No. of medications (%)	
1	36 (42.9%)
2	37 (44.0%)
3	10 (11.9%)
4	1 (1.2%)
IMT (mm)	0.67 ± 0.19
ABI	1.16 ± 0.17
baPWV (cm/s)	1788 ± 269
Biochemical test	
UA (mg/dL)	5.61 ± 1.46
BUN (mg/dL)	16.6 ± 4.6
Cr (mg/dL)	0.79 ± 0.20
LDL (mg/dL)	112.5 ± 24.4
HDL (mg/dL)	55.5 ± 12.8
TG (mg/dL)	133 ± 115
Glucose (mg/dL)	117 ± 30
HbA1c (%)	5.6 ± 0.6

ABI, ankle brachial index; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; Cr, creatinine; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL, low-density lipoprotein cholesterol; TG, triglyceride; UA, uric acid; UN, urea nitrogen.

therapy in 34 patients (40.4%), whereas triple therapy was administered to eight patients (9.5%), and quadruple agent therapy to one patient (1.2%). Furthermore, 14 patients (17.3%) had concurrent diabetes and 31 patients (36.9%) had concurrent dyslipidemia. Hemoglobin A1c, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and trigycleride values were 5.9 ± 0.6, 112.5 ± 24.4, 55.5 ± 12.8 and 133 ± 115, respectively.

Quantitative evaluation of WMH

Table 2 summarizes the result of quantitative evaluation on MRI. The WMH volume was 6.67 ± 8.03 mL, more than 80% of which was PVH, whereas there was very little deep WMH. The ratio of white matter lesion occupying the cerebrum (WMH/parenchyma) was 0.610 ± 0.740%. In addition, possible relationships between age, body mass index, blood and physiological tests with WMH were examined by linear regression analysis, but no correlations were found.

Table 2 Quantitative evaluation of magnetic resonance imaging

MRI imaging	
WMH (mL)	6.67 ± 8.03
PVH (mL)	5.83 ± 7.17
DWMH (mL)	0.83 ± 1.44
IC (mL)	1433 ± 128
PAR (mL)	1095 ± 104
PAR/IC (%)	76.4 ± 2.53
WMH/PAR (%)	0.610 ± 0.740

DWMH, deep subcortical white matter hyperintensity; IC, intracranial space; MRI, magnetic resonance imaging; PAR, parenchyma; PVH, periventricular white matter hyperintensity; WMH, white matter hyperintensity.

Office BP and ABPM

The results of BP measurement are shown in Table 3. Office BP was 133 ± 12/77 ± 8 mmHg, with heart rate of 72 ± 11 b.p.m., and most patients had good BP control. On BP analysis using ABPM, the 24-h mean BP, mean daytime BP, and mean night-time BP were 130 ± 11/75 ± 7 mmHg, 132 ± 11/78 ± 7 mmHg and 121 ± 14/69 ± 9 mmHg, respectively. Linear regression analysis showed no correlation between office BP and WMH; however, night-time mean systolic BP alone correlated to WMH with a significant difference ($r = 0.328$, $P = 0.013$).

On calculating the night–day systolic BP ratio as an indicator of circadian BP variation, a little less than half appeared to be in the dipper group (night–day systolic blood pressure ratio is 0.9 or less). Examination of the relationship with WMH volume showed that although this tendency to be in the dipper group was recognized, there was no statistical significance ($r = 0.251$, $P = 0.06$).

Two-group comparison based on night-time systolic BP

To clarify the effect of night-time mean systolic BP on WMH volume, we next classified patients into two night-time systolic BP groups as follows: <125 mmHg ($n = 47$) and ≥125 mmHg ($n = 37$).

A comparison of background factors based on mean night-time systolic BP is shown in Table 4. There was

Table 3 Relationship between blood pressure profiles and white matter hyperintensity volumes

	Mean ± SD	*r*	*P*
Office BP			
Systolic (mmHg)	133 ± 12	−0.052	0.69
Diastolic (mmHg)	77 ± 8	−0.022	0.86
HR (b.p.m.)	72 ± 11	0.121	0.36
ABPM			
All-day			
Systolic (mmHg)	130 ± 11	0.241	0.071
Diastolic (mmHg)	75 ± 7	0.074	0.58
HR (b.p.m.)	66 ± 8	−0.096	0.49
Day-time			
Systolic (mmHg)	132 ± 11	0.181	0.17
Diastolic (mmHg)	78 ± 7	0.039	0.77
HR (b.p.m.)	68 ± 9	−0.082	0.54
Night-time			
Systolic (mmHg)	121 ± 14	0.328	0.013
Diastolic (mmHg)	69 ± 9	0.171	0.2
HR (b.p.m.)	72 ± 11	0.015	0.91
Night-time/daytime systolic BP ratio	0.91 ± 0.8	0.251	0.06

