Relationship between the striatal and cerebellar glucose metabolism on FDG PET study and the responsiveness to levodopa treatment in patients with multiple system atrophy

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Relationship between the striatal and cerebellar glucose metabolism on FDG PET study and the responsiveness to levodopa treatment in patients with multiple system atrophy

Directed by Professor Myung Sik Lee

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10년 전 학술지에 처음으로 쓴 논문이 출판되어 나올 때의 그 기쁨을 아직도 기억합니다. 그리고, 오늘 완성된 학위 논문의 감사의 말씀을 쓰면서 또 다른 기쁨을 느낍니다.

그 누구보다도 지난 10년 간 부족한 저자에게 너무나도 많은 가르침을 주셨던 지도교수님이신 이 명식 선생님께 감사의 말씀을 올립니다. 그리고, 이 논문이 완성되는 동안 아낌없는 조언을 주신 유 형식 선생님, 장 진우 선생님, 손 영호 선생님, 유 영훈 선생님께도 감사의 말씀을 올립니다. 어렵고 힘든 검사를 진행하느라 수고해 준 신경과 의국원들과 참여해 주셨던 모든 환자분, 자원자 여러분들께 감사 드립니다. 끝으로 항상 곁에서 힘이 되어주신 부모님과 사랑하는 아내에게 감사의 말씀을 전하면서, 사랑하는 승헌이와 승윤이와 함께 기쁨을 나누고 싶습니다.

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Relationship between the striatal and cerebellar glucose metabolism on FDG PET study and the responsiveness to levodopa treatment in patients with multiple system atrophy

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Introduction: About two thirds of patients with MSA may not respond to levodopa treatment. Postmortem studies attributed such poor response to the striatal degeneration. Also, retrospective FDG PET study of the patients with MSA reported a relationship between the striatal glucose metabolism and the responsiveness to levodopa treatment. We prospectively investigated whether the metabolic activities of striatum or cerebellum are related with the levodopa responsiveness in patients with MSA. **Methods:** This study included 39 patients with MSA (MSA-P:MSA-C=24:15, 19 *de novo* and 20 treated, mean age=64.5±10.0years, mean duration of disease=29.6±16.0months). To evaluate the improvement before and after the levodopa treatment, UPDRS motor score and two sets of timed motor tests (first, two point tapping and stand-walk-sit test, and second, Purdue peg board test) were measured. After the quantitative FDG PET and baseline evaluation, treatment was started with 3 tablets of Sinemet® 25/250mg a day. Same clinical assessments were

performed monthly for three times. The metabolic activities of the caudate, anterior putamen, posterior putamen, cerebellar cortex and cerebellar vermis were measured and we compared the striatal or cerebellar glucose metabolic activity and the mean percentages of changes in the measurements of motor function. Also, using statistical parametric mapping (SPM2) analysis, we searched for the brain areas of which metabolism correlates with the clinical improvement. **Results:** Mean percentages of improvements of UPDRS motor scores were significantly correlated with the glucose metabolism of posterior putamen (Pearson's correlation; P=0.037, r=0.334) and cerebellar vermis (P=0.004, r=0.446) and the mean percentages of improvements of performance in Purdue peg board test showed significant correlation with the glucose metabolism of the cerebellar cortex (P=0.008, r=0.421) and the vermis (P=0.005, r=0.445). The statistical parametric mapping analysis showed that the cerebellar glucose metabolism was correlated with the improvement of UPDRS motor score and the performance of two timed motor tests. **Conclusion:** Although the present study showed inconsistent results in all timed motor tests, severity of damage to posterior putamen measured by the FDG PET scan may be a factor associated with the amount of levodopa response in patients with MSA. Interestingly, the integrity of cerebellum is an important factor associated with the improvement of motor function by the levodopa treatment.

