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Differentiating between multiple system atrophy and Parkinson's disease by positron emission tomography with ^{18}F-dopa and ^{18}F-FDG

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Both the striatal ^{18}F-dopa uptake and brain glucose metabolism were studied by PET with 6-L-[^{18}F]fluorodopa (FD) and [^{18}F]fluorodeoxyglucose (FDG) in 9 patients with multiple system atrophy (MSA) and 15 patients with idiopathic Parkinson's disease (PD). Five of the 9 MSA patients were diagnosed as having olivopontocerebellar atrophy, whereas 2 had striatonigral degeneration and 2 demonstrated Shy-Drager syndrome. The FD uptake ratios to the occipital cortex in the MSA patients at 120 min after the administration of FD were 2.07 ± 0.31 (mean ± SD) and 1.96 ± 0.29 in the caudate and the putamen, respectively, and decreased compared to those in the controls (2.72 ± 0.11, 2.71 ± 0.10). The same ratios in the PD patients were 2.07 ± 0.36 and 1.74 ± 0.24, respectively, which also decreased, but the decreased uptake in the putamen was more prominent. The caudate-putamen index (CPI) (%), which was calculated by a formula based on the difference in the uptakes in the caudate and putamen divided by the caudate uptake, indicated 5.6 ± 4.6 in the MSA patients and 14.8 ± 5.4 in the PD patients. The CPI for all PD patients was more than 7.0, which was the mean + 2SD for the controls, but the CPI for 3 MSA patients was more than 7.0 (accuracy: 88%). The glucose metabolic rates for each region in the PD patients showed no difference from the normal controls. The frontal and the temporal cortical glucose metabolism and the caudate, the putaminal, the cerebellar and the brainstem glucose metabolism in the MSA patients decreased significantly in comparison to those in the controls. But, as the glucose metabolic rates in such regions of each patient overlapped in the two groups, the accuracy of the FDG study for differentiation was lower than that of the FD study. The putaminal glucose metabolic rates, for example, in 3 PD patients were less than 6.8 (mg/min/100 m*l*), which was the mean – 2SD for the controls, while those in 3 MSA patients were more than 6.8 (accuracy: 75%). In addition, the combination of these two methods slightly improved the accuracy. The glucose metabolism is useful for evaluating the regional metabolic activity of the brain, and the FD study, which is specific to the dopamine system, seems to be more useful for differentiating between MSA and PD.

Key words: multiple system atrophy; Parkinson's disease; ^{18}F-dopa uptake; glucose metabolism

INTRODUCTION

MULTIPLE SYSTEM ATROPHY (MSA) is clinically characterized by a poorly L-dopa responsive akinetic-rigid syndrome, and includes striatonigral degeneration (SND), olivopontocerebellar atrophy (OPCA) and Shy-Drager syndrome (SDS) in its spectrum. Its pathology is distinct from idiopathic Parkinson's disease (PD), and demonstrates neuronal degeneration in the absense of inclusion bodies in the caudate and putamen, the substantia nigra, cerebellar Purkinje cells, inferior olives, and the intermediolateral columns of the spinal cord.[1,2] In spite of the clear pathological differences between MSA and PD,

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Table 1 Clinical features of the patients with multiple system atrophy (MSA)

	Case number								
	1	2	3	4	5	6	7	8	9
Clinical diagnosis[a]	OPCA	OPCA	OPCA	OPCA	OPCA	SND	SND	SDS	SDS
Age/Sex	63/F	37/M	58/F	44/F	30/M	74/F	48/M	57/M	57/F
Disease duration (y)	1	14	3	13	14	3	4	2	4
Clinical stage[b]	2	2	3	3	3	2	3	2	2
Dominantly affected side[c]	B	B	B	B	B	B	B	L	B
Tremor	0	0	+1	0	0	+1	0	+1	0
Rigidity	+1	+1	+2	+1	+3	+1	+3	+1	+1
Akinesia	+1	+1	+2	+1	+2	+1	+2	+1	+1
Dysarthria	+1	+1	+2	+2	+2	0	+1	+1	0
Cerebellar ataxia	+2	+2	+3	+3	+3	0	+1	+1	+1
Pyramidal sign	+1	+1	0	+1	0	0	0	+1	+1
Postural hypotension	0	0	0	0	0	0	0	+1	+1
Urinary incontinence	0	0	+1	0	0	0	0	0	+1
Decreased sweating	0	0	0	0	0	0	0	0	+1
Brainstem atrophy	+1	+2	+2	+2	+1	0	0	0	+1

