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Clinical significance of reduced cerebral metabolism in multiple sclerosis: A combined PET and MRI study

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Magnetic resonance imaging (MRI) in patients with multiple sclerosis (MS) has provided major insights into the disease's natural history, and many studies have focussed on possible correlations between MRI findings and the clinical manifestations of MS. In contrast, there are few reports on possible relationships between functional imaging data and cognitive function. The present study assessed the relationship between clinical presentation and combined anatomical and functional imaging data in MS. Twenty patients with definite MS underwent MRI and positron emission tomography (PET) to evaluate cerebral blood flow (rCBF) and oxygen metabolism ($rCMRO_2$). The relationships between these neuroimaging findings and clinical data, including the Expanded Disability Status Scale (EDSS), Mini-mental status scale, Hasegawa Dementia Scale and relapse time, were evaluated with Spearman's rank correlation coefficients. A general reduction in rCBF and $rCMRO_2$ in the gray and white matter were found in the MS patients. EDSS was correlated with the number and size of the lesions on MRI and was negatively correlated with $rCMRO_2$. A correlation between the decrease in $rCMRO_2$ and the level of cognitive impairment was also found. The severity of cerebral hypometabolism was also related to the number of relapses. Morphological and functional findings obtained by MRI and PET are closely related to the clinical status in MS. Our results suggest that measurement of cerebral metabolism in MS has the potential to be an objective marker for monitoring disease activity and to provide prognostic information.

Key words: multiple sclerosis, cerebral oxygen metabolism, magnetic resonance imaging, hypometabolism, prognosis

INTRODUCTION

THE NATURAL HISTORY of multiple sclerosis (MS) is not fully known, although anatomic imaging studies with magnetic resonance imaging (MRI) in MS patients have provided major insights into the disease.[1-3] The possible correlation between the level of disability and the lesion burden detected on MRI indicates that this imaging method might serve as an objective clinical parameter for monitoring therapy,[4-6] but there is pathophysiological heterogeneity of lesions, so that all appear the same on conventional MRI.[3] Investigation of the functional pathophysiological impairments in relation to the lesion load detected by MRI in MS patients should improve our understanding of the disease.

A functional imaging study with positron emission tomography (PET) previously demonstrated generalized hypometabolism in the gray and white matter of MS patients.[7] Another study with single photon emission computed tomography (SPECT) showed a regional reduction in the frontal lobes and the left temporal lobe.[8] Both of these studies gave important information about metabolic or blood flow abnormalities of the brain in MS patients and showed that cerebral hypometabolism was well correlated with cognitive impairment, but no previous study has explored both quantitative functional

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Table 1 Clinical profile of the MS patients

No. of patients	20 (F/M 10/10)
Age (years)	38.6 ± 11.1
Disease duration (months)	108.2 ± 69.2
Total number of relapses	4.6 ± 3.7
Post-PET follow-up (months)	50.8 ± 14.3
Post-PET relapses	1.9 ± 2.4
Clinical course	number (%)
Relapsing-remitting	16 (80)
Chronic-stable	2 (10)
Chronic-progressive	1 (5)
Benign	1 (5)
EDSS	2.6 ± 1.5
MMS	26.8 ± 2.7
HDS	27.9 ± 3.7

Values represent the mean ± standard deviation.
EDSS: Kurtzke expanded disability status scale
MMS: Mini-mental state scale
HDS: Hasegawa dementia scale
PET: Positron emission tomography

imaging data and the clinical status of the patients.

The present work was initiated to determine the relationship between brain hypometabolism and the clinical features of MS, as well as to reexamine correlations between the lesion load on MRI and cognitive function and physical disability.