Key Words: multiple system atrophy, levodopa, striatum, cerebellum, positron emission tomography

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Ⅰ. INTRODUCTION

Multiple system atrophy (MSA) is the second most common parkinsonian syndrome after the Parkinson's disease (PD). Its clinical features are characterized by a variable mixture of parkinsonism, cerebellar deficits, autonomic failure and pyramidal tract signs.[1]

In more than 90% of patients wih PD, good response to levodopa treatment could be maintained throughout their lives.[2, 3] Although patients with MSA may show clinical features indistinguishable from those with PD,[1] only 30% of patients with MSA respond to levodopa treatment.[4] Unfortunately, such favorable response does not last longer than about 3 years and only 10% of the patients with MSA enjoy the beneficial effect until they die.[4-6] Therefore, objective measurement of the amount of response to levodopa treatment may provide an important clue for the differential diagnosis between parkinsonian syndromes, and enable to avoid useless levodopa treatment. However, it is laborious to measure the amount of response to levodopa

treatment using objective scales.

Several postmortem studies of MSA attributed the unresponsiveness to the levodopa treatment to the degeneration of the striatal neurons.[7-11] However, they were retrospective studies and adopted report from patients or physician's impression for the evaluation of responsiveness to levodopa treatment.

In [^{11}C]-raclopride positron emission tomography (PET) studies, patients with MSA showed decreased striatal uptake in contrast to those with PD who had normal or increased striatal uptake.[12, 13] Striatal [^{11}C]-raclopride uptake was inversely correlated with the parkinsonian motor deficits like the postmortem study.[13] In patients with MSA, [^{18}F]-deoxyglucose PET (FDG PET) studies showed reduced glucose uptake at the posterodorsal putamen[12-15] but it did not correlate with the severity of parkinsonian motor deficits.[13] However, there was a correlation between the striatal glucose metabolism and the striatal [^{11}C]-raclopride uptake.[13] Besides, a FDG PET study showed positive correlation between the amount of striatal glucose metabolism and the response to levodopa treatment in patients with MSA.[16] Again, this study used patients' report, but not the objective scale for the evaluation of improvement of motor function.

To define the value of FDG PET studies for the prediction of responsiveness to levodopa treatment in patients with MSA, we studied the amount of striatal and cerebellar glucose metabolism and that of response to levodopa treatment using objective scales.

Ⅱ. MATERIALS AND METHODS

1. Included subjects

From June 2004 to December 2005, we enrolled the patients with MSA who fulfilled the fulfilled the Gilman's diagnostic criteria of probable MSA[17] except the item of levodopa responsiveness. We excluded the patient with high fasting glucose level resulted from unsatisfactorily controlled diabetes mellitus or previous cerebrovascular disease demonstrated on the brain magnetic resonance image (MRI) studies. We also excluded the patients who could not take levodopa because of the side effects such as vomiting. The present study included 39 patients with MSA and 16 age matched controls.

2. Clinical evaluation of the patients

A. The study design for clinical evaluation

Both scale for clinical disability and measurements of timed motor tests were performed before and after the administration of levodopa. In the patients who had been already taking the levodopa, the dopaminergic medications were withheld for 14 days and we performed the baseline evaluation. The levodopa effect was evaluated monthly for 3 times. After the baseline evaluation, all the patients were started with Sinemet® 25/250mg t.i.d. Post-levodopa clinical disability rating and timed motor tests were performed three hours after the morning dose of levodopa. If the unified Parkinson's disease rating scale (UPDRS) motor score at follow up did not improve comparing to that of the baseline measurement, the levodopa dosage was increased to Sinemet® 25/250mg q.i.d.[17]

B. The clinical disability rating and the timed motor tests

The clinical disability rating scores were measured using the UPDRS motor score and the international cerebellar ataxia rating score (ICARS).[18]

We performed two timed motor tests. First, we used a modification of the timed motor test (modified CAPIT test) shown in the Core Assessment Program for Intracerebral Transplantations (CAPIT) protocol.[19] We measured the time taken to finish touching two points separated by 20 cm apart with each hand and foot. Also, we measured the time required to stand up from a chair, walk 5 m, turn, walk back to the chair and sit (stand-walk-sit test). Another timed motor test, Purdue peg board test,[20] was performed in three different tasks. Patients were instructed to put the pins into the holes using each hand and with both hands. Also, the task assembling the pin, washer and collar were performed with both hands. The number of pins put in the holes within 30 or 60 seconds was counted and we considered the median as the baseline measurement. Each test was repeated five times and we considered the sum of the medians of each item as the measurement of each test.