[a]OPCA: olivopontocerebellar atrophy, SND: striatonigral degeneration, SDS: Shy-Drager syndrome. [b]from Hoehn and Yahr[35].
[c]R: right, L: left, B: bilateral. 0 = no, +1 = mild, +2 = moderate, +3 = severe

these akinetic-rigid syndromes can cause diagnostic difficulties in their early clinical stages.[3]

Positron emission tomography (PET) studies with [^{18}F]fluorodeoxyglucose (FDG) have demonstrated differences between MSA and PD cases. Striatal hypometabolism in cases of SND has been reported in comparison with the normal glucose metabolism in cases of PD.[4,5] We previously reported that the glucose metabolism decreased in the frontal, temporal and parietal cortices, as well as in the caudate and putamen, the cerebellum and the brainstem in patients with MSA, but it was preserved in patients with PD.[6] Nevertheless, it does not seem to be easy to differentiate the two akinetic-rigid syndromes based on the glucose metabolic values because of the relatively large inter-patient variations.[6] PET studies with 6-L-[^{18}F]fluorodopa (FD) also have been used to evaluate the nigrostriatal dopaminergic function, and it has also been reported that the FD uptake patterns of MSA and PD patients were different. The FD uptake decreased substantially in the putamen, but it was relatively spared in the caudate nucleus in patients with PD[7–11] in comparison with the homogeneously decreased FD uptake in the caudate and putamen in patients with MSA.[10] We previously reported that patients who were tentatively diagnosed as atypical parkinsonism including SND, SDS and pure akinesia also showed uniformly reduced FD uptakes in both the caudate and the putamen,[11] but it has yet to be elucidated which PET study with FD or FDG is more useful in differentiating these two akinetic-rigid syndromes.

In this study, we performed PET studies with both FD and FDG in patients with MSA or PD in order to evaluate which study appears to be more useful in differentiating between these two akinetic-rigid syndromes.

MATERIALS AND METHODS

Nine patients with MSA were studied. Five of them were diagnosed as having OPCA, while 2 had SND and 2 demonstrated SDS (Table 1). All patients had poorly or non-L-dopa-responsive akinetic-rigid syndrome. Five patients with OPCA were diagnosed based on a modification of Greenfield's classification[12] and were referred to as cases #6, #8, #9, #10 and #11 in our previous paper.[13] Two patients presented progressive limb rigidity and bradykinesia associated with an early impairment of balance and gait. Their clinical findings were compatible with SND.[14] They were also referred to as cases #12 and #15 in another previous paper.[11] The other two patients had autonomic failure and cerebellar ataxia. Their clinical findings were compatible with SDS.[1] Case 8 was described as case #13 in our previous paper.[11]

Fifteen patients with PD were also studied. All patients had L-dopa-responsive akinetic-rigid syndrome without any evidence of cerebellar ataxia, pyramidal sign, or autonomic failure (Table 2). They were referred to as cases #1, #2, #3, #4, #5, #6, #7, #8, #9, #11, #12, #13, #14, #16 and #17 in our previous paper.[15] None of the PD patients were demented.

Eight normal volunteers with a mean age of 50.1 (SD 13.8) years underwent FDG studies, and 8 normal volunteers with a mean age of 41.1 (SD 17.3) years underwent FD studies. None of the volunteers had any neurological deficits. Normal brain CT scans were obtained from volunteers over 50 years old.

