Changes in Cerebral Blood Flow and Oxygen Metabolism Related to Magnetic Resonance Imaging White Matter Hyperintensities in Alzheimer's Disease

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We studied changes in cerebral perfusion and oxygen metabolism to elucidate the pathophysiological nature and clinical significance of white matter hyperintensities in Alzheimer's disease (AD). **Methods:** Sixteen AD patients (age 71.6 ± 3.1 yr) whose T2-weighted MR images showed white matter hyperintensities, and 16 age-matched AD patients (age 71.0 ± 4.3 yr) without white matter hyperintensities were compared. Regional cerebral blood flow (CBF), oxygen metabolism ($CMRO_2$) and oxygen extraction fraction (OEF) were measured by using ^{15}O steady-state method and PET. **Results:** There was no significant difference in cognitive impairment between the two groups. Compared to the patients without white matter hyperintensities, those with them had significantly low CBF values and significantly high OEF values in all cortical and white matter regions. However, there were no significant differences in $CMRO_2$ values between the two groups. Severity of white matter hyperintensities correlated with the mean cortical and mean white matter OEF. **Conclusion:** In AD patients, white matter hyperintensities on T2-weighted MR images represent ischemic changes in which oxygen metabolism and function are fairly compensated. These changes are not disease-specific but are age-associated coincidences, as in normal aging with or without vascular risk factors.

Key Words: Alzheimer's disease; white matter hyperintensity; PET; cerebral blood flow; cerebral oxygen metabolism

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Development of MRI has helped raise sensitivity for detecting cerebral vascular diseases. On the other hand, incidental white matter hyperintensities (WMH) are often demonstrated on T2-weighted images in patients without evidence of stroke. WMH appear in 70%–100% of patients with vascular dementia (*1,2*). Their presence or extent are correlated with increasing age (*3,4*) and vascular risk factors (*5,6*) but not with cognitive function in normal elderly or hypertensive subjects. (*5,7–10*). Fazekas et al. (*11*) reported that WMH increased from 30% in the fourth decade to 83% in subjects more than 70 yr of age. It has been documented in a clinico-pathological study that severity of deep white matter hyperintensity (DWMH) in these subjects corresponds to increasing severity of ischemic tissue damage. PET studies on cerebral blood flow (CBF) and metabolism have demonstrated that CBF is decreased in the absence of cerebral metabolic rate for oxygen ($CMRO_2$) changes in subjects with WMH who lack cognitive impairments, whereas both CBF and $CMRO_2$ are decreased in association with periventricular (PVH) and dementia, as in patients with Binswanger-type dementia (*12,13*).

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WMH often are demonstrated in patients with Alzheimer's disease (AD) and sometimes result in a diagnostic dilemma and a suspicion of concomitant cognitive changes of vascular origin. Leys et al. (*14*) failed to find any difference in WMH on MR images between patients with AD and normal elderly subjects without vascular risk factors. Marder et al. (*15*) found that performance on neuropsychological tests in AD patients with similarly impaired WMH compared to those without WMH. Although these clinical findings suggested that WMH in AD patients is not a disease-specific change but an age-associated coincidence that has little clinical importance (*1,6*), the nature of WMH and its effect on cognitive function in AD patients remains undetermined in terms of CBF and metabolism. To elucidate the pathophysiological nature and clinical significance of WMH in AD, we studied changes in cerebral perfusion and oxygen metabolism in relation to WMH using PET.