After 3 months' follow up, we calculated the means of three clinical rating scores and measurements of timed motor tests evaluated at each visit. We considered the percentages of improvements of those clinical rating scores and timed motor tests as the index of clinical improvement comparing to the baseline measurements.

3. Quantitative brain FDG PET study

The subjects fasted overnight prior to the FDG PET scan. To minimize the environmental stimuli, all the procedures were performed in a quiet and dimly lit

room with the subject's eyes were open. 45 to 55 minutes after the injection of 0.14 mCi/kg of FDG through the antecubital vein, PET scan was performed using Allegro PET scanner (Phillips Medical Systems; gadolinium oxyorthosilicate crystals) for the acquisition of high resolution three dimensional PET images. After 1.5 minute of transmission, 17 minutes of emission and final 1.5 minute of transmission scans, 3D PET image was reconstructed using 3D-RAMLA (3D version of the row action maximum likelihood algorithm). The time course of [^{18}F]-radioactivity was obtained with repetitive sampling of radial arterial blood for 40 minutes after the administration of FDG prior to PET scan. Finally, three-dimensional parametric PET image representing absolute glucose metabolism was acquired using a software PMOD version 2.61 (PMOD technologies Ltd., Zurich, Switzerland) with FDG-autoradiography method[21] (lump constant=0.437, k_1=0.102, k_2=0.13, k_3=0.062, k_4=0.0068).

4. Analysis of local cerebral metabolic rate of glucose

A. Statistical parametric mapping (SPM)

We used SPM2 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) software[22] implemented to MATLAB 7.0 (MathWorks, Natick, MA) to statistically analyze the PET data and to find the brain areas correlating with the improvement of clinical rating scores and the timed motor tasks. The PET images were spatially normalized and smoothed with 10 mm of full width half maximum (FWHM). With simple correlation method in the SPM2, we searched significant brain regions.

B. Template volume of interest (VOI)

To minimize the examiner's error, we adopted the template VOI drawn in the Montreal Neurological Institute 152 (MNI152) template brain image. The cylindrical VOIs with 5 mm diameter were drawn at caudate, anterior putamen and posterior putamen and cylindrical VOIs with 7 mm diameter at cerebellar vermis, medial cerebellar cortex and lateral cerebellar cortex. A set of VOIs was overlaid on the spatially normalized individual PET image and the regional cerebral metabolic rate of glucose (rCMRglu) was calculated.

Ⅲ. RESULTS

1. Characteristics of subjects

The mean (±SD) age of 16 controls (60.8±4.1 years; range = 54 - 70 years) were not significantly different from that of 39 patients with MSA (64.5±10.0 years; range = 44 - 84 years) (independent t-test; $P>0.05$). The mean age of onset was 62.2±9.8 (range = 40 - 82) years and the mean of disease duration was 29.6±16.0 (range = 2 - 60) months. The predominant clinical feature was parkinsonism (MSA-P) in 24 patients and cerebellar deficits (MSA-C) in 15 patients. 19 patients had never been treated and the other 20 patients had been taking the dopaminergic medications. At the baseline, the mean UPDRS motor score was 26.1±9.6 (range = 4 - 44) and the mean ICARS was 26.3±14.5 (range = 4 - 63).