PET was performed with the HEADTOME III (Shimadzu Corp., Japan) at a spatial resolution of 8.2 mm full width at half maximum (FWHM).[16] A transmission scan with a ^{68}Ge/^{68}Ga ring source was obtained for a correction of attenuation. Five slices were taken in the

Table 2 Clinical features of the patients with Parkinson's disease (PD)

	Case number														
	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Age/Sex	37/F	41/M	62/F	52/M	37/M	40/F	41/M	41/M	45/M	50/M	47/M	56/F	67/F	64/F	55/F
Disease duration (y)	5	2	3	4	6	3	3	8	12	6	1	2	7	14	29
Clinical stage[a]	1	1	1	1	1	1	1	2	2	2	3	3	3	3	3
Dominantly affected side[b]	L	R	R	R	R	L	R	B	L	B	L	B	B	B	B
Tremor	+1	+2	+1	+2	0	0	+1	+1	0	+1	+1	+1	+2	+1	+2
Rigidity	+1	+1	+1	+2	+1	+1	+2	+2	+2	+2	+3	+2	+2	+2	+3
Akinesia	+1	+1	+1	+1	+1	+1	+1	+1	+2	+1	+2	+2	+1	+1	+3
Dysarthria	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cerebellar ataxia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pyramidal sign	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Postural hypotension	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Urinary incontinence	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Decreased sweating	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Brainstem atrophy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

[a]from Hoehn and Yahr[35]. [b]R: right, L: left, B: bilateral. 0 = no, +1 = mild, +2 = moderate, +3 = severe

Table 3 The FD uptake ratios and the CPI in MSA, PD and the normal controls

	MSA (n = 9)	PD (n = 15)	Control (n = 8)
FD uptake ratio			
Caudate nucleus	2.07 ± 0.31[a]	2.07 ± 0.36[a]	2.72 ± 0.11
Putamen	1.96 ± 0.29[a]	1.74 ± 0.24[a]	2.71 ± 0.10
CPI	5.6 ± 4.6	14.8 ± 5.4[b]	2.3 ± 2.3

mean ± SD, [a]decreased from the control group, $p < 0.01$, [b]increased from the control group and MSA group, $p < 0.01$

orbitomeatal line (OM) + 2 cm, + 3.5 cm, + 5 cm, + 6.5 cm and + 8 cm planes by single scanning. The regions-of-interest (ROIs) were visually placed or outlined by referring to the MRI images as described previously.[11,17] The regions of the cerebellum and brainstem were placed in the OM + 2 cm plane, the region of the temporal cortex was placed in the OM + 3.5 cm plane, the regions of the frontal cortex and thalamus were placed in the OM + 5 cm plane, the region of the occipital cortex was placed in the OM + 6.5 cm plane, and the region of the parietal cortex was placed in the OM + 8 cm plane, respectively. The regions of the caudate nucleus and putamen were outlined in the OM + 5 cm plane on the glucose metabolic images and then transferred to the FD images.

The regional cerebral metabolic rate for glucose was measured with FDG. A single injection of 6.3 to 9.3 mCi (230 to 340 MBq) of [^{18}F]fluorodeoxyglucose was administered intravenously and arterial blood samples were obtained. The glucose metabolic rates were determined from the emission scan data obtained between 63 and 71 minutes post injection and blood curve data by using the model of Sokoloff et al.[18] and Phelps et al.[19] which was later modified by Brooks.[20]

The FD study was performed by a single injection of 2.9 to 6.4 mCi (110 to 240 MBq) of 6-L-[^{18}F]fluorodopa. The PET data were obtained between 112 and 127 minutes

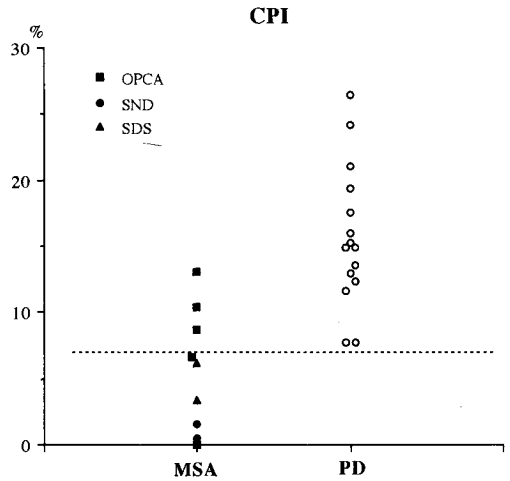

Fig. 1 The CPI in the patients with MSA (OPCA: ■, SND: ●, SDS: ▲) and those with PD (○). The dotted line represents the mean + 2SD for the controls.