MATERIALS AND METHODS

Patients

Twenty patients (10 women and 10 men) with clinically definite multiple sclerosis[9] (mean age ± SD; 38.6 ± 11.1 years) were studied after giving informed consent. The mean total disease duration was 108.2 ± 69.2 months. The clinical course of the patients is shown in Table 1. Eighty percent of the patients had relapsing and remitting MS. Fourteen age-matched normal controls (43.6 ± 13.3 years) also participated in the PET study. PET and MRI were performed in all patients during remission. Disability was scored with Kurtzke's Expanded Disability Status Scale (EDSS).[10] The mean EDSS score was 2.7 ± 1.4, indicating that this group of patients had mild to moderate disability. Cognitive function was assessed with the Mini-mental status scale (MMS)[11] and the Hasegawa Dementia Scale (HDS; full score, 32.5 points).[12] The mean MMS and HDS scores were 26.8 ± 2.8 and 27.9 ± 3.7, respectively, suggesting the existence of focal cognitive impairment. These scales were assessed just before the PET study. The number of relapses during follow-up after PET and MRI was determined in 16 patients with a follow-up period of over one year. The total number of relapses was determined in 17 patients with a total disease duration of over one year. Relapse was defined as the appearance of a new symptom or deterioration of existing symptoms and signs for at least 24 hours, after excluding involvement of other diseases. The mean annual relapse rate during the total disease period and during follow-up was 0.43 and 0.52, respectively.

Magnetic resonance imaging

T2-weighted and proton MRI of the brain was performed in 16 patients with a Siemens system operating at 1.5 T (SE 2,400/90 and 2,400/20, 256 × 256 image matrix). Contiguous 7-mm thick slices of the whole brain were obtained from the foramen magnum to the higher convexity. The remaining four patients underwent T2-weighted and proton MRI with a 0.5 T Philips Gyroscan TS-NT (SE 2,500/90 and 2,500/20, 256 × 256 image matrix). A computerized image analysis system was used to quantify the total areas of lesions detected by MRI. Lesion borders were delineated on all axial slices displayed on a computer monitor with a mouse cursor and the lesion area per slice was calculated with an image analysis software. The total number of lesions was also counted in the same pictures, so that the total area and number of lesions were obtained for each patient. Confirmation of the results was done by another doctor independently.

Positron emission tomography

PET was performed with a PCT-H1 (Hitachi, Japan), which has four rings with 128 bismuth germanate oxide detectors providing seven views per scan cycle.[13,14] The best spatial resolution was 7.4 mm (full width at half maximum) at the center of the scanning field, and the axial resolution at the center was 16 mm (the slice thickness). Prior to the PET study, CT scanning (CT-HSF, Hitachi) was done to identify the anatomical structures in the PET views. The PET and CT scanners were located side by side and joined by rails on which the bed moved with the patient's position fixed, thus providing identical tomographic planes. The patient's head was fixed to the headrest to obtain a tomographic plane parallel to the orbitomeatal line. The initial positioning and the absence of head tilt during the scan were ensured by crossed beams projected onto ink marks drawn on the patient's face. A 10-min transmission scan with germanium-68 and gallium-68 was performed for attenuation correction. Calibration factors between the PET scanner and the well counter were obtained in each study. The oxygen-15 steady state technique was employed to measure regional cerebral blood flow (rCBF) and the regional cerebral metabolic rate of oxygen ($rCMRO_2$).[13,15] Oxygen-15 gas (750–1,100 MBq/min) and then oxygen-15 labeled carbon dioxide (350–550 MBq/min) were inhaled continuously while scan data were collected for 5–8 minutes. Blood samples were obtained 3 times during each scanning process from a cannula in the radial artery, and were used for determination of oxygen-15 radioactivity in whole blood and plasma as well as for blood cell counts and blood gas analysis. Correction for intravascular oxygen-15 labeled oxyhemoglobin was performed by means of bolus inhala-

tion of oxygen-15-labeled carbon monoxide.[15]

Image data were processed in a Hitachi image processing computer with system subroutines to reconstruct functional images of 128 × 128 pixels. These images were visually evaluated for any focal or regional reduction in rCBF and $rCMRO_2$. Then regions of interest (ROIs) were set in the bilateral cerebral cortices and the cerebellar hemispheres according to the CT images.[14] On each slice, cortical ribbons of frontal, temporal, parietal, and occipital lobe cortices, and outlines of the cerebellar hemispheres were traced with a track ball, avoiding the sinuses and cerebrospinal fluid spaces. The same ROIs were then superimposed on the rCBF and $rCMRO_2$ tomographic planes identical to the CT image. The mean rCBF and $rCMRO_2$ of the gray matter were calculated from the ROIs of all cerebral cortices, and were designated as G-CBF and G-$CMRO_2$, respectively. The mean rCBF and $rCMRO_2$ for white matter were obtained from the right and left centrum semiovale, and were designated as W-CBF and W-$CMRO_2$, respectively.