2. Improvement of clinical rating scores and timed motor tests

The effect of the levodopa was variable and parkinsonian deficits were worsened

in about half of the patients. The mean percentage of improvement of UPDRS motor score was 1.0±22.8 (ranged from -54.8 to 41.7) % and that of the ICARS was -4.3±37.0 (ranged from -158.3 to 74.4) %. There was significant correlation between the improvement of UPDRS motor score and ICARS (Pearson's correlation; r=0.542, P<0.001). The timed motor tests, modified CAPIT test and Purdue peg board test showed similar pattern of changes. The mean percentage of improvement of the measurements in the modified CAPIT test was 4.1±21.8 (ranged from -48.6 to 56.0) % and that of Purdue peg board test was 14.0±22.9 (ranged from -36.9 to 62.3) %. There was a significant correlation between the improvements of two timed motor tests (Pearson's correlation; r=0.662, P<0.001). The improvements of both timed motor tests also significantly correlated with that of the improvement of UPDRS motor score and the ICARS (Pearson's correlation; modified CAPIT test vs. UPDRS motor score: r=0.331, P=0.04; Purdue peg board test vs. UPDRS motor score: r=0.383, P=0.016; modified CAPIT test vs. ICARS: r=0.494, P=0.001; Purdue peg board test vs. ICARS: r=0.337, P=0. 036).

3. Comparison of rCMRglu of striatum and cerebellum between the patients with MSA and normal controls

The rCMRglu values of all measured VOIs of patients with MSA were significantly lower than those of controls. When we divide the patients with MSA into the MSA-P and MSA-C and compare each group with controls, both groups of patients showed significantly lower rCMRglu values in all VOIs than those of controls. (Figure 1, Table 1)

	MSA (n=39)	MSA-P (n=24)	MSA-C (n=15)	normal (n=16)
caudate	6.6 ± 1.0^{a}	6.5 ± 0.8^{a}	6.9 ± 1.3^{c}	7.9 ± 0.8
anterior putamen	7.6 ± 1.2^{a}	7.6 ± 1.0^{a}	7.6 ± 1.5^{b}	9.0 ± 0.9
posterior putamen	7.2 ± 1.5^{b}	7.4 ± 1.5^{c}	6.8 ± 1.5^{b}	8.2 ± 0.8
cerebellar cortex	4.6 ± 1.3^{a}	5.1 ± 1.2^{a}	3.8 ± 1.0^{a}	6.4 ± 0.7
cerebellar vermis	4.8 ± 1.1^{a}	5.2 ± 1.0^{c}	4.2 ± 1.1^{a}	5.9 ± 0.7

Table 1. Comparisons of the regional cerebral metabolic rate of glucose (mg/min/100g) of subgroups of MSA and normal controls. [independent t-test; a (P<0.001), b (P<0.01) and c (P<0.05)]

