Table 2 Clinical Charasteristics of the PD patients

Symptom duration, year	6.0 ± 4.4
More affected side	Right 55/Left 46
Hoehn-Yahr stage, on	2.4 ± 0.9
Hoehn-Yahr stage, off	3.3 ± 1.1
UPDRS score	
Total motor	30.3 ± 16
Bradykinesia	9.86 ± 6.3
Rigidity	6.15 ± 3.8
Axial	9.54 ± 6.2
Tremor	4.80 ± 4.0

UPDRS, Unified Parkinson's Disease Rating Scale.
Data are given as mean ± standard deviation (SD) values.

years (SD 11.1), respectively. A wide range of duration and severity of symptoms was represented among the patients. The mean duration of symptoms was 6.0 years (SD 4.4) and the mean UPDRS motor score was 30.3 (SD 16.0). The right side was more affected in 55 patients.

Subregional analysis of FMT uptake

Figure 1 shows representative images of FMT uptake in a normal subject and in early- and late-stage PD patients. Among the patients, FMT uptake showed the most marked decrease in the posterior putamen, regardless of disease duration, but significant decrease was seen throughout the striatum compared with the healthy controls. There were significant differences between side (ipsi- vs. contralateral to the more affected limbs), region (anterior vs. posterior putamen), and diagnosis (healthy subjects vs. PD group) ($P < 0.001$) (Figure 2a). Asymmetry between the striatum of the more and less affected sides is preserved, but shows a decrease with disease progression (Figure 2b).

Decline in FMT uptake with disease duration

Figure 3 shows scatterplots of FMT uptake against symptom duration in three regions of the putamen contralateral to the more affected limbs. Because age-related factors such as age at onset of symptoms and age-related Alzheimer-type pathology may influence disease duration, we excluded elderly-onset patients (> 70 years old; $n = 19$) in this analysis. Exponential regression curves that best fitted the data for each of the three regions analyzed are superimposed on the figure. Between 10 and 15 years of symptom duration, the FMT for all three curves leveled off to constant values that showed a statistically significant difference between the anterior and posterior putamen ($p < 0.001$). In the control group, there was no significant difference in SCR of FMT uptake between younger (< 59 years old, $n = 10$) and older (≥ 60 years old, $n = 9$) subjects (putamen, $p = 0.87$; caudate, $p = 0.81$).

Correlation of cardinal symptoms and FMT uptake

To minimize the possibility of including patients with alternative diagnoses, we analyzed patients who had cardinal motor symptoms for at least 3 years ($n = 42$). We obtained positive correlations between the severities of major motor symptoms: rigidity vs. axial symptoms ($r = 0.68$, $p < 0.001$), rigidity vs. bradykinesia ($r = 0.56$, $p < 0.001$), bradykinesia vs. postural instability ($r = 0.54$, $p < 0.001$), and tremor vs. bradykinesia ($r = 0.39$, $p = 0.014$). However, tremor did not have a significant relation with rigidity ($r = 0.20$, $p = 0.20$) or with axial symptoms ($r =$

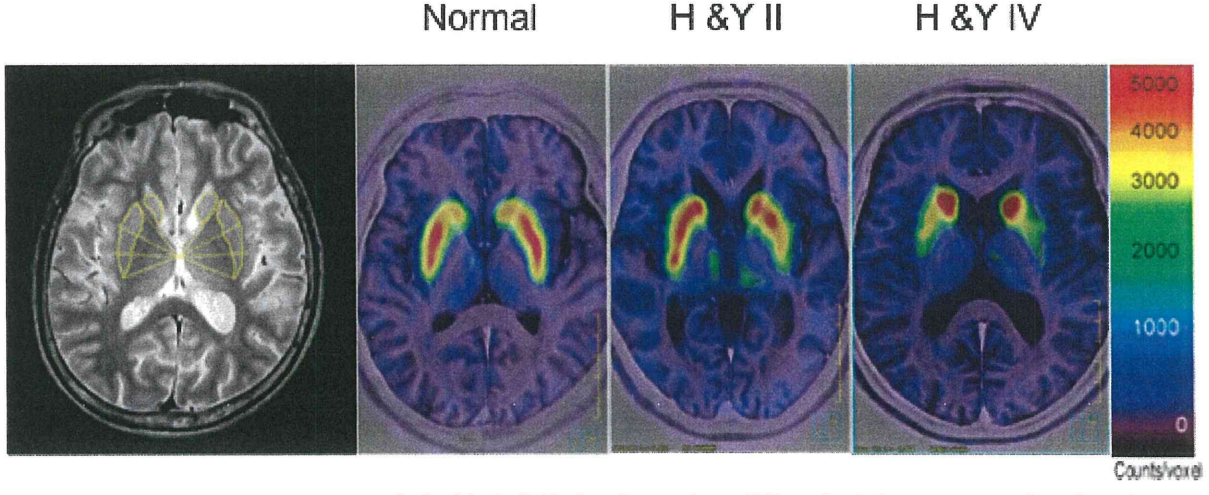

Figure 1 Representative FMT-PET images of a healthy individual and PD patients. FMT uptake declines asymmetrically in the early stages, mostly in the posterior putamen. Left: Regions-of-interest in the putamen. H &Y, Hohen and Yahr stage. The bar indicates the range of radioactive counts per voxel.

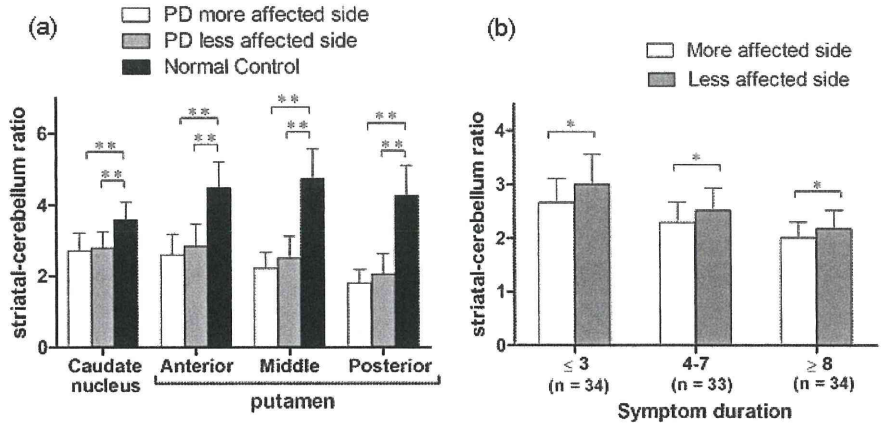

Figure 2 FMT uptake in different subregions of the striatum. Mean FMT uptake in different subregions of the striatum in normal control and PD patients (a). Comparison by side (b) shows persistant side-side asymmetry of putaminal uptake throughout the disease course. *$P < 0.05$, ** $P < 0.01$.