METHODS

Patients

We studied patients with a clinical diagnosis of AD of mild-to-moderate functional severity [Grades 1 and 2 on the Clinical Dementia Rating (*16*)] who were examined by both neurologists and psychiatrists and underwent MRI of the brain, MR angiography of the neck and head, electroencephalography and standard neuropsychological examinations that fulfilled National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD (*17*). Patients with MR evidence of focal brain lesions, MR angiographic evidence of occlusive lesions in the cervical and intracranial arteries, complication of other neurological diseases or of ill physical conditions, or presence of severe language, attention and behavioral disorders that would make PET procedures difficult were excluded. We selected 16 patients whose MR images showed mild-to-severe WMH (WMH-positive, 4 men, 12 women, age range 66–76 yr; mean ± s.d. age 71.1 ± 3.1 yr) and 16 patients whose MR images showed little evidence of WMH (WMH-negative, 3 men and 13 women, age range 63–78 yr, mean ± s.d. age 71.0 ± 4.3 yr). Cognitive function was assessed with the mini-mental state examination (MMSE) (*18*) and Alzheimer's Disease Assessment Scale (ADAS) (*19*).

MRI

All MR studies were performed on a 1.5-T MR unit using a circularly polarized head coil as both transmitter and receiver. Sagittal, coronal and axial T1-weighted, spin-echo images (repetition time [TR] msec/echo time [TE] msec = 550/15, two excitations, 5-mm thickness, 2.5-mm gap) and axial T2-weighted fast spin-echo images (3000/21,105, two excitations) were obtained for

TABLE 1
Grading of Periventricular Hyperintensity and Deep White Matter Hyperintensity

	DWMH			
PVH	Grade 0	Grade 1	Grade 2	Grade 3
Grade 0	*9*	*1*	0	0
Grade 1	*4*	*2*	1	0
Grade 2	2	7	2	1
Grade 3	1	2	0	0

Numbers in italics denote patients without WMH. PVH = periventricular hyperintensity; DWMH = deep white matter hyperintensity. Grades 2 and 3 of either PVH or DWMH were regarded as WMH-positive.

diagnosis. Three-dimensional spoiled gradient echo (3D-SPGR) imagings (TR 14 msec, TE 3 msec, flip angle 20°, 1.5-mm thickness by 124 slices) were served for an anatomical reference for analysis of PET images. WMH were determined on axial T2-weighted images. Two neuroradiologists reviewed the images without knowledge of the clinical status, classified WMH into PVH and DWMH, and rated their severity into four grades according to Fazekas et al. (*6*): for PVH, "absent" = Grade 0, "caps or pencil-thin lining" = Grade 1, "smooth halo or thin band" = Grade 2 and "irregular periventricular hyperintensity extending into the deep white matter or broad band" = Grade 3; for DWMH, "absent" = Grade 0, "punctate" = Grade 1, "beginning of confluence" = Grade 2 and "confluent" = Grade 3. In this study, the greater one represents the severity of WMH, and Grades 2 and 3 were defined as WMH-positive. The results of evaluation are shown in Table 1.

PET

The entire study strictly followed the Clinical Study Guideline, Ethical Committee, Hyogo Institute for Aging Brain and Cognitive Disorders, 1993 and was approved by the Internal Review Board and Ethical Committee. Before the examination, written informed consent was obtained from all patients and their relatives according to the Declaration of Human Rights, Helsinki, 1975. Detailed PET procedures have been reported elsewhere (*20*). In brief, imaging was performed with a PET scanner that has four rings located 13 mm apart and yields a transverse resolution of 4.5 mm FWHM. The slice thickness was 11 mm and the slice interval was 6.5 mm with z-motion mode. A transmission scan was performed using $^{68}Ga/^{68}Ge$ for absorption correction after each patient was positioned. CBF, $CMRO_2$ and oxygen extraction fraction (OEF) were determined by using the steady-state technique (*21*). CBF was measured under continuous inhalation of 200 MBq/200 ml/min $C^{15}O_2$ through a mask. Measurements of $CMRO_2$ and OEF were done under continuous inhalation of 500 MBq/200 ml/min $^{15}O_2$. Acquisition time for each measurement was 10 min. A 1-min inhalation of 2000 MBq $C^{15}O$ was used to measure cerebral blood volume (CBV). Intermittent arterial blood samplings were done throughout scanning. $CMRO_2$ and OEF were corrected by CBV (*22*).