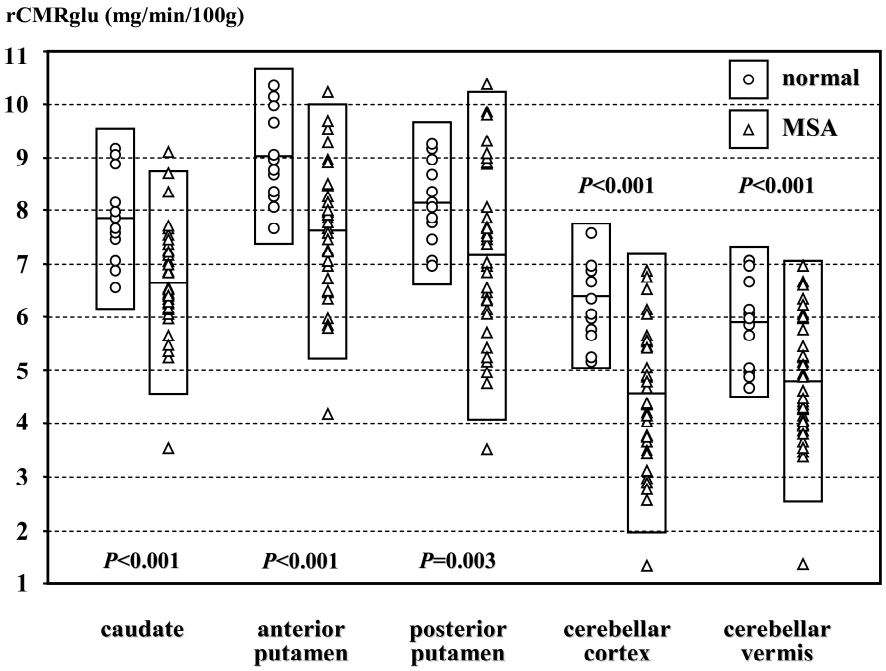

Figure 1. Scatter diagram of the regional cerebral metabolic rate of glucose (rCMRglu) of striatum and cerebellum. The independent t-test was applied for the comparison between MSA and controls. Upper and lower bounds of vertical bars indicate two standard deviations of rCMRglu values. The middle horizontal lines of vertical bars indicate the mean rCMRglu values.

4. Brain regions correlated with the clinical improvement analyzed with SPM2

The rCMRglu values of the cerebellar cortex and vermis showed correlation with the clinical improvement by the levodopa treatment. The improvement in Purdue peg board tests correlated with the cerebellar glucose metabolism (uncorrected $P<0.001$). However, there was no voxel of which rCMRglu values correlated with the improvement of UPDRS motor scores or the measurements of modified CAPIT tests when the level of significance was uncorrected $P<0.001$. Although it did not reach statistical significance, the cerebellar cortex and vermis also showed correlation with the improvements of both motor assessments when we adopted the level of significance at uncorrected $P<0.01$. (Figure 2)

5. Correlations between the clinical improvement and the rCMRglu of striatum and cerebellum analyzed with template VOIs

The percentages of improvements in UPDRS motor scores were significantly correlated with the glucose metabolism of posterior putamen (Pearson's correlation; $r=0.334$, $P=0.037$) and cerebellar vermis ($r=0.446$, $P=0.004$). The improvement in

Purdue peg board tests showed significant correlation with the glucose metabolism of cerebellar cortex (r=0.421, P=0.008) and vermis (r=0.445, P=0.005). However, the improvements of the modified CAPIT test showed no correlation with the striatal or cerebellar glucose metabolism. (Figure 3, Table 2)

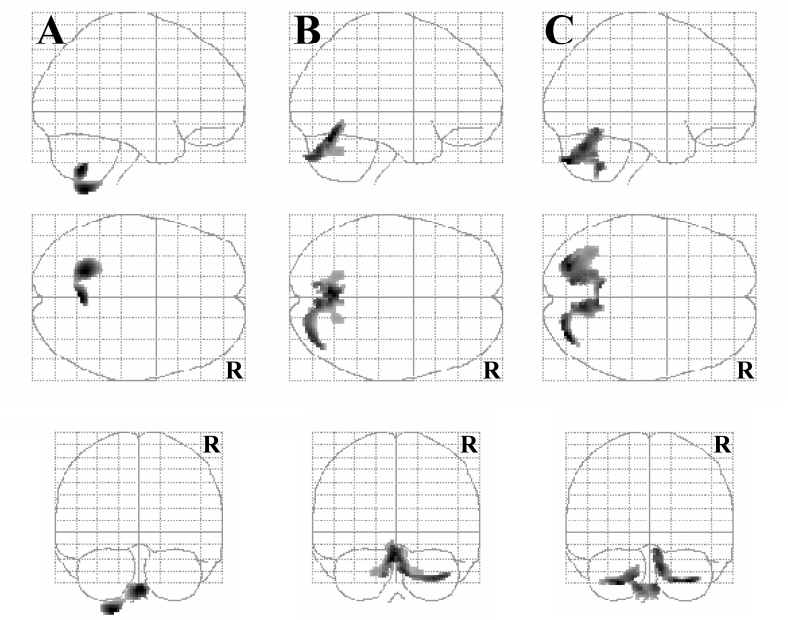

Figure 2. The brain regions showing significant correlation between the glucose metabolism and the degree of clinical improvement on SPM projection. A: improvement of UPDRS motor score (uncorrected P<0.01), B: improvement of the measurements of modified CAPIT test (uncorrected P<0.01), C: improvement of the measurements of Purdue peg board test (uncorrected P<0.001) Thresholded at the spatial extent of clusters above 100 voxels.