post injection (with a mean time of 120 minutes post injection). The ratio of the caudate or the putamen to the occipital cortex at 120 minutes was evaluated, since we previously showed that the ratio method at 120 minutes was comparable to the graphical analysis for estimating the presynaptic dopaminergic function.[21] The caudate-putamen index (CPI) (%), which was calculated by a formula based on the difference in the uptakes of the caudate and putamen divided by the caudate uptake, was also evaluated.[15]

All subjects were examined with their eyes open during the PET studies. The glucose study and the FD study were performed with intervals of two to 23 days in each patient. All subjects received a full explanation of the diagnostic procedure and gave their informed consent.

The mean values for the bilateral side in all cases were evaluated for the glucose metabolism, since the values for

Table 4 The regional glucose metabolic rates in MSA, PD and the normal controls

	Region		
	MSA (n = 9)	PD (n = 15)	Control (n = 8)
Frontanl cortex	6.10 ± 1.30[b]	6.49 ± 0.91	7.34 ± 0.41
Temporal cortex	5.99 ± 1.02[b]	6.47 ± 0.76	7.13 ± 0.66
Parietal cortex	6.82 ± 0.98	6.75 ± 0.93	7.56 ± 0.60
Occipital cortex	6.25 ± 1.52	6.31 ± 0.79	6.80 ± 0.92
Caudate nucleus	6.15 ± 1.03[a,c]	7.27 ± 0.74	7.54 ± 0.42
Putamen	6.29 ± 0.68[a,c]	7.74 ± 0.86	7.65 ± 0.39
Thalamus	6.08 ± 1.06	6.60 ± 0.73	6.55 ± 0.95
Cerebellum	5.08 ± o.73[a,c]	6.66 ± 0.84	6.62 ± 0.71
Brainstem	3.67 ± 0.67[a,c]	4.80 ± 0.57	5.27 ± 0.64

mean ± SD (mg/min/100 m*l*), [a]regional value in the MSA group < control group, $p < 0.01$, [b]regional value in the MSA group < control group, $p < 0.05$, [c]regional value in the MSA group < PD group, $p < 0.01$

glucose metabolism did not decrease (or increase) in either the prominently affected side or the opposite side. On the other hand, since the FD uptake values on the opposite side of the brain for the prominently affected body side decreased more than on the other side, the contralateral brain side in the cases demonstrating asymmetry in their symptoms and the mean of the bilateral side in the other cases showing no asymmetry in their symptoms were evaluated for the FD uptakes. The statistical analyses were done by one factor ANOVA with the Newman-Keuls multiple comparison test. All PET studies were performed after clinical diagnosis, and no diagnostic changes were attributed to the PET results.

RESULTS

The ratios of caudate and the putaminal FD uptake to the occipital cortex in the patients with MSA and PD decreased in comparison to the normal controls (Table 3). The CPI in the patients with PD significantly increased in comparison to both the MSA patients and the controls. The CPI for all MSA and PD patients are shown in Fig. 1. The CPI for all PD patients were more than 7.0, which was the mean + 2SD for the controls and is shown as a dotted line in Fig. 1. If the patients with a CPI of less than 7.0 are classified as MSA cases and those with a CPI of more than 7.0 are classified as PD cases, then three MSA patients would thus have been misclassified, and the total accuracy would therefore be 88%.

The glucose metabolic rates for each region in the PD patients showed no difference from those for the normal controls. The frontal and temporal cortical glucose metabolic rates and the caudate, the putaminal, the cerebellar and the brainstem glucose metabolic rates in the MSA patients significantly decreased in comparison to the controls. In addition, the glucose metabolic rates in the caudate and putamen, the brainstem and the cerebellum in the patients with MSA were significantly decreased in