Data Analysis

PET and MR image datasets were directly transmitted to a workstation and analyzed with image analyzing software. MR images of identical three-dimensional scales and coordinates to PET images were made for anatomical references. Both PET and MR images were displayed side by side on a display monitor, and two or three circular ROIs, of 10-mm diameter, were determined on each cerebral region on the CBF image, of which anatomical coordinates were verified on the corresponding MR image. Multiple ROIs were placed on the medial temporal cortex (the hippocampus and parahippocampal gyrus), lateral temporal cortex (superior and middle temporal gyri), occipital cortex (cuneus), frontal lobe (superior and middle frontal gyri), parietal lobe (supramarginal and angular gyri), paracentral region and white matter in the centrum semiovale (frontal and parietal regions at supraventricular level). The same ROIs were transferred to the OEF and $CMRO_2$ images to measure regional OEF and $CMRO_2$. CBF, OEF and $CMRO_2$ values in each region were expressed as an average of both sides.

Differences between groups were assessed with analysis of variance (ANOVA) for repeated measures, with one within-subject factor (brain regions) and one between-subject factor (WMH). In addition, we applied the Pearson correlation coefficient to examine the relationship between severity of WMH and each perfusion/metabolism parameter and to explore the effect of WMH and each perfusion/metabolism parameter on cognitive function, where the cortical perfusion/metabolism parameter was expressed as the mean value of all cortical regions. The significance level was set at $p < 0.05$.

TABLE 2
Clinical Characteristics of Subjects with and without WMH

	WMH-positive	WMH-negative	p value*
Age (yr)	71.6 ± 3.1	71.0 ± 4.3	ns
Sex (male/female)	4/12	3/13	ns
MMSE	19.1 ± 2.9	17.8 ± 3.2	ns
ADAS	20.8 ± 3.5	22.6 ± 6.2	ns
Duration of illness (yr)	3.3 ± 1.6	3.4 ± 2.4	ns
Education (yr)	9.2 ± 2.4	9.9 ± 2.3	ns
Diabetes mellitus	4	1	ns
Hyperlipidemia	0	0	ns
Hypertension	1	2	ns
Smoking	2	2	ns

*One-tailed Student t-test or Fisher exact probability test.
WMH = white matter hyperintensities on T2-weighted images; MMSE = Mini-Mental State Examination; ADAS = Alzheimer's Disease Assessment Scale; ns = not significant.

RESULTS

Table 2 summarizes patient characteristics. There was no difference in prevalence of diabetes mellitus, hypertension, hyperlipidemia and smoking. No significant differences were noted in MMSE score, ADAS score, duration of illness or educational attainment between the two groups. Table 3 summarizes the patients' arterial blood gas data at the time of the PET examination. There was no difference in blood gas condition between the two groups.

Results of ROI measurements are shown in Table 4. In each ROI, the mean regional CBF (rCBF) was lower in the WMH-positive group than in the WMH-negative group, and the mean

TABLE 3
Blood Gas Data at Time of PET Examination

	WMH-positive	WMH-negative	p value*
pH	7.41 ± 0.01	7.41 ± 0.01	ns
PaO_2 (mmHg)	88.7 ± 12.2	96.4 ± 8.2	ns
$PaCO_2$ (mmHg)	40.0 ± 1.9	41.4 ± 1.6	ns
Hb (g/dl)	11.5 ± 0.9	11.3 ± 0.8	ns

*One-tailed Student's t-test.
WMH = white matter hyperintensities on T2-weighted images; Hb = hemoglobin; ns = not significant.