		caudate	anterior putamen	posterior putamen	cerebellar cortex	cerebellar vermis
UPDRS motor score	*r*	0.000	0.181	0.334	0.259	0.446
	P	0.999	0.271	**0.037**[c]	0.111	**0.004**[b]
modified CAPIT test	*r*	-0.053	0.008	0.067	0.156	0.260
	P	0.748	0.961	0.687	0.343	0.110
Purdue peg board test	*r*	-0.035	0.087	0.220	0.421	0.445
	P	0.831	0.598	0.178	**0.008**[b]	**0.005**[b]

Table 2. Correlation between the clinical improvement and rCMRglu of striatum and cerebellum. The Pearson's correlation was applied to the statistical analysis. The level of significance is labeled as b (P<0.01) and c (P<0.05). The r and P denote the Pearson's correlation coefficient and the P-value, respectively.

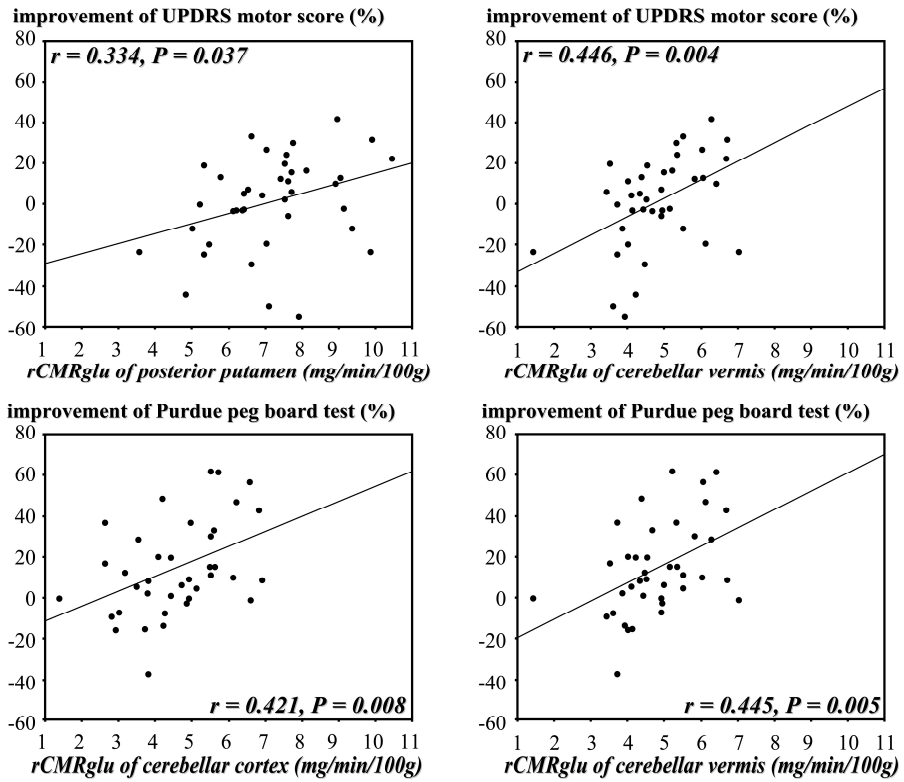

Figure 3. Scatter diagram showing the correlation between the improvement in UPDRS scores and Purdue peg board tests and the measurements of rCMRglu. The Pearson's correlation was applied for the statistical analysis.