0.12, $p = 0.45$). Axial symptoms, rigidity, and bradykinesia scores showed a correlation with FMT uptake in the contralateral putamen, with the highest correlation in the anterior putamen, but not in the contralateral caudate (Table 3). No significant correlation was evident between unilateral tremor scores from the most severely affected limbs and any of the striatal regions. To assess the potential influence of age, we analyzed older patients (> 60 years old; $n = 25$) separately and found similar correlations between major symptoms and FMT uptake (Table 4).

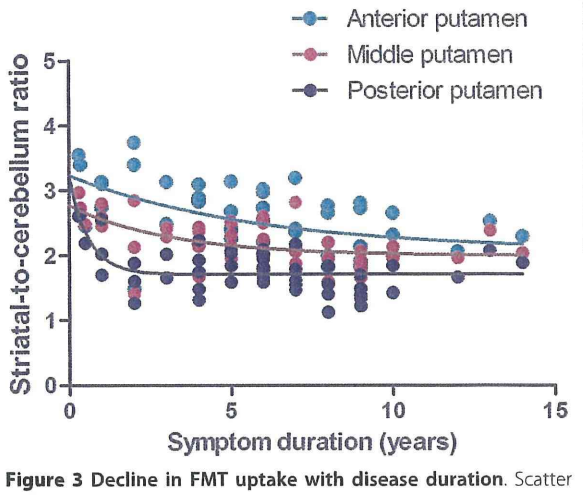

Figure 3 Decline in FMT uptake with disease duration. Scatter plots of FMT uptake against symptom duration in the putamen contralateral to the more affected limb in PD patients. Exponential decline is observed in all subregions of the putamen. Reduction of uptake is prominent at onset of the disease.

Discussion

Idiopathic PD is defined as a synucleinopathy in which Lewy bodies, pathological aggregations of the synaptic protein α-synuclein, are found in the dopaminergic neurons in the substantia nigra [14,15]. A reduction of dopamine in the striatum is a consistent finding in PD, although the clinical features are heterogeneous and include different predominant symptoms (resting tremor, bradykinesia, rigidity, or postural instability and gait disorder) with different rates of progression, and with or without dementia [16-19]. PET imaging is a valuable tool for assessing altered dopaminergic function in the striatum in PD. While FDOPA is suitable for assessing the metabolism of levodopa, FMT is superior for estimating AADC activity because it enables the production of higher-quality brain images [7,20-22]. The high resolution of FMT-PET images enables analysis of

Table 3 Correlations of UPDRS scores and FMT uptake ratio values in the each part of the putamen

Putamen	Anterior	Middle	Posterior	Whole
Symptom duration, year	-0.52 (<0.001)	-0.56 (<0.001)	-0.51 (<0.001)	-0.58 (<0.001)
Total motor score	-0.56 (<0.001)	-0.48 (0.002)	-0.41 (0.008)	-0.51 (0.001)
Bradykinesia	-0.54 (<0.001)	-0.53 (<0.001)	-0.44 (0.005)	-0.55 (<0.001)
Rigidity	-0.50 (0.001)	-0.43 (0.006)	-0.37 (0.018)	-0.44 (0.005)
Axial	-0.60 (<0.001)	-0.51 (0.001)	-0.37 (0.016)	-0.50 (0.001)
Tremor	0.069 (0.658)	0.085 (0.587)	0.015 (0.925)	0.050 (0.747)

Data are given as r (p) values. These values were calculated by Spearman's rank correlation coefficient test. UPDRS motor score in off-medication state was evaluated in 42 subjects.

Table 4 Correlations of UPDRS scores and FMT uptake ratio values in the each part of the putamen in elder patients

Putamen	Anterior	Middle	Posterior	Whole
Symptom duration, year	-0.70 (<0.001)	-0.63 (<0.005)	-0.45 (<0.05)	-0.70 (<0.001)
Total motor score	-0.56 (<0.01)	-0.50 (<0.05)	-0.37 (0.07)	-0.49 (<0.05)
Bradykinesia	-0.46 (<0.05)	-0.46 (<0.05)	-0.34(0.08)	-0.46 (<0.05)
Rigidity	-0.46 (<0.05)	-0.39 (0.05)	-0.31 (0.12)	-0.37 (0.06)
Axial	-0.69 (<0.001)	-0.59 (<0.01)	-0.45 (<0.05)	-0.58 (<0.01)
Tremor	0.26 (0.21)	0.12 (0.58)	0.06 (0.77)	0.14 (0.51)

Data are given as *r* (*p*) values. These values were calculated by Spearman's rank correlation coefficient test. UPDRS motor score in off-medication state was evaluated in 25 subjects.

dopaminergic presynaptic changes in each subregion of the striatum.

In the present study, FMT uptake in PD was reduced in the putamen, particularly in the posterior part. The anterior-to-posterior gradient of the uptake decrease in the putamen persisted to the advanced stage of PD. These results are consistent with those of previous reports that used other tracers of presynaptic dopaminergic terminals, and are considered to reflect the selective degeneration of nigrostriatal pathways that project into the posterior part of the putamen [23-25]. The lowest value of FMT uptake was observed in the posterior part of the putamen contralateral to the more affected limbs, even in the early stage of the disease. Because we analyzed regions in the posterior one-third of the putamen on high-resolution images, it is unlikely that the decreases in uptake were caused by partial volume effects, which may arise from placement of a small ROI on inaccurately co-registered images.