TABLE 4
Mean rCBF, OEF and CBV in Alzheimer's Disease Patients with and without WMH

		Medial temporal lobe	Lateral temporal lobe	Occipital lobe	Frontal lobe	Paracentral cortices	Parietal lobe	White matter
CBF*	WMH-positive	41.3 ± 4.7	47.6 ± 7.4	59.8 ± 10.7	48.7 ± 8.4	54.0 ± 6.3	47.5 ± 9.2	20.7 ± 5.3
	WMH-negative	46.1 ± 8.0	52.0 ± 6.5	69.8 ± 10.8	52.0 ± 6.5	62.4 ± 7.4	48.7 ± 5.7	24.1 ± 3.7
$CMRO_2$	WMH-positive	2.30 ± 0.43	3.24 ± 0.46	4.09 ± 0.80	3.32 ± 0.61	3.54 ± 0.54	3.42 ± 0.73	2.37 ± 0.61
	WMH-negative	2.11 ± 0.42	3.14 ± 0.66	4.16 ± 0.83	3.15 ± 0.61	3.56 ± 0.66	3.05 ± 0.51	2.48 ± 0.76
OEF†	WMH-positive	36.3 ± 4.7	44.6 ± 4.0	44.7 ± 3.7	44.6 ± 3.9	42.6 ± 4.0	47.0 ± 3.5	43.6 ± 4.1
	WMH-negative	30.7 ± 5.9	39.7 ± 4.5	39.6 ± 4.6	39.9 ± 4.3	37.5 ± 3.8	41.4 ± 4.4	38.0 ± 4.9
CBV	WMH-positive	5.97 ± 1.24	5.56 ± 1.00	6.32 ± 1.16	4.32 ± 0.66	4.60 ± 0.72	4.29 ± 0.71	1.56 ± 0.56
	WMH-negative	6.91 ± 1.15	6.23 ± 1.00	6.74 ± 1.47	4.97 ± 0.90	5.26 ± 1.14	4.96 ± 0.99	1.71 ± 0.69

*WMH-positive subjects have significantly lower rCBF values than WMH-negatives ($F = 4.41$, $p = 0.04$, ANOVA).
†WMH-positive subjects have significantly higher rOEF values than WMH-negatives ($F = 7.68$, $p = 0.01$, ANOVA).
Values are expressed as mean ± 1 s.d. WMH = white matter hyperintensities on T2-weighted images; CBF = cerebral blood flow (ml/100 ml/min); $CMRO_2$ = cerebral metabolic ratio for oxygen (ml/100 ml/min); OEF = oxygen extraction fraction (%); CBV = cerebral blood volume (ml/100 ml).

regional OEF (rOEF) was higher in the WMH-positive group than in the WMH-negative group. In an ANOVA for rCBF, the group effect and region effect were significant ($F = 4.406$, $p = 0.044$ and $F = 113.2$, $p < 0.0001$, respectively), but region-by-group interaction was not significant ($F = 50.39$, $p = 0.181$). Similarly, in an ANOVA for rOEF, the group effect and region effect were significant ($F = 7.684$, $p = 0.009$, and $F = 45.29$, $p < 0.0001$, respectively), but region-by-group interaction was not significant ($F = 0.131$, $p = 0.992$). These imply that both rCBF and rOEF for all regions differ significantly in a similar manner between the two groups. The regional $CMRO_2$ (group effect of $F = 0.21$, $p = 0.65$ and group-by-region interaction of $F = 0.623, 0.712$) and regional CBV (group effect of $F = 2.73$, $p = 0.109$ and group-by-region interaction of $F = 0.692$, $p = 0.656$) were both comparable in the two groups (Table 4).

Severity of WMH correlated with the mean cortical OEF ($r = 0.435$, $p = 0.013$) and with the mean white matter OEF ($r = 0.458$, $p = 0.008$), but did not correlate significantly with CBF or $CMRO_2$ either of the cortex or of the white matter. No significant correlations were noted between severity of WMH and each cognitive test score (MMSE or ADAS) and between each perfusion/metabolism parameter either of the cortex or of the white matter and each cognitive test score.

DISCUSSION

Our study indicated that WMH-positives were associated with low CBF and high OEF in cortical and white matter regions compared with WMH-negatives, whereas no difference was noted in $CMRO_2$ between the two groups. Severity of WMH correlated with the mean cortical and white matter OEF. There were no significant differences in MMSE and ADAS scores between the two groups. Cognitive test scores did not correlate with severity of WMH nor with each perfusion/metabolism parameter.