Ⅳ. DISCUSSION

1. Striatal glucose metabolism and the responsiveness to levodopa

The akinesia of the parkinsonian rat model induced by administration of 6-hydroxydopamine responds to levodopa treatment. However, subsequent intrastriatal injection of quinolinic acid to destroy the striatal neurons ameliorates the beneficial effect of levodopa treatment.[23] Also, in non-human primate, rendered parkinsonism by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine responds to levodopa treatment. Whereas, subsequent chronic administration of 3-nitropropionic acid causes selective excitotoxic striatal lesion and abolishes levodopa responsiveness.[24] Those are the animal models mimicking the pathology of striatonigral degeneration (SND) with poor response to levodopa treatment.

In the retrospective clinicopathological studies of the patients with MSA, poor levodopa responsiveness has been attributed to the degeneration of the striatal dopaminergic neurons along with the progression of disease.[7-11] There have been several patients with MSA who showed levodopa induced dyskinesia and excellent response to levodopa treatment for up to 9 years. Such patients have only minimal striatal damage in postmortem pathological studies.[25-28] Therefore, the integrity of the postsynaptic striatal neuron is closely related to the responsiveness to the

levodopa treatment.

In accordance with the previous animal studies and clinicopathological reports, present study showed significant correlation between the improvement of UPDRS motor score and the rCMRglu of the VOI of posterior putamen. However, there were no significant correlations between the improvement in the timed motor tests and the striatal glucose metabolism. Also, the SPM analysis did not show significant striatal region of which rCMRglu correlated with the improvement of UPDRS motor score. The rCMRglu represents the activity of the local synapses rather than that of the neuronal cell body.[29] According to the multiple tracer study in the patients with MSA, the severity of parkinsonian motor deficits inversely correlated with the uptake of [^{18}F]-fluorodopa and the [^{11}C]-raclopride in putamen. Whereas, the FDG PET scan did not show the significant correlation between the striatal glucose metabolism and the degree of parkinsonian motor deficits.[13] It can be assumed that the FDG PET scan cannot correctly reflect the degeneration of striatal neurons and the progression of disease process in patients with MSA. This discrepancy might result in the inconsistent results of the correlation statistics of the present study. However, present study showed that the severity of damage to the posterior putamen on FDG PET scan may have a value in predicting the levodopa responsiveness in patients with MSA.

2. Cerebellar glucose metabolism and the responsiveness to levodopa

Previous clinicopathological reports focused on the degree of striatal pathology in terms of the levodopa responsiveness[7-11] and the involvement of cerebellum drew

less attention than that of striatum. In the present study, the glucose metabolism of cerebellum associated more closely with the clinical improvement after the levodopa treatment than that of striatum. One postmortem study reported that patients with MSA-P show moderate to good response to levodopa treatment more frequently than those with MSA-C. In patients with SND pathology, there was a tendency that the higher the pathological grade of the cerebellum more limits the response to levodopa treatment.[30]

The parkinsonian features were infrequently observed in patients with MSA-C accompanying the SND pathology and the cerebellar dysfunction may hide the underlying parkinsonian features.[30] Some parkinsonian signs can be reduced by the damage to the cerebellum as shown in a case with PD whose rigidity was abolished after the ipsilateral large cerebellar infarction.[31] Conversely, the patients with cerebellar deficits may show delayed initiation and execution of movement as those with basal ganglia damage.[32] In patients with MSA, the cerebellar dysfunction mask or worsen the parkinsonian bradykinesia. In such cases, the bradykinesia induced by cerebellar dysfunction remains unaffected by the levodopa treatment. Therefore, the amount of the improvement of parkinsonian motor deficits observed in MSA may be reduced by the cerebellar dysfunction.

More than 50% of MSA may have subclinical olivopontocerebellar atrophy pathology. The pathological changes in the cerebellum can be found in the patients without the clinical features of cerebellar dysfunction.[11, 33] Therefore, cerebellar dysfunction in MSA may aggravate parkinsonian deficits induced by a damage to

the substantia nigra and striatum, and reduced cerebellar glucose metabolism in FDG PET study can be one of the factors predicting the levodopa responsiveness.