Statistical procedures

The mean age, rCBF, and $rCMRO_2$ values for the MS patients were compared with those of the controls and statistical differences were determined by Student's t-test. Correlations of PET values with EDSS, MMS, HDS and relapsing time were evaluated by Spearman's rank correlation coefficient (SRCC) analysis. Correlations between the quantitative MRI data and the above clinical parameters were also evaluated by SRCC analysis.

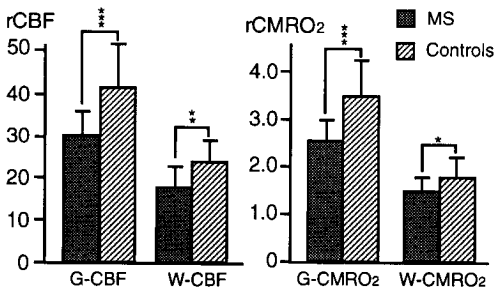

Fig. 1 Comparison of rCBF and $rCMRO_2$ between the MS patients and normal controls. Mean CBF in the gray matter (G-CBF) and white matter (W-CBF) of the 20 MS patients was 30.3 ± 6.2 and 17.7 ± 5.0, respectively, as compared with 41.7 ± 10.0 and 23.9 ± 5.6 in the 14 normal controls. Mean $CMRO_2$ in the gray matter (G-$CMRO_2$) and white matter (W-$CMRO_2$) of the MS patients was 2.6 ± 0.5 and 1.5 ± 0.3, respectively, as compared with 3.5 ± 0.8 and 1.8 ± 0.5 in the normal controls. *$p < 0.05$, *$p < 0.01$ and ***$p < 0.001$.

RESULTS

Magnetic Resonance Imaging Findings

Sixteen of the 20 MS patients had one or more lesions in the cerebral white matter of varying severity, but 4 had no lesion. The brainstem was involved in 7 patients and the spinal cord in 9 with or without white matter involvement. The total lesion load in the brain was quantified in terms of lesion area and lesion number; the mean area of the total lesions was 10.9 ± 13.0 cm^2, and the mean number of lesions was 10.9 ± 15.2. There were no concomitant abnormal findings, including brain atrophy.

Positron Emission Tomography Findings

A generalized significant reduction in rCBF and $rCMRO_2$ in the cerebral gray matter was found in the MS patients, with a 28% reduction in G-CBF and 27% decrease in G-$CMRO_2$ as compared with the normal controls. These changes were paralleled by a reduction of 26% in W-CBF and 16% in W-$CMRO_2$ (Figure 1). Similar changes were found in the rCBF and $rCMRO_2$ of the cerebellar hemispheres in the MS patients (data not shown). Visual analysis of the gray matter of rCBF and $rCMRO_2$ revealed no regional decrease in the patients compared with the normal controls (data not shown), indicating that diffuse pathophysiological impairment associated with white matter lesions was a general finding in the MS group, but one patient who had acalculia showed definite left temporo-parietal lobar hypometabolism.

Correlations between Imaging Data and Clinical Findings (Table 2)

The relationship between imaging data and clinical findings was assessed by SRCC analysis. A strong negative correlation was found between the lesion load on MRI and the

Table 2 Correlations between MRI, PET and clinical parameters

	MRI lesions		PET findings	
	total areas	total numbers	rCBF	$rCMRO_2$
EDSS	0.473 *	0.486 *	−0.560 *	−0.456 *
MMS	−0.677 **	−0.532 *	0.401	0.542 *
HDS	−0.816 ***	−0.532 *	0.488	0.518 *
Relapses during follow-up	0.235	0.274	−0.365	−0.537 *
Total number of relapses	0.214	0.120	−0.180	−0.514 *

EDSS, Kurtzke expanded disability status scale; MSS, Mini-mental state scale; HDS, Hasegawa dementia scale; rCBF, regional cerebral blood flow; $rCMRO_2$, regional cerebral metabolic rate of oxygen; *, $p < 0.05$; **, $p < 0.01$; and ***, $p < 0.001$.