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; HR, heart rate.

no significant difference observed for age, sex and BMI. Similar results were found for patients with concurrent diabetes, and there was no difference in hemoglobin A1c observed. Concurrent dyslipidemia tended to be common among patients in the group with higher night-time systolic BP; however, there was no statistical difference, and no significant difference was observed in intima media thickness, ankle brachial index, brachial-ankle pulse wave velocity, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride. With regard to office BP and heart rate, there was no significant difference observed. Furthermore, the dipper type of circadian BP variation was significantly common in the group with lower night-time systolic BP. A comparison of WMH volume showed a significantly higher volume in the group with high mean night-time systolic BP (9.0 ± 8.4 mL *vs* 4.1 ± 4.3 mL, $P = 0.015$), which we found was primarily attributed to elevated PVH volumes (Fig. 1).

Furthermore, to assess the effect of circadian BP variation, WMH volumes of the dipper and non-dipper group were evaluated. In the group with lower night-time systolic BP, WMH volumes were similar in the dipper and non-dipper group (4.1 ± 4.0 mL *vs* 4.1 ± 4.7 mL, $P = 0.99$). In the group with higher night-time systolic BP, there was a tendency of increasing WMH volumes in the non-dipper group, but there was no statistical difference (6.4 ± 8.3 mL *vs* 9.7 ± 8.6 mL, $P = 0.14$).

Discussion

The major findings of the present study were that mean night-time systolic BP positively correlated to WMH volumes, and that office BP showed no correlation with WMH volume.

Many studies have shown that circadian BP variation rather than night-time BP is an exacerbating factor of WMH.[17,18] In the results of the present study, dipper-type circadian variation was significantly common in the group with lower night-time BP. In contrast, mean night-time systolic BP was more significantly related to WMH volume than circadian BP variation, and it is assumed that insufficient nocturnal BP decrease might be one major factor that exacerbates WMH. In a recent study, the importance of nocturnal BP has been shown, as it has been reported that high nocturnal BP is associated with an increase in all-cause mortality and cardiovascular events,[20] as well as the onset of chronic kidney disease.[21] Such reports support the present results. We believe that decreasing nocturnal BP is an important part of controlling WMH.

Unfortunately, the nature of the association between lowering nocturnal BP and cerebral blood flow (CBF) is not known. In hypertension, arteriosclerotic changes in the cerebral blood vessels lead to functional alternations in the cerebral microcirculations and limit the autoregulation of CBF through various mechanisms. It has been reported that adequate nocturnal BP decrease was

Table 4 Two-group comparison based on night-time systolic blood pressure

Parameters	NBP < 125 (n = 47)	NBP ≥ 125 (n = 37)	P
Age (years)	69.7 ± 3.6	69.8 ± 3.6	0.96
Male (%)	24 (51.1%)	16 (43.2%)	0.47
Height (cm)	159.4 ± 8.4	155.9 ± 7.4	0.098
Bodyweight (kg)	60.0 ± 10.1	57.2 ± 10.6	0.31
BMI (kg/m^2)	23.5 ± 3.4	23.3 ± 3.4	0.82
Diabetes	7 (14.9%)	7 (18.9%)	0.62
Lipidemia	14 (29.8%)	17 (45.9%)	0.12
Office BP			
Systolic (mmHg)	133.7 ± 12.2	132.0 ± 12.4	0.61
Diastolic (mmHg)	78.3 ± 6.5	75.8 ± 9.9	0.24
HR (b.p.m.)	72.4 ± 12.5	71.2 ± 8.5	0.68
Dipper (%)	30 (63.8)	8 (21.6)	0.0002
IMT (mm)	0.66 ± 0.02	0.71 ± 0.03	0.13
ABI	1.14 ± 0.22	1.14 ± 0.07	0.81
baPWV (cm/s)	1726 ± 273	1858 ± 265	0.07
UA (mg/dL)	5.4 ± 1.1	5.7 ± 1.8	0.45
BUN (mg/dL)	16.7 ± 3.8	16.1 ± 5.7	0.62
Cr (mg/dL)	0.82 ± 0.18	0.78 ± 0.22	0.53
LDL (mg/dL)	113 ± 18	111 ± 31	0.81
HDL (mg/dL)	54 ± 13	57 ± 12	0.41
TG (mg/dL)	150 ± 153	116 ± 49	0.24
glucose (mg/dL)	119 ± 33	116 ± 28	0.69
HbA1c (%)	6.0 ± 0.5	6.1 ± 0.7	0.64