Post-mortem investigations of PD demonstrate that the rate of decrease of nigral neurons is rapid in the initial stage of the disease: approximately 40%-50% are lost in the first decade, possibly with a slower rate of degeneration later on, to finally approach a normal age-related linear decline [26]. In the present study, loss of FMT was well fitted to symptom duration using a single exponential approximation. The exponential model provided a better fit than a linear model, indicating that the rate of decline in FMT uptake in the contralateral putamen was faster at the beginning of the disease and slowed down as the disease progressed, in agreement with the results of previous studies that used radiotracers for imaging nigrostriatal nerve terminals [23-25]. Because we performed cross-sectional analysis in the present study, and because all of the participants were on medication, the data do not provide accurate information regarding the natural course of the disease, even if PET measurements were taken in off-medication state. Even so, the present data are important for assessing the progression of dopaminergic hypofunction in the striatum under optimal medical treatment, and can provide the basis for the development of even better therapeutic strategies [27,28].

We applied striatal count ratios to analyze the relationships between subregional putaminal FMT uptake and clinical symptoms. Striatal count ratios using the cerebellum as the denominator have a strong correlation with striatal uptake constants (Ki values) [29,30]. The present FMT-PET study showed a significant correlation between cardinal motor symptoms (rigidity, bradykinesia, and axial symptoms) and uptake of the tracer in the putamen, and no significant correlation was found between tremor score and FMT uptake. These findings are consistent with the results of previous PET studies [31-33]. The clinical correlations were more significant in the anterior part of the putamen than in the posterior part, possibly reflecting a floor effect for the uptake of FMT in the posterior part of the putamen, where the decrease was severe even in the early stage of the disease.

The pathophysiological mechanism of tremor is not fully understood [34]. Tremor does not respond to L-dopa as well as do bradykinesia and rigidity. The fact that stereotactic lesion or deep brain stimulation of the ventral intermediate nucleus (Vim) of the thalamus successfully improves tremor indicates a strong association between non-dopaminergic thalamic and cerebellar systems, and tremor generation [35,36].

Conclusions

Our results indicate that FMT-PET is useful for evaluating PD patients from the early stage of the disease and for studying the relationship between AADC activity and various clinical features. Decrease of FMT uptake in the posterior putamen appears to be most sensitive in mild PD, and uptake in the anterior putamen may reflect the severity of main motor symptoms, except for tremor. These data provide an important baseline for evaluating the effects of surgical interventions, such as gene therapy for PD.

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Authors' contributions

SA participated in designing the study, data collection, conducted the statistical analyses, interpreted data and drafted the first manuscript.
KF participated in data collection and interpretation of data.
AM participated in data collection and interpretation of data.
TS participated in data collection and interpretation of data.
IN participated in designing the study and interpretation of data.
SM conceived the study, participated in its design, data collection, interpretation of data and drafting the manuscript.
All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Brief Communication

Preclinical substantia nigra dysfunction in rapid eye movement sleep behaviour disorder

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ABSTRACT

Objectives: Transcranial sonography (TCS) has been shown to reveal hyperechogenicity of the substantia nigra (SN) in people with Parkinson's disease and in approximately 10% of healthy subjects. It is hypothesized that SN hyperechogenicity in healthy subjects and patients with idiopathic rapid eye movement (REM) sleep behaviour disorder (iRBD) patients is a marker of vulnerability for Parkinson's disease.
Methods: TCS and positron emission tomography (PET) with 6-[^{18}F] fluoro-meta-tyrosine (FMT), which can assess the level of the presynaptic dopaminergic nerve, were performed in 19 male patients with iRBD, mean age 66.4 (standard deviation [SD] 4.9) years, to assess nigrostriatal function.
Results: Nine patients had pathological SN hyperechogenicity (mean age 66.8 [SD 3.9] years; 0.31 [SD 0.12] cm^2) and 10 patients did not have SN hyperechogenicity (mean age 66.0 [SD 5.8] years; 0.11 [SD 0.06] cm^2). FMT uptake at the putamen and caudate was significantly lower in iRBD patients with pathological SN hyperechogenicity compared with those without SN hyperechogenicity. However, no correlation was found between SN echogenicity and FMT uptake. This is in conflict with previous findings which showed that subjects with hyperechogenicity had lower FMT uptake in the striatum.
Conclusion: Pathological hyperechogenic alterations in the SN in patients with iRBD may suggest the existence of preclinical SN dysfunction as determined by FMT-PET.
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1. Introduction

Rapid eye movement (REM) sleep behaviour disorder (RBD) is a parasomnia characterised by dream-enacting behaviours, unpleasant dreams and lack of muscle atonia during REM sleep. RBD may be idiopathic or related to neurological disease [1]. Patients with idiopathic RBD (iRBD) have been reported to be at increased risk for developing Parkinson's disease (PD) [2]. Transcranial sonography (TCS) has been shown to reveal hyperechogenicity of the substantia nigra (SN) in patients with PD and in approximately 10% of healthy subjects, and has been suggested as a risk marker for PD in non-Parkinsonian subjects [3]. However, Berg et al. reported that SN hyperechogenicity in the elderly is non-specific and of limited usefulness in predicting an individual's risk for PD [4]. Recently, two case-control studies [5,6] showed that pathological SN hyperechogenicity was significantly more common in patients with iRBD compared to control subjects. iRBD is regarded as one of the non-motor symptoms of PD, and precedes motor symptoms. Schenck et al. identified the development of Parkinsonism in 11 of 29 men initially diagnosed with iRBD [7]. It is hypothesized that SN hyperechogenicity in healthy subjects and patients with iRBD is a vulnerability marker for PD. Although there is strong evidence that the echo originates from increased local iron content, the exact pathophysiological mechanisms for SN hyperechogenicity are not completely understood.

In order to verify the hypothesis that hyperechogenic alterations in the SN may be suggestive of preclinical nigrostriatal dopaminergic dysfunction for patients with iRBD, this study evaluated the presynaptic dopaminergic function in the striatum using 6-[^{18}F] fluoro-meta-tyrosine (FMT) positron emission tomography (PET).

2. Methods

This study was performed in accordance with the Declaration of Helsinki. Procedures were approved by the Ethics Review Committee of Dokkyo Medical University, and informed consent was obtained from each subject. TCS and 6-[^{18}F]FMT PET were performed in 19 males with iRBD confirmed by polysomnography.