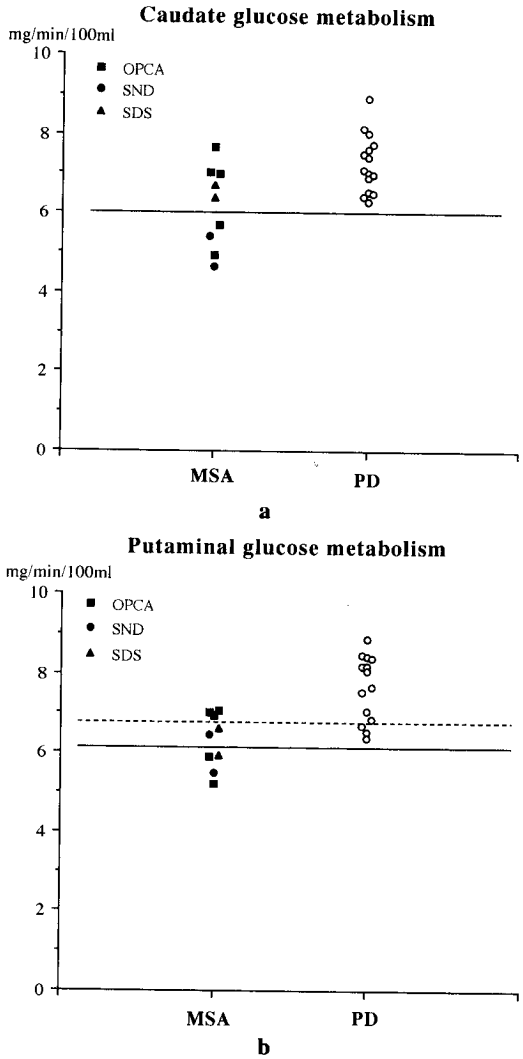

Fig. 2 The caudate (a) and the putaminal (b) glucose metabolism in the patients with MSA and those with PD. The solid lines represent at values of 6.0 (a) and 6.2 (b), respectively, which are lower than any values of PD. The dotted line represents the mean − 2SD for the controls (b).

comparison to the patients with PD (Table 4). Since the glucose metabolic rates in both the brainstem and the cerebellum seem to be mainly due to the atrophy of such regions,[6] the glucose metabolic rates in the caudate and the putamen thus seem to be more reliable for differentiating between MSA and PD. The glucose metabolic rates in the caudate and in the putamen for all the patients are shown in Figs. 2a and 2b, respectively. The glucose metabolic rates in the putamen in 3 MSA patients were more than 6.8 (mg/min/100 m*l*), which was the mean − 2SD for the controls and are shown as a dotted line in Fig. 2b, but the same rates in 3 PD patients were less than 6.8. If the two groups are thus classified on the basis of the 6.8 value, these 6 patients would be misclassified, and the total accuracy would be 77%. If the differentiation line between the two groups is placed at a value of 6.2, which is shown by the solid line in Fig. 2b, then 5 MSA patients

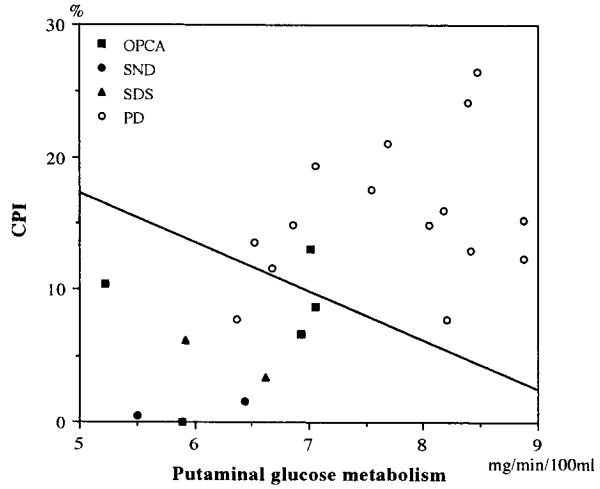

Fig. 3 Correlation between the CPI and the putaminal glucose metabolism in the patients with MSA and those with PD. The solid line is drawn to get the highest accuracy for differentiating between the two groups.

would be misclassified, and the total accuracy would be 79%. The caudate glucose metabolic rates for the patients in the two groups overlapped more closely than the putaminal glucose metabolism, and the total accuracy of the differentiation between the two groups was thus either the same or worse (Fig. 2a).