ABI, ankle-brachial index; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; Cr, creatinine; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; HR, heart rate; IMT, intima media thickness; LDL, low-density lipoprotein cholesterol; TG, triglyceride; UA, uric acid; UN, urea nitrogen.

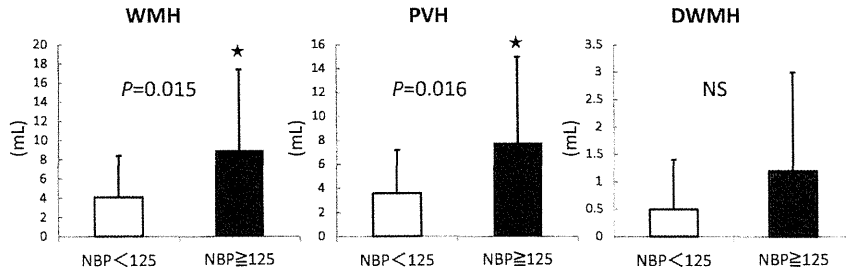

Figure 1 The relationship between night-time mean systolic blood pressure and white matter hyperintensity (WMH) volumes. WMH volume was significantly greater in the group with night-time systolic blood pressure (NBP) ≥125 mmHg than that in the <125 mmHg group, primarily attributed to elevated periventricular hyperintensity (PVH) volumes. DWMH, deep white matter hyperintensity; NS, not significant.

associated with increased CBF in patients with a history of cerebral infarction.[22] Non-dipping of nocturnal BP is associated with increased levels of markers of endothelial dysfunction and inflammation.[23] Taken together, nocturnal BP might be linked to CBF regulation, and lowering nocturnal might may have a favorable impact on cerebral circulation.

To date, no studies have investigated whether lowering nocturnal BP inhibits the progression of WMH. In contrast, very few studies have examined whether the administration of antihypertensive agents prevents the progression of WMH. In the MRI substudy of the PROGRESS trial, 192 patients were given a perindopril-based treatment, as an angiotensin-converting enzyme

inhibitor, with the diuretic indapamide or a placebo.[24] After follow up for 36 months, the volume of new WMH was lower in the treatment group compared with the placebo group. Systolic BP had decreased by a mean of 11.2 mmHg, and diastolic BP had decreased 4.3 mmHg in the treatment group compared with the placebo group. In the Prevention Regimen for Effectively Avoiding Second Stroke study, 771 patients were given antiplatelet agents after cerebral infarction and followed up for approximately 28 months. The patients were divided into a group given additional telmisartan, an angiotensin II receptor blocker, and a group given an additional placebo. There was no significant difference observed in WMH progression between the two groups.[25] Mean BP was just 3.0/1.3 mmHg lower in the treatment group compared with the placebo group. At the present stage, it has been shown that aggressive antihypertensive treatment only inhibits WMH progression. However, both studies evaluated office BP only, and we believe that in the future, BP should be strictly controlled using ABPM to investigate changes in WMH.

Here, we would like to re-emphasize the importance of controlling BP using ABPM as an indicator to control WMH. In the present results, there was no correlation observed between office BP and WMH volume. This is because of the fact that all patients were receiving antihypertensive treatment, and thus in most cases the office BP was well controlled. Therefore, even if the office BP is controlled well, WMH can progress in the event of nocturnal hypertension, or non-dipper type circadian BP variation. Many studies to date have shown that ABPM is a prognostic factor for cardiac, renal, and cerebral disease in middle aged and older people with hypertension.[26] A recent study showed that for elderly individuals, BP measurements obtained by ABPM rather than office BP are a predictive factor of cerebrovascular disease and cognitive decline.[27] Another important point of measuring night-time BP with ABPM is the superior reproducibility compared with other time periods. BP is more variable during the day than during the night because of physical and mental activity. Therefore, we believe that management of WMH should be carried out using ABPM.