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The mean age of subjects was 66.4 (standard deviation [SD] 4.9) years, the mean estimated duration of RBD was 3.5 (SD 1.8) years, the mean score on the Mini-Mental State Examination (MMSE) was 28.4 (SD 2.0), and the mean score on the Unified Parkinson's Disease Rating Scale (UPDRS) part III was 0.9 (SD 1) (range 0–3). Subjects were recruited from a sleep disorders clinic at Dokkyo Medical University Hospital between July 2008 and 2010. All had a history of recurrent dream-enacting behaviours, and RBD was diagnosed according to the International Classification of Sleep Disorders, second edition [8].

2.1. 6-[^{18}F] Fluoro-meta-tyrosine positron emission tomography

The PET radiotracer FMT is a substrate of the dopamine-synthesizing enzyme. Most FMT signals result from tracer that has been metabolized by aromatic amino acid decarboxylase (AADC) and monoamine oxidase-A, and is trapped in axon terminals as 6-fluoro-m-hydrophenylacetic acid without being released or further processed. FMT signals represent the extent of AADC activity more fully [9,10].

For 6-[^{18}F]FMT PET, the subject was placed on the scanner bed in a GEMINI-TF64 (Philips, Amsterdam, The Netherlands) in the supine position. 6-[^{18}F]FMT (weight × 0.12 mCi) was injected intravenously using a syringe pump. Carbidopa pretreatment was used (weight × 2.5 mg). A 10-min static scan was obtained 80 min following injection of 6-[^{18}F]FMT. 6-[^{18}F]FMT PET and magnetic resonance imaging (MRI) scans were fused using a Putamen Analyzer (WebNet Technology, Nasushiobara, Japan). Regions of interest were placed manually at the perimeters of the right/left putamen, caudate and cerebellum in MRI scans of the same subjects. Right/left putamen:cerebellum (putamen) or caudate:cerebellum (caudate) ratios of 6-[^{18}F]FMT-derived radioactivity were estimated. The sizes of the regions of interest were not fixed. Tissue concentrations of 6-[^{18}F]FMT-derived radioactivity (in mCi/cc) were adjusted for the dose per unit of body mass and expressed in units of mCi-kg/cc-mCi (Fig. 1A and B).

2.2. Transcranial sonography

TCS was performed using a conventional transcranial Doppler sonograph equipped with a 2.5-MHz phased-array transducer as described previously [5]. Hyperechogenic areas on both sides were analysed separately. To compare areas of echogenicity and the frequency of hyperechogenicity, the side of the midbrain (right or left) with the greater area of SN echogenicity in each subject was used for these statistical comparisons. Planimetric quantification of the areas of increased echogenicity was done on both sides of the SN independently (Fig. 1C and D). In accordance with previously reported cut-off values, areas of echogenicity <0.20 cm^2 were classified as normal, and areas of echogenicity ⩾0.20 cm^2 were classified as pathological [3].

The mean interval between performance of TCS and FMT-PET was 126.6 (SD 174.8) days. TCS is performed routinely to assess preclinical condition at the study institute. Berg et al. reported that the echogenic area of the SN did not change in the course of PD during a 5-year follow-up study [11]. Therefore, the interval between the performance of TCS and FMT-PET cannot be considered to influence the results.

Clinical examinations, including the MMSE and UPDRS, FMT-PET and TCS were performed independently by physicians who were blinded to the results of other examinations.

2.3. Statistical analysis

Values are expressed as mean (SD). p-values were determined using the Mann–Whitney U-test. A p-value <0.05 was taken to indicate statistical significance. A statistical comparison of factors such as age of patients, MMSE score, UPDRS part III score and 6-[^{18}F]FMT uptake was performed between the groups of patients with iRBD based on the presence or absence of pathological SN hyperechogenicity. The Spearman's correlation coefficient was used for analysis of the correlation between the echogenic area of the SN and the degree of 6-[^{18}F]FMT uptake.

3. Results

Demographic and clinical data on patients with iRBD are summarized in Table 1. Nine of the patients with iRBD had pathological SN hyperechogenicity (mean 0.31 [SD 0.12] cm^2) and 10 did not have SN hyperechogenicity (mean 0.11 [SD 0.06] cm^2). Therefore, the 19 patients were divided into two groups: those with and those without SN hyperechogenicity. Age distributions, MMSE scores, and UPDRS part III scores did not differ significantly between the groups. Evaluation of motor activity using the UPDRS part III score ranged from zero to three points, which did not fulfill the diagnostic criteria for probable PD. Compared with the patients without SN hyperechogenicity, the patients with SN hyperechogenicity had significantly lower uptake of 6-[^{18}F]FMT in the putamen (mean 4.40 [SD 0.83] and 3.22 [SD 0.98], respectively; $p = 0.027$) and the caudate (mean 3.69 [SD 0.42] and 2.86 [SD 0.82], respectively; $p = 0.014$) (Table 1). However, the echogenic area of the SN did not correlate with the degree of 6-[^{18}F]FMT uptake in the putamen ($r = -0.4465$, $p = 0.0553$) or the caudate ($r = -0.4007$, $p = 0.0891$). In addition, the UPDRS part III scores did not correlate with the degree of 6-[^{18}F]FMT uptake in the putamen ($r = -0.240$, $p = 0.323$), the caudate ($r = -0.040$, $p = 0.871$), or the echogenic area of the SN ($r = -0.216$, $p = 0.375$).

4. Discussion

Unger et al. [12] identified a significant association between midbrain hyperechogenicity and iRBD, and reported that two out of five iRBD patients with SN hyperechogenicity had unremarkable findings by presynaptic dopamine transporter imaging with fluoropropyl-carbomethoxy-iodophenyl-tropane (FP-CIT) single-photon emission computed tomography (SPECT). Iranzo et al. [13] recently reported that ^{123}I-FP-CIT striatal binding did not correlate with the extent of SN echogenicity in patients with iRBD. In the present study, FMT uptake in the putamen and caudate was significantly lower in iRBD patients with pathological SN hyperechogenicity than in those without SN hyperechogenicity. In contrast to the present results, Iranzo et al. [13] found that patients with SN hyperechogenicity did not have lower tracer uptake compared with patients without SN hyperechogenicity and they did not find a correlation between SN size and tracer uptake.