Our cerebral perfusion/oxygen metabolism findings are similar to those noted in normal elderly subjects and in those at vascular risk. Herholtz et al. (*23*), using ^{18}fluoromethane PET, demonstrated that multiple large or confluent white matter lesions were associated with reduced CBF in patients with atherosclerotic carotid artery disease and WMH but without cognitive impairments. In a study of patients with severe WMH, Yao et al. (*12*), using a steady-state PET method, demonstrated that white matter OEF was significantly increased with somewhat reduced CBF and preserved $CMRO_2$ in cognitively normal subjects. They also reported that patients with Binswanger-type dementia had significantly reduced CBF and $CMRO_2$ in the cortical and white matter regions. Meguro et al. (*13*), using cognitively normal subjects with or without PVH and a steady-state PET method, demonstrated significantly decreased CBF and preserved $CMRO_2$ in patients with severe PVH as compared with those with no or mild PVH. Therefore, the status of cerebral perfusion and oxygen metabolism associated with WMH in AD patients is comparable to that occurring in normal aging or patients at vascular risk, but would be different from that in patients with Binswanger-type dementia. Fazekas et al. (*11*), who correlated brain MRI and microscopic pathological findings, indicated that DWMH corresponded to increasing ischemic tissue damage. Irregular PVH was characterized by microcystic infarcts and patchy rarefaction of myelin, while mild PVH-like "caps" were of nonischemic origin. Although the nature of WMH in AD patients also is likely to be related to ischemic changes, clinicopathological studies were needed to confirm this assumption.

The combination of low CBF with high OEF and preserved $CMRO_2$ is consistent with "misery perfusion" syndrome, which is originally described in the ipsilateral hemisphere to the occlusions or stenoses of the internal carotid artery (*24*). However, changes in CBV, which reportedly increase as a result of vasodilatation compensatory to hypoperfusion to raise OEF (*25*), was not observed in this study. A different mechanism, other than vasodilatation, to ensure the oxygen demand would be postulated to be predominantly attributable to this state of "misery perfusion" in subjects and AD patients where major arterial occlusive lesions were not present.

Our findings about the effect of WMH on cognitive impairments are consistent with those of Marder et al. (*13*). They pointed out that AD patients with WMH were not clinically differentiated from those without WMH in terms of neuropsychological test scores. In our study, MMSE and ADAS scores in the WMH-positive patients did not differ from those of WMH-negative patients, and the test scores did not correlate with severity of WMH. It is conceivable that the preserved $CMRO_2$, under the circumstances of decreased blood flow, keeps the function unaffected. This is further supported by the findings that each perfusion/metabolism parameter did not correlate with cognitive impairments. Only when $CMRO_2$ would decline, additional cognitive impairments would appear. In this respect, changes in $CMRO_2$ should be a better indicator of cognitive impairments than CBF, as reported earlier (*26*). However, since patients with severe WMH were generally excluded from this study on the basis of the subject selection criteria because of

accompanying lacunar infarcts in deep cerebral regions, the changes in oxygen metabolism and function associated with severe WMH should be examined further.

CONCLUSION

Low CBF, preserved $CMRO_2$ and high OEF in the cerebral hemisphere were associated with WMH seen in AD patients. WMH in AD patients is comparable to that in normal aging and cognitively unimpaired subjects at vascular risk, which probably indicates that a common pathophysiological mechanism is involved. The forebrain is probably suffering from an ischemic state in some degree in AD patients with WMH, as in cognitively unimpaired subjects with WMH. Nevertheless, cognitive functions are not affected by the low CBF, in that oxygen metabolism is preserved. This gives further support that mild-to-moderate WMH in AD patients is not a disease-specific change but an age-associated coincidence of no clinical importance.

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