The present study had some limitations. First, the details of antihypertensive treatment were an issue. To be specific, many different antihypertensive agents were given, and the number of agents given varied. As the present study was a relatively small-scale cross-sectional study, the effect of each antihypertensive agent could not be examined.

Second, metabolic diseases (diabetes and dyslipidemia) were included. However, as there were no correlations between WMH volume and values for hemoglobin A1c, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride, we believe that they did not affect the results of our study.

The present study showed that elevated mean night-time systolic blood pressure was a major risk factor for the development and exacerbation of WMH. To prevent the progression of WMH, management by office BP alone is insufficient, and we recommend controlling BP on the basis of ABPM. Further studies are required to determine whether lowering nocturnal blood pressure should be targeted to prevent the progression of WMH.

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Disclosure statement

The authors declare no conflict of interest.

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REVIEW ARTICLE

White matter hyperintensities and geriatric syndrome: An important role of arterial stiffness

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White matter hyperintensities (WMH) are defined as cerebral white matter changes presumed to be of vascular origin, bilateral and mostly symmetrical. They can appear as hyperintense on T2-weighted and fluid-attenuated inversion recovery sequences, and as isointense or hypointense on T1-weighted magnetic resonance imaging of the brain. WMH have been focused on because of their clinical importance as a risk factor for cerebrovascular diseases and cognitive impairment. WMH are associated with geriatric syndrome, which is defined by clinical symptoms characteristic of older adults, including cognitive and functional impairment and falls.

Cerebral small vessel diseases, such as WMH, might play an important role as risk factors for cerebrovascular diseases, cognitive impairment and geriatric syndrome through the mechanism of arterial stiffness. However, the vascular, physiological and metabolic roles of arterial stiffness remain unclear. Basically, arterial stiffness indicates microvessel arteriosclerosis presenting with vascular endothelial dysfunction. These changes might arise from hemodynamic stress as a result of a "tsunami effect" on cerebral parenchyma. In the present article, we review the clinical characteristics of WMH, focusing particularly on two associations: (i) those between cerebral small vessel diseases including WMH and arterial stiffness; and (ii) those between WMH and geriatric syndrome. **Geriatr Gerontol Int 2015; 15 (Suppl. 1): 17–25.**

Keywords: arterial stiffness, cerebral small vessel disease, cognitive impairment, geriatric syndrome, white matter hyperintensities.

Introduction

White matter hyperintensities (WMH) are defined as cerebral white matter changes presumed to be of vascular origin, bilateral and mostly symmetrical. They can appear as hyperintense on T2-weighted and fluid-attenuated inversion recovery sequences, and as isointense or hypointense on T1-weighted magnetic resonance imaging of the brain (Fig. 1).[1] WMH have been focused on because of their clinical importance as a risk factor for cerebrovascular diseases and cognitive impairment. There are some variants of the term WMH, such as leukoaraiosis and white matter lesions (Table 1).[1] Generally, WMH are used in terminology regarding neuroimaging.

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Recently, the concept of vascular cognitive impairment (VCI) has become widespread, and the continuity of cerebrovascular diseases and cognitive impairment is one of the latest topics.[2] In particular, cerebral small vessel diseases (SVD) might play an important role as risk factors for both cerebrovascular diseases[3] and cognitive impairment.[4] This role could arise through the mechanism of arterial stiffness indicating microvessel arteriosclerosis presenting with vascular endothelial dysfunction (Fig. 2). Furthermore, recent studies suggest associations between arterial stiffness and geriatric syndrome.[5–8] Geriatric syndrome is relevant given an increasing aging society; geriatric syndrome is known to increase caregiver burden.[9,10] An increased number and proportion of older patients presenting with geriatric syndrome in populations of Japan and other countries contribute to the financial pressures on many healthcare systems. Herein, we review the characteristics of WMH, focusing particularly on two associations: those between cerebral SVD including WMH and arterial stiffness, and those between WMH and geriatric syndrome based on our previous studies.