Booij et al. [14] reported that motor signs of PD started when the decrease in the percentage of ^{123}I-FP-CIT binding ratios in the putamen was 46–64% using age-corrected data. Spiegel et al. [15] and Doepp et al. [16] reported a lack of correlation between SN echogenicity and striatal FP-CIT uptake in patients with PD. Spiegel et al. [15] hypothesized that the pathogenic substrate of SN hyperechogenicity is different from that associated with degeneration of dopaminergic SN projection neurons. Berg et al. [11] failed to find evidence of an increase in the size of the echogenic SN area in a 5-year longitudinal study on PD patients with substantial progression of motor symptoms.

On the other hand, Weise et al. [17] reported a significant correlation between the extension of the echogenic SN area and striatal β-CIT binding. They discussed the possibility that the extension of SN echogenicity may be a consequence of degeneration of dopaminergic neurons in the SN, rather than an independent and

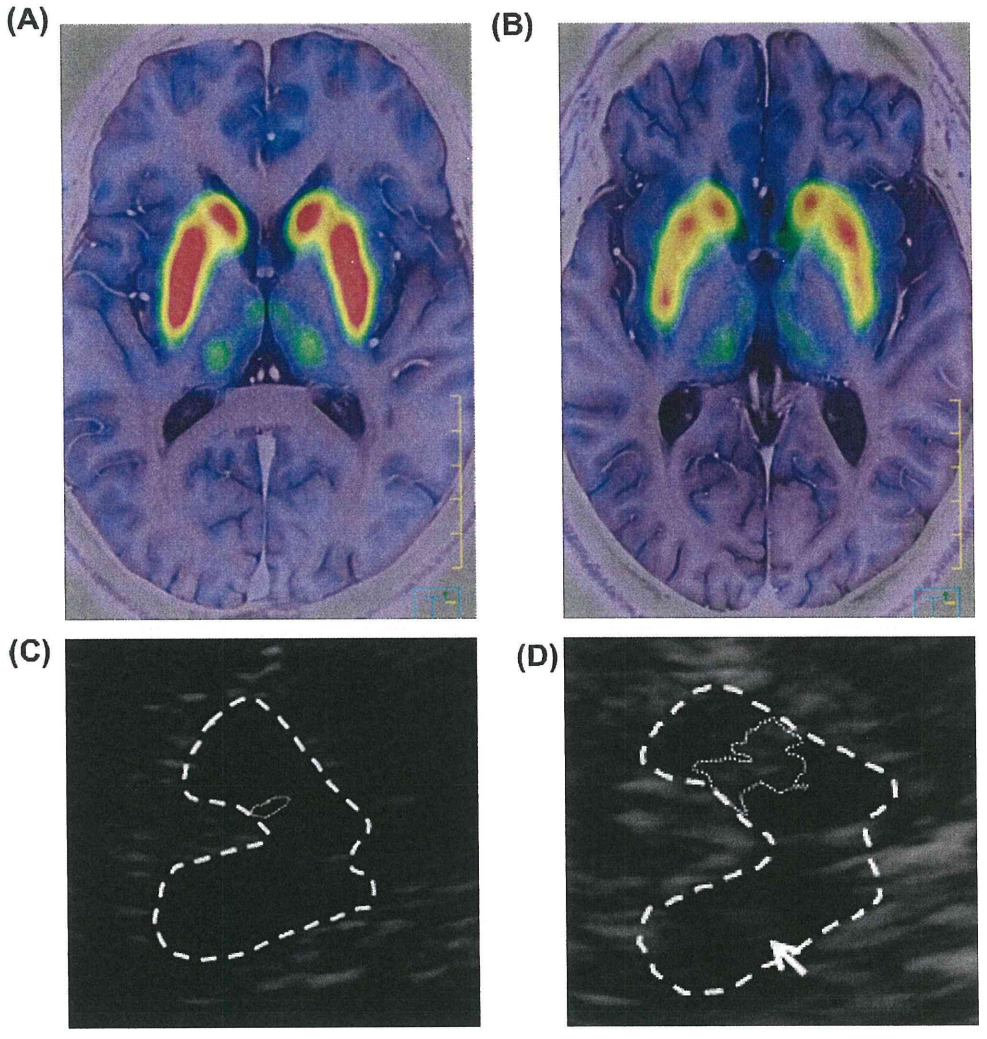

Fig. 1. (A) 6-[^{18}F] Fluoro-meta-tyrosine positron emission tomography (6-[^{18}F]FMT PET) on magnetic resonance imaging (MRI). This demonstrates preserved dopamine terminals in the caudate and putamen in a healthy subject. (B) 6-[^{18}F]FMT PET on MRI. This demonstrates patchy decreased dopamine terminals in the caudate and putamen in a patient with idiopathic rapid eye movement sleep behaviour disorder (iRBD). (C) Transcranial sonography (TCS) of bilateral substantia nigra (SN) hyperechogenicity in a healthy subject. The area of hyperechogenic SN signal within the hypo-echogenic crus cerebri is encircled on the ipsilateral side for planimetric measurement (0.10 cm^2). (D) TCS of bilateral SN hyperechogenicity in a patient with iRBD. The area of the hyperechogenic SN signal within the hypo-echogenic crus cerebri is encircled on the ipsilateral side for planimetric measurement (0.44 cm^2).

Table 1
Area of hyperechogenic substantia nigra (SN) signals in two groups of patients with idiopathic rapid eye movement sleep behaviour disorder (n = 19).