Ⅴ. CONCLUSION

Although the present study showed inconsistent results in all timed motor tests, severity of damage to posterior putamen measured by the FDG PET scan may be a factor associated with the levodopa responsiveness in patients with MSA. The integrity of cerebellum is an important factor associated with the amount of improvement in motor function in patients with MSA.

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국문요약

다계통위축증 환자에서 레보도파 반응도와 FDG PET에 나타난 선조체 및 소뇌 포도당 대사량의 관계

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서론: 다계통위축증 환자의 약 3분의 2는 레보도파 치료에 호전되지 않는다. 이와 같이 레보도파에 대한 반응이 떨어지는 원인으로 사후 부검을 통해 선조체 변성과 관련 있음이 알려졌으며, FDG PET을 이용한 후향적 연구에서도 선조체 포도당 대사량과 레보도파 반응도에 상관관계가 있음이 보고되었다. 그러나, 지금까지의 연구는 레보도파에 대한 반응도를 객관적으로 측정하지 않았으며 모두 환자의 주관적인 보고에 의존한 후향적 연구였다. 이에 본 연구자 등은 다계통위축증 환자에서 선조체와 소뇌의 포도당 대사량이 레보도파 반응도와 관련이 있는지를 객관적인 측정치를 이용하여 전향적 방법으로 연구하였다.
방법: 39명의 다계통위축증 환자 (MSA-P : MSA-C = 24 : 15, 치료받지 않은 환자 : 치료받은 환자 = 19 : 20, 평균 연령 = 64.5±10.0세, 평균 질병이환기간 = 29.6±16.0개월)를 대상으로 하였다. 레보도파 치료 전과 후의 임상적 호전 정도를 알아보기 위해서 UPDRS 운동 점수와 두 가지의 운동능력 측정법 (① 손과 발을 이용한 두 점 왕복, 10 m 왕복, ② Purdue peg board 검사)을 사용하였다. 정량적 FDG PET 검사와 투약 전 운동능력 측정이 끝난 뒤 Sinemet® 25/250mg을 하루 세 번 복용하는 것으로 레보도파 투여를 시작했고, 3개월 동안 매 달 동일한 방법으로 운동능력을 측정하였다. 꼬리핵, 앞쪽 및 뒤쪽 조갑핵, 소뇌피질과

벌레엽의 포도당 대사량을 측정하여 임상적인 호전 정도와 관련이 있는지를 조사했고 statistical parametric mapping (SPM2) 분석법을 사용하여 임상적인 호전 정도와 관련이 있는 뇌 부위를 조사했다. **결과:** UPDRS 운동 점수의 호전 정도는 뒤쪽 조갑핵 (Pearson's correlation; P=0.037, r=0.334)과 소뇌벌레엽 (P=0.004, r=0.446)의 포도당 대사량과 상관관계가 있었고, Purdue peg board 검사의 호전 정도는 소뇌 피질 (P=0.008, r=0.421)과 소뇌벌레엽 (P=0.005, r=0.445)의 포도당 대사량과 상관관계가 있었다. SPM2 분석에서는 소뇌피질과 소뇌벌레엽의 포도당 대사량이 UPDRS 운동 점수와 두 가지 운동능력 측정치의 호전 정도와 상관관계를 나타냈다. **결론:** 본 연구에서는 모든 운동능력 측정 방법이 동일한 결과를 나타내지는 못 했지만, FDG PET으로 측정한 뒤쪽 조갑핵의 손상 정도가 다계통위축증 환자의 레보도파 반응도와 일부 관련 있었다. 그리고, 소뇌가 잘 유지 되어 있는 것이 레보도파 치료를 통하여 운동능력을 향상시키는 것에 중요한 인자가 됨을 알 수 있었다.

핵심되는 말: 다계통위축증, 레보도파, 선조체, 소뇌,
양전자방출 단층촬영