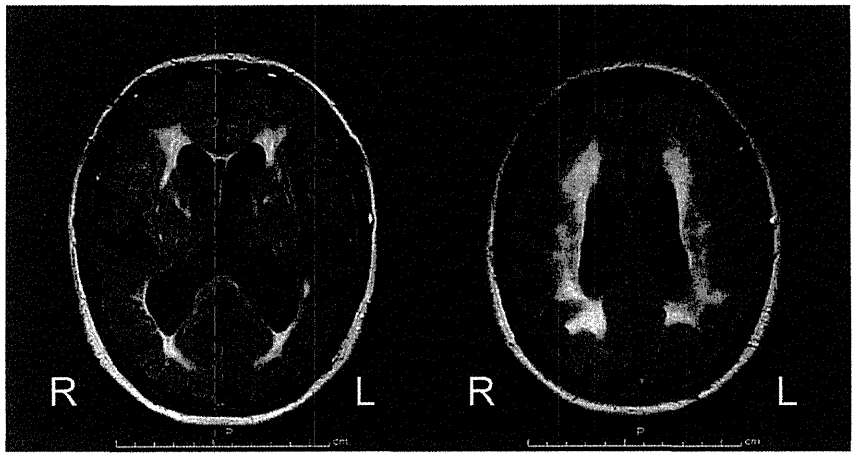

Figure 1 Brain magnetic resonance imaging of a representative patient presenting with white matter hyperintensities. Fluid-attenuated inversion recovery sequences of the brain magnetic resonance imaging show bilateral and symmetrical hyperintense on the periventricular white matter and subcortical lesions.

Table 1 Variants of the term: white matter hyperintensities[1]

Variants	(%)
Leukoaraiosis	31%
White matter lesions	24%
White matter hyperintensity	19%
White matter changes	12%
Leukoencephalopathy	7%
White matter disease	4%
White matter damage	0%
Ischemic white matter disease	0%

Data were derived from Reference 1: the use of this term in the title or abstract (n = 1144), using a structured literature search; for the methodology, search strategy and selection criteria, please see Reference 1.

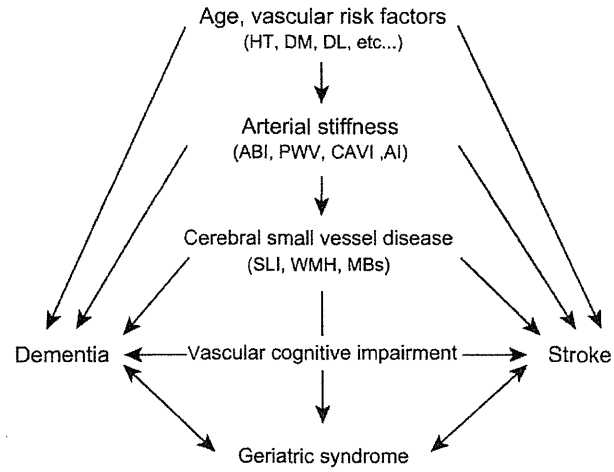

Figure 2 Schema of factors associated with geriatric syndrome. ABI, ankle-brachial index; AI, augmentation index; CAVI, cardio-ankle vascular index; DL, dyslipidemia; DM, diabetes mellitus; HT, hypertension; MB, cerebral microbleeds; PWV, pulse wave velocity; SLI, silent lacunar infarcts; WMH, white matter hyperintensities.

WMH and arterial stiffness

In general, arterial stiffness is a risk factor for mortality, cardiovascular diseases, cerebrovascular diseases and cognitive decline (Fig. 2).[3] There are some surrogate markers of arterial stiffness, such as the ankle-brachial index (ABI), pulse wave velocity (PWV; e.g. aortic, brachial-ankle and carotid-femoral PWV), cardio-ankle vascular index and the augmentation index. In this section, we review associations between WMH and cerebral damage, such as silent cerebral lesions, stroke, cognitive impairment and geriatric syndrome arising through the mechanism of arterial stiffness.

Silent cerebral lesions

Cerebral SVD, such as WMH, silent lacunar infarcts and cerebral microbleeds, have been considered as silent cerebral changes.[1,11] Furthermore, acute lacunar infarcts are associated with WMH, because the mechanism of acute lacunar infarcts mostly depends on cerebral SVD. In general, age and hypertension are well-known risk factors for cerebral SVD including WMH.[1] Similarly, calcifications in the carotid siphon might be a risk factor for cerebral SVD.[12]

Our studies show that arterial stiffness is independently associated with cerebral SVD, such as WMH and silent lacunar infarcts (Fig. 2).[13–15] The mechanism of cerebral SVD is considered to involve vascular endothelial dysfunction as a result of arterial stiffness, which causes blood–brain barrier failure or progression of arteriosclerotic changes and leads to cerebral parenchyma damage.[16] Taken together, there is a robust association between WMH and arterial stiffness, although there are some methodological differences among the surrogate markers of arterial stiffness.[15,17]