	SN hyperechogenicity*		p-Value
	Normal (<0.20 cm^2) (n = 10)	Pathological (⩾0.20 cm^2) (n = 9)	
Age (years), mean (SD)	66.0 (5.8)	66.8 (3.9)	0.623
Range, years	58–77	62–72	N/A
Sex, male/female	10/0	9/0	N/A
Estimated duration of RBD (years), mean (SD)	3.9 (1.7)	4.3 (2.1)	0.389
MMSE score, mean (SD)	28.4 (2.1)	28.4 (1.9)	0.864
UPDRS part III score, mean (SD)	0.9 (1.1)	1.0 (1.0)	0.729
Uptake of 6-[^{18}F] FMT, mean (SD)			
Putamen	4.40 (0.83)	3.22 (0.98)	0.027
Caudate	3.69 (0.42)	2.86 (0.82)	0.014
Putamen/caudate ratio	1.19 (0.19)	1.12 (0.10)	0.514

RBD, rapid eye movement sleep behaviour disorder; MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale; FMT, fluoro-meta-tyrosine; SD, standard deviation; N/A, not applicable.
Transcranial sonography (TCS) was considered pathological when SN echogenicity was ⩾0.20 cm^2.
p-Value was determined by Mann–Whitney U-test.
*Side of the midbrain (right or left) with the greater area of SN echogenicity.

mechanistically unrelated phenomenon. SN echogenicity is sensitive to degeneration of dopaminergic neurons. A report by Behnke et al. [18] showed that ^{18}fluoro-DOPA uptake was lowest in patients with PD, followed by individuals with SN hyperechogenicity, and finally healthy controls without SN hyperechogenicity. The difference was significant between the three groups. Walter et al. [19] reported that brain parenchyma sonography demonstrated SN hyperechogenicity in concordance with abnormal nigrostriatal ^{18}F-DOPA PET in all symptomatic and three asymptomatic *Parkin* mutation carriers. Thus, they suggested SN hyperechogenicity as an early marker for detection of preclinical Parkinsonism. DelleDonne et al. [20] showed that incidental Lewy body disease (ILBD) has nigrostriatal pathological features that are intermediate between those in pathologically normal persons and patients with PD. Among the participants with ILBD, decreased striatal dopaminergic immunoreactivity was documented for both tyrosine hydroxylase and vesicular monoamine transporter 2 in comparison with the pathologically normal subjects; the reductions were even greater in patients with PD. Also, SN neuronal loss correlated with both striatal vesicular monoamine transporter 2 and tyrosine hydroxylase. Thus, ILBD probably represents presymptomatic PD rather than non-specific, age-related α-synuclein pathological changes.

The current study compared FMT-PET findings in patients with iRBD with and without SN hyperechogenicity. Pathological SN hyperechogenicity in iRBD may be suggestive of nigrostriatal dopaminergic dysfunction, as determined by FMT-PET. However, there was no significant correlation between the area of SN hyperechogenicity and the degree of 6-[^{18}F]FMT uptake. It may be that these two parameters have different characteristics. In other words, the area of SN echogenicity is thought to be a stable marker, whereas the uptake of dopaminergic tracer changes progressively with time.

Iranzo et al. found that 19% of 43 patients developed a neurodegenerative syndrome such as PD, dementia with Lewy bodies (DLB), or multiple system atrophy (MSA) 2.5 years after TCS and ^{123}I-FP-CIT SPECT. They postulated that the combined use of ^{123}I-FP-CIT SPECT and TCS is a potential strategy for early identification of patients with iRBD who are at risk for development of a synucleinopathy [13]. They also reported that one case of iRBD who developed MSA had decreased striatal ^{123}I-FP-CIT uptake and normal echogenic SN, and this discrepancy might be explained by the fact that SN hyperechogenicity is less common in MSA than in PD or DLB [13]. Even when SN echogenicity is normal in iRBD, the risk for developing MSA remains. Therefore, patients with iRBD who are at risk for developing not only PD or DLB, but also MSA need to be followed-up.

This study had several limitations. One weak point was that the mean interval between TCS and FMT-PET was approximately four months. Berg et al. reported that the area of SN echogenicity did not change with time in PD [11], but this has not been investigated in patients with iRBD. Due to the lack of a control group in this study, it was not possible to assess if those patients with abnormal PET results had a greater or different echogenic size than those with normal PET results. Satisfactory results of TCS are difficult to obtain in females [5], and all subjects in the study were male. In the future, in order to clarify whether there is a gender difference in the relationship between SN hyperechogenicity and FMT-PET findings, it may be helpful to determine the background of the gender differences in the onset of PD.

Hyperechogenic alterations in the SN may suggest the existence of preclinical SN dysfunction and of an underlying neurodegenerative disorder such as PD or DLB associated with nigrostriatal dysfunction in patients with iRBD. In terms of clinical interest and use of the study findings, there is a need for close clinical follow-up to detect the early signs of a disease characterised by Parkinsonism, and also to test neuroprotective therapies in the near future in such patients.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi:10.1016/j.sleep.2011.03.024.

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＜原　著＞

Telestrokeの有用性と課題

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長谷部直幸[1)]　平沼　初音[3)]　高橋　康二[3)]　羽根田　俊[4)]　守屋　潔[5)]

要旨：【目的】脳卒中専門医不在の地域基幹病院において遠隔脳卒中診療(telestroke)を試み，その有用性と課題を検証する．【方法】脳卒中専門医チームを有する医療機関と脳卒中専門医不在の地域基幹病院をTV会議システムと放射線画像読影システムで結んだ．地域基幹病院に脳卒中を疑われた患者が搬送されたとき，TV会議システムを用いて得られた神経所見と放射線画像読影システムで転送された画像所見から，臨床診断し，治療方針を決定した．Telestrokeによる脳卒中診療の有用性および課題を検討した．【結果】Telestrokeにより患者の意識状態や麻痺の状態などを直接観察することができた．地域基幹病院で撮影した神経画像をリアルタイムで読影できた．脳卒中専門医のいる医療機関に直接搬送されるときより診断までの時間，治療開始までの時間が短縮した．診療点数が算定されないことが課題であった．【結論】Telestrokeは脳卒中専門医のいない地域基幹病院での脳卒中診療に有用と考えられた．

Key words：telestroke, stroke telemedicine, TV conferencing system
(脳卒中 33：84-88，2011)