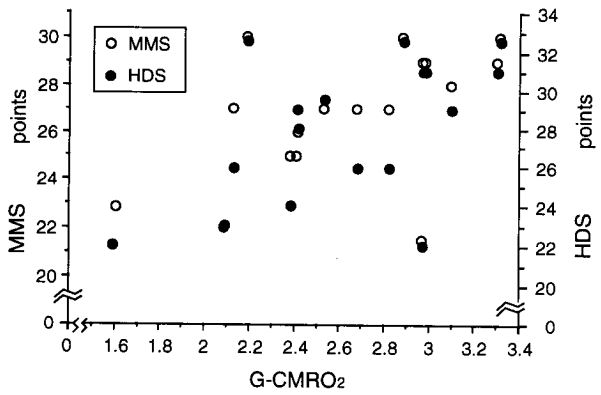

Fig. 2 Positive correlation between cerebral metabolism and cognitive function. SRCC = 0.542 (n = 17, $p < 0.05$) for the MMS score and SRCC = 0.518 (n = 17, $p < 0.05$) for HDS score.

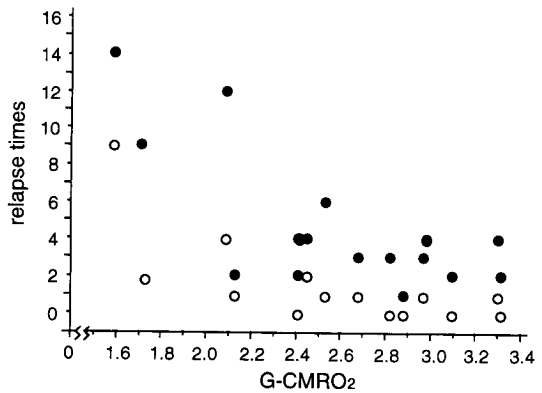

Fig. 3 Negative correlation between cerebral metabolism and the number of relapses during follow-up after PET or during the total disease duration. SRCC = −0.537 (n = 16, $p < 0.05$) during follow-up (open circles) and SRCC = −0.514 (n = 17, $p < 0.05$) during the total disease duration (closed circles).

cognitive scores (SRCC = −0.677 and $p < 0.01$ for MMS; SRCC = −0.816 and $p < 0.001$ for HDS). In addition, a positive correlation was found between gray matter metabolism and cognitive function (Figure 2). The number of lesions on MRI was correlated with the severity of clinical disability (SRCC = 0.542 and $p < 0.05$). Furthermore, the total lesion area on MRI was correlated with the EDSS score (SRCC = 0.486 and $p < 0.05$), and a coupled decrease in G-CBF and G-$CMRO_2$ in the gray matter of MS patients was negatively correlated with the EDSS score (SRCC = −0.560 and $p < 0.05$), indicating a relationship between cerebral metabolism and clinical disability.

The relationship between cerebral metabolism measured by PET and relapse time during follow-up (ranging from 21 to 83 months) or the total disease period (ranging from 22 to 248 months) was analyzed. G-$CMRO_2$ was significantly correlated with the number of relapses both during follow-up and during the total disease period (Figure 3), but no relationship between G-CBF and relapse was found.

Cognitive function, physical disability and relapse time were not correlated with W-CBF or W-$CMRO_2$.

DISCUSSION

MRI is clinically useful in the diagnosis of MS. Clinicopathological examination of demyelinated lesions with a high signal intensity on T2-weighted images in the brains of MS patients has indicated the reliability and validity of lesion measurement by MRI.[16] Previous studies have extensively investigated the relationship between MRI lesions and the clinical status of MS patients, but because controversy has arisen as a consequence of the wide range of disease presentation and the limitations of MRI,[17] a well-defined relationship between functional abnormalities of the MS brain and the extent and sites of lesions on MRI remains to be established.

In the present study, PET confirmed the global reduction in cerebral rCBF and r$CMRO_2$ in MS patients. This hypometabolism is unlikely to be explained solely by atrophy of the central white matter and cortical gray matter,[7] since no atrophy of the brain was detected by MRI in our patients, but the frequent occurrence of plaques (especially in the periventricular area) was noted, so that white matter lesions appeared to influence cortical metabolism.