The correlation between the CPI and the putaminal glucose metabolism is plotted in Fig. 3. The patients in the two groups still overlapped, but if the differentiation line between the two groups is drawn as the solid line in Fig. 3, only one PD and one MSA patients would be misclassified, and then the total accuracy would be 92%.

DISCUSSION

MSA showed a homogeneously reduced FD uptake in the caudate and the putamen, but the reduced FD uptake in the putamen was more prominent than in the caudate in patients with PD in this study. These findings are consistent with previous PET reports[10,11] and the pathological findings showing that the dopaminergic neurons in the ventrolateral portion of the substantia nigra projecting to the putamen decreased more than the neurons in the dorsomedial portion of the substantia nigra projecting to the caudate nucleus in patients with PD.[22] FD studies can allow for the visualization of the capacity of dopamine storage in the caudate and putamen *in vivo*, and have been shown to correlate with both the dopamine cell counts in the substantia nigra and the dopamine levels in the caudate and putamen.[23] PET studies showed a more reduced FD uptake in the putamen than in the caudate in patients with PD, and this finding was compatible to the relatively preserved dopamine level in the caudate head in autopsy studies.[24–26] The greater cell loss of the substantia nigra in patients with SND than in patients with PD in autopsy studies[22] might have caused the homogeneously reduced FD uptake in the caudate and putamen in patients with SND, whereas the degree of cell loss was still relatively preserved in the dorsomedial portion of the substantia nigra which is connected to the caudate nucleus.[22]

In this study, the CPI seems to be able to differentiate between MSA and PD patients. All PD patients demonstrated a high CPI and only three MSA patients with a high CPI were misclassified and the total accuracy for the differentiation between the two groups was therefore 88%. The reason why the three MSA patients had a high CPI is uncertain, but since the three MSA patients with a high CPI were diagnosed as having OPCA and another OPCA patient also had a moderate CPI (6.70), it might thus have been due to the fact that they were patients with OPCA.

Decreased glucose metabolic rates were observed in the caudate and putamen, in the frontal and the temporal cortices, in the brainstem and in the cerebellum in the MSA patients in the present study. De Volder et al.[4] and Eidelberg et al.[5] also reported that glucose metabolism in the caudate and putamen was decreased in SND patients, which is consistent with neural loss and gliosis involving the striatum in histopathological examinations in SND.[14,27,28] The glucose metabolic rates for each region in the PD patients thus showed no difference in comparison to the normal controls. Since the frontal and the temporal cortical glucose metabolic rates in the PD patients slightly decreased compared to the controls, but the change was not statistically significant, the decreased glucose metabolic rates in only the caudate and putamen, the brainstem and the cerebellum in the patients with MSA were significantly different from the patients with PD. Moreover, as the glucose metabolic rates in the brainstem and in the cerebellum seem to mainly be due to the atrophy of such regions,[6] the glucose metabolic rates in the caudate and the putamen therefore seem to be more reliable for differentiating between MSA and PD. The glucose metabolic rates in the putamen in each patient of the two groups overlapped to such a degree that the accuracy of the putaminal glucose metabolic rates in differentiating between the two groups was lower than that obtained with the CPI.

Although critics may say that the clinical stages of PD patients were lower than those of MSA patients in this study, the CPI was not correlated with the clinical stage in the previous paper[15] and MSA patients with higher clinical stages would show more decreased metabolism[4,5] than PD patients with lower clinical stages, so that differentiation between the two groups by means of glucose metabolism should be easier, but a future study with a greater number of patients is still called for. The age range of the patients in this study was relatively large. The patient's age, however, does not seem to affect the results, since the FD uptake was reported no decline with age[29] and the cerebral glucose metabolism was also reported no decline in the carefully screened healthy subjects.[30,31]

Striatal receptor binding studies for differentiating between SND and PD have also been reported[32–34] and some of them may possibly be even more sensitive tools, but such studies have so far only been performed at a small number of institutes.

In conclusion, our findings suggest that glucose metabolism is useful for evaluating the regional total metabolic activity of the brain, but the FD study, which is specific to the dopamine system, seems to be more useful for differentiating between MSA and PD. In addition, the combination of these two methods may also potentially improve the overall accuracy.

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