はじめに

北海道は一つの医療圏が広く，また脳卒中を専門とする神経内科医や脳神経外科医が不在の地域が数多く存在する．したがって，このような地域では脳卒中急性期に専門医による適切な診療を受ける機会を逸することが予測される．一方，stroke unitを利用した脳卒中専門チームによる治療を行うことにより脳卒中患者の死亡率減少，機能予後改善が得られることが知られており[1)~4)]，脳卒中専門医不在の地域の脳卒中診療のレベルを維持し，脳卒中診療の地域差を解消する取り組みはきわめて重要と考えられる．このような観点から，1990年代の終わりから2000年にかけて欧米では脳卒中センターから遠隔地の脳卒中急性期患者にtissue plasminogen activator(t-PA)の使用を主な目的としてstroke telemedicine(telestroke)が発達してきた[5)]．そこで，本邦でも脳卒中専門医不在の地域基幹病院で遠隔脳卒中診療(telestroke)を試み，その有用性と課題を検証することを目的とした．

[1)]旭川医科大学神経内科
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(2010年8月30日受付，2010年9月28日受理)

方　法

旭川医科大学では脳卒中診療レベルの向上と標準化のため2005年12月に神経内科と脳神経外科，循環器内科，救急部，放射線科などがストロークチームを結成した．主に神経内科と脳神経外科の脳卒中専門医が脳卒中の初期対応を行い，毎週合同ファレンスを行っている．旭川医科大学病院ストロークチームと脳卒中専門医不在の地域基幹病院(富良野病院)救急室をTV会議システム(video-conferencing system)で結んだ．脳卒中患者が富良野病院へ搬送された時に，旭川医科大学の脳卒中専門医がTV会議システムを用い救急搬送されたベッド上の患者のバイタルサイン，意識状態，神経所見を富良野病院の救急担当医と確認するようにした．TV会議システムは専用の光回線により結んで，リアルタイムで患者の状態を確認できるようにした(図1，2)．

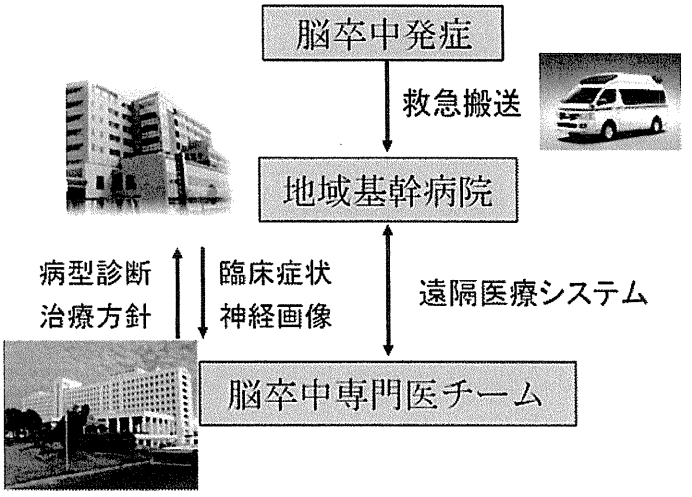

図1　Telestroke(脳卒中遠隔医療)の概念図

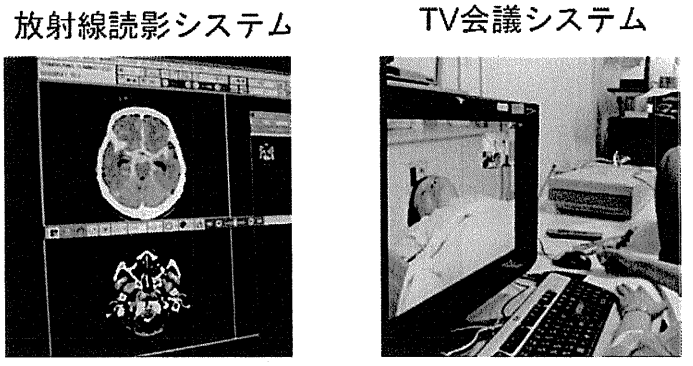

図2　放射線読影システムとTV会議システム
放射線読影システムにより地域基幹病院で撮像された画像を大学病院へ転送する．TV会議システムにより脳卒中患者の状態をリアルタイムで観察でき，地域基幹病院のスタッフあるいは患者自身とも会話ができる．

TV会議システムにはTandberg 880MXPを用い，通信回線にはNTT光回線(Bフレッツ)とセキュリティーのためフレッツVPNを使用した．ビットレートは1152 kbpsで，フレームレートは30フレーム/秒，解像度は4CIF(704×576ピクセル)，映像圧縮方式はH.264，音声符号化方式はG.722，TVモニターは20型デジタル液晶TV(シャープAQUOS)を用いた．音声は880MXPの機能で映像と同時に伝送し，マイクは880MXP内蔵，スピーカーはTVモニター内蔵を使用した．ビデオカメラはキャスター付台に載せて移動が自由に行えるようにした．放射線画像伝送システムにはTV会議システムとは別の光回線とVPNを使用した．

富良野病院と旭川医科大学とは既に放射線画像伝送システムを整備し遠隔画像診断が可能な体制にして，富良野病院で撮像されたCTやMRIなどの画像は旭川医科大学放射線科に転送され，画像診断を行えるようにした．すなわちリアルタイム型の脳卒中診療支援を行えるようにした．

臨床所見と放射線画像読影システムで転送された画像所見を合わせ，脳卒中の臨床診断を行い，治療方針を決定した．今回，初めてのシステム運用のため日中

表1　Telestroke 症例のまとめ

	年齢	性	病名	症状	入院科	発症から富良野病院まで	富良野受診から当院まで	治療	転帰
No. 1	75	M	くも膜下出血	意識障害	当院脳神経外科	30 min	1h	保存的	当院へ転院，死亡
No. 2	66	M	横静脈洞血栓症	けいれん	当院神経内科	30 min	3d	ヘパリン	当院へ転院，軽快後悪化
No. 3	75	M	心原性脳塞栓	歩行障害	当院神経内科	18h	5h	エダラボン，ヘパリン	当院へ転院，軽快
No. 4	81	M	視床出血	半身の異常感覚	近医脳外科出張病院	2d		降圧	近医転院，軽快
No. 5	76	M	外傷性くも膜下出血	頭痛	近医脳外科出張病院	30 min		保存的	近医転院，軽快
No. 6	62	M	ラクナ梗塞	半身の異常感覚	当院神経内科	2d	1h	エダラボン，オザグレル	当院へ転院，軽快
No. 7	65	F	くも膜下出血	頭痛	当院脳神経外科	1d	2.5h	クリッピング	当院へ転院，治癒
No. 8	81	F	多発性脳塞栓	右不全麻痺，構音障害	富良野病院	3h		エダラボン，ヘパリン	入院，軽快