A few previous studies have pointed out that white matter lesions can be associated with reduced cerebral metabolism.[18] In MS, the white matter plaques represent myelin breakdown and gliosis.[19] These lesions seem to disturb axonal transport and to exert a depressant effect on the cerebral cortex. The relapse of MS superimposed on a generalized disease process affecting multiple white matter regions would aggravate cerebral hypometabolism. This global (i.e., non-focal) reduction in brain metabolism, obviously recognized with visual inspection and shown in Figure 1, suggests that cortical functional changes in MS are likely to be caused not only by the white matter lesions identified by MRI, but also by functional disturbance in the normal-appearing white matter. This is partly supported by Husted et al. who have shown biochemical alterations in MS lesions and normal-appearing white matter detected by magnetic resonance spectroscopic methods.[20] Alternatively, cerebral metabolic hypoactivity detected by PET might represent a consequence of autoimmune changes in the brain that are independent of the visible lesion(s). The fact that no regional metabolism abnormality was found in the whole population agreed with the results reported by Brooks et al.[7]

In this study, a strong correlation was shown between the lesion burden (in terms of total lesion area and total lesion number) on T2-weighted MRI and cognitive scores. These findings extend previous results by demonstrating the usefulness of the screening tests for the evaluation of cognitive function in association with MRI data in MS.[21-23] Employment of a rapid dementia scale as a

routine test for MS should be practical and is clinically important since cognitive impairment occurs in 13% to 65% of MS patients.[24] A correlation between lesion burden on MRI and the disability score was also found in this study, a result that conflicted with some previous reports.[25] Differences in the selection of patients and technical considerations can readily explain these discrepancies. First, studies of a patient group more homogeneous in the clinical course seem to give clearer correlations in MS. In our patient group, 80% showed a relapsing-remitting course (Table 1). Another recent study has also reported that relapsing and remitting MS is likely to show a strong association between the MRI lesion load and the degree of disability.[6] Second, the field strength of the MRI scanner seems to have a great influence upon the detection of plaques.[18] Therefore, our MRI scanner (operating at 1.5 Tesla) may have been more accurate in detecting and quantitating the lesion load. The correlation between lesion burden and the degree of disability suggests that accumulated brain lesions in the white matter play a very important role in causing physical functional impairment in MS.

In the present study, a correlation between cerebral cortical metabolism and the disability score was shown for the first time, as opposed to previous findings.[7] It is difficult to compare our data quantitatively evaluating physical disability with the previous study that only graded the severity of locomotor dysfunction.[7] More global and quantitative assessment of physical disability should contribute to a better understanding of the natural history of MS because of the wide variations in clinical presentation. We suggest that the white matter lesion(s) might be one of the factors which cause diffuse cerebral hypometabolism responsible for clinical disability.

Another important finding of this study was that the decreased gray matter metabolism was related to relapse during follow-up and during the total disease period. This correlation between metabolic disturbance and relapse after PET (in the follow-up period) seems to be of clinical importance, suggesting that measurement of cerebral metabolism in MS has the potential to be an objective marker for providing prognostic information as well as monitoring disease activity. In contrast, there was no relationship between relapse and MRI data, although the reason for this was not clear. Reduced global cerebral metabolism indicates wide-ranging disturbance of neuronal function, which is probably caused by the disease process in the white matter. Therefore, the reduction in cortical metabolism may reflect functional derangement in the white matter which MRI cannot find out before relapsing of the disease occurs. These results suggest that PET might have the potential to be an objective marker for monitoring disease activity. We also found that there was no correlation between cerebral rCBF and the above clinical parameters, but the reason remains unclear. The direct correlation between cerebral hypometabolism and relapse time could be a reflection of a basic cerebral metabolic defect due to a number of factors, rather than a secondary effect of the decreased rCBF.

Finally, cerebral blood flow and oxygen metabolism in the white matter, which seem to directly reflect the disease process, were not correlated with the clinical parameters. The ROIs for W-CBF and W-$CMRO_2$ were placed in the centrum semiovale, which may show the demyelinating lesion(s) on MRI. Because of technical limitations, the ROI included the demyelinating lesion(s) in some patients and did not in others. Therefore, the W-CBF and W-$CMRO_2$ may not have represented overall cerebral perfusion and metabolism in the white matter. Improved spatial resolution of the PET could reveal the relationship between cerebral blood flow and metabolism in the white matter and clinical status in MS patients.

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