のみに限定して開始した．2009年10月から2010年2月までの5カ月間に富良野病院へ救急搬送された脳卒中を疑われた8症例を対象とした．診断，治療，転帰，ならびに時間経過を検討し，telestrokeの有用性と課題を検討した．

結　果

8症例のまとめを表1に示した．Telestrokeを用いることにより，旭川医科大学において富良野病院に搬送された患者のバイタルサイン，意識状態，神経所見を明瞭にかつリアルタイムで確認することができた．ズームによる観察も可能で患者の表情の詳細まで把握できた．また患者と直接会話し，発語異常の有無や口頭指示による反応を確認することができた．同時に富良野病院で撮像されたCTやMRI，MRAを読影することができた．いずれの症例も富良野病院でtelestrokeにより診断を確定し治療方針と治療場所の決定を行った．8例中，5例は最終的に当院へ搬送し，2例は脳神経外科医が出張している富良野の近医へ転院した．1例は富良野病院で加療を継続した．すなわち4割弱が地域の医療機関で加療した．脳梗塞は3例で，発症から富良野病院搬入までの時間が最短で3時間，最長2日であり，t-PAの適応のある症例はいなかった．

二次搬送された5症例のうち症例3と症例6は脳梗塞で治療を開始して搬送したが，静脈洞血栓症の症例2は二次搬送した後に治療を開始した．残りの2例はくも膜下出血で，降圧療法を開始して搬送した．

富良野病院から当院までは救急車を用いると約1時間を要する．したがってtelestrokeを使用することにより診断および治療開始まで約1時間短縮すると考えられた．富良野病院から当院へ搬送された患者のうち2例は救急車を使用し約1時間で到着したが，他の2例はそれぞれ2時間と5時間を要した．その原因としては富良野病院受診時に救急車を使用せず，その後当院へ受診する際にも救急車を使用しなかったためと考えられた．当院へ搬送された患者に関しては受け入れ態勢の整備が前もって可能であった．

考　察

今回の検討でTV会議システムと放射線画像伝送システムを用いることにより，少数例ながらリアルタイムのtelestrokeを行うことができた．Telestrokeを用いることにより，これらの症例の診断から治療方針決定までの時間短縮は富良野病院から大学病院までの搬送時間である約1時間と考えられた．

診断後は富良野病院で加療を受けた場合にはその場で治療が開始され，大学病院まで搬送された症例も一

部を除き治療を開始して搬送された．

また，今まで富良野市で発症した脳卒中患者は主に脳卒中専門医のいる旭川市へ搬送されていたが，一部の例は富良野の医療機関で適切に治療まで行うことができたことは搬送費用や家族の交通費など診療以外に付随する費用の軽減につながるものと思われた．

1995年に発表されたNational Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study trial[6]で3時間以内のt-PA静注療法が脳梗塞の3カ月後の機能予後の改善に有効とされてから，t-PA治療は脳梗塞発症から3時間以内の使用が原則である．今回は症例数が少なく適応症例がいなかったが，症例数が増加するに従い適応症例が見込まれると思われる．最近ではt-PAの使用が4.5時間まで延長しても有効との報告が相次いでおり[7)~9)]，今後，適応症例が拡大される可能性も示唆されている．しかし，発症から受診までの時間が長く，t-PA治療の適応時間を過ぎる例が多いことを考慮すると，脳卒中に関する知識を一般の方へ周知することがより重要な課題と考えられる．

今回の検討ではt-PA静注用法の適応症例がいなかったため，実際にこのシステムがt-PA静注療法に有用かどうかについては明らかでない．富良野病院でNIHSSスコアの正確な評価ができるか，t-PA静注療法に必要な問診や検査が適切に行えるかについて実証する必要がある．また，富良野病院でt-PA投与が可能であれば，救急隊から直接にt-PA可能な遠隔地への搬送(ストロークバイパス)より有効である可能性が高まると思われる．

富良野病院より当院へ搬送，受診するために要する時間が予測以上に長い症例に関しては，脳卒中が救急疾患であるとの認識の周知が徹底していなかった可能性があり，反省すべきものと考えられる．また救急車に加えドクターヘリなどの活用も搬送時間を短縮する有用な手段であり，考慮すべきものと考えられる．

Telestrokeによる富良野病院の利点として脳卒中専門医による診療あるいはコンサルトをいつでも受けられ，必要に応じ脳卒中専門医のいる大学病院への転院が可能であること，さらにそれにより地域基幹病院医師・患者・患者家族の安心感がえられることが考えられた．

Telestrokeの問題点の一つとしては，従事した病院への診療点数が算定されないことがある．今後telestrokeを進めるにあたり解決すべき課題と考えられる．Telestrokeの意義および有用性については脳卒中専門医のいない地域での脳卒中診療レベルの向上のみならず，患者自身の運搬費用と家族の交通費などの波及する医療経済学的観点，さらには機能予後の改善効果などを含め総合的に検証していく必要があると考えられる．

結　論

Telestrokeは脳卒中専門医のいない地域基幹病院での脳卒中診療に有用である．

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Abstract

Telestroke in clinical practice

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Background and Purpose: To examine whether a telestroke system is an effective method of providing expert stroke care to patients in rural areas.

Methods: Videoconferencing and radiological imaging linked the stroke center of Asahikawa Medical University Hospital and the emergency room of Furano Hospital (a rural hospital without access to a stroke specialist). The stroke patients referred to Furano Hospital were diagnosed using the telestroke system and started on medication. The clinical courses and outcomes of the patients were reviewed.

Results: A stroke specialist at a university hospital obtained clinical information on stroke patients at Furano Hospital through the videoconferencing system and viewed brain MRI/MRA/CT images of the patients. As a result, the time from the onset to starting treatment for the stroke patients was shortened.

Conclusions: The telestroke system is a useful tool for rural stroke medicine.

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