INTRODUCTION

In humans, homovanillic acid (HVA) is the major end-product of dopamine metabolism. The HVA in the cerebrospinal fluid (CSF) is largely derived from the nigrostriatal dopaminergic pathway; therefore, HVA concentration in the CSF has been used as an index of dopamine synthesis and presumed to reflect nigrostriatal dopaminergic function. However, even with the availability of a rigorous collection protocol, especially with respect to puncture time and pre-procedural resting, considerable interindividual and intraindividual variability has been reported with regard to the concentration of CSF HVA in subjects with normal nigrostriatal function.(1-3) Therefore, the extent to which CSF HVA concentrations reflect the nigrostriatal dopaminergic function is still unknown, and no study has specifically elucidated the association between the concentration of CSF HVA and the function of nigrostriatal dopamine.

Many studies have shown that the concentration of CSF HVA substantially reduces in patients with Parkinson's disease (PD), which is a neurodegenerative disorder caused by nigrostriatal dopaminergic dysfunction.(4-12) However, the extent of reduction also varied a great deal among patients with PD. Because of the variability, the relationship of clinical disability with CSF HVA concentrations and the accuracy of CSF HVA concentrations in differentiating PD from other parkinsonian syndromes have yet to be determined. Several authors have reported an inverse relationship between CSF HVA concentrations and the clinical severity,(5-7, 10, 11) while others have denied such a relationship.(9, 12, 13) Other neurodegenerative disorders caused by the dysfunction of nigrostriatal dopaminergic system, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration, also show the reductions of CSF HVA concentrations as compared to normal subjects.(8, 14, 15) Therefore, the usefulness of measuring CSF HVA concentrations in daily clinical practice has not yet been established.

In order to address the physiological and pathophysiological backgrounds of these issues, we evaluated the correlation between CSF HVA concentrations and nigrostriatal dopaminergic function. Furthermore, we have discussed the mechanism by which the

concentration of CSF HVA reduces in patients with PD.

As means of evaluating nigrostriatal dopaminergic function, we performed carbon-11-labeled 2β-carbomethoxy-3β-(4-fluorophenyl)-tropane (^{11}C-CFT) positron emission tomography (PET) scans which can reveal the dopamine transporter (DAT) density in the striatum. DAT imaging has been recognized as a standard marker for the diagnosis of PD, because it is a very sensitive, reproducible, and reliable marker of nigrostriatal dopaminergic function.(16-21)

MATERIALS AND METHODS

Subjects

The present study was a retrospective study. The subjects comprised 35 patients (19 men and 16 women; ages, 60–83 years [mean age = 71.7, SD = 6.0]). They visited the neurological outpatient clinic at Tokyo Metropolitan Geriatric Hospital from April 2001 to November 2004. Of the 35 patients, 29 had parkinsonian symptoms and on the basis of each clinical criteria,(22-24) 21 were diagnosed with PD, 3 with MSA, and 5 with PSP. The remaining six patients had no parkinsonian symptoms: 3 were clinically diagnosed with Alzheimer's disease (AD), 2 with spinocerebellar degeneration (SCD), and one with amyotrophic lateral sclerosis (ALS). Table 1 shows the demographic data. The patients with MSA and PSP were classified in the patients with non-PD (NPD) group, while the patients with AD, SCD, and ALS were classified in the patients with non-parkinsonian syndromes (NPS) group. The CSF examinations and the ^{11}C-CFT PET scans were performed within 5 months of each other. None of the patients had any concomitant hereditary disorder that could cause parkinsonian symptoms. All the patients were drug naive.

The normal range of HVA was determined by examining the CSF of 13 normal control subjects (5 men and 8 women; age, 65–88 years [mean = 77.2, SD = 8.2]). Similarly, the normal range for nigrostriatal dopaminergic function was determined by performing ^{11}C-CFT PET scans of 8 normal control subjects (five men and three women; age, 55–74 years [mean age = 62.3, SD = 6.9]). All the control subjects were healthy and did not have any underlying diseases or abnormities, as determined on the basis of their

medical history and their physical and neurological examinations. None of them were on any medications at the time of the study. All the subjects also underwent routine MRI examinations.

All the CSF examinations and ^{11}C-CFT PET scans were performed for research. This study protocol was approved by the Ethics Committee of the Tokyo Metropolitan Institute of Gerontology and written informed consents were obtained from all the participants.

CSF analysis

Lumbar puncture was performed in the lateral decubitus position to obtain CSF samples from each subject. The first few milliliter of CFS was discarded. The next 3-milliliter of CFS was used for routine determinations of cell counts, protein and sugar, and an additional 2-milliliter was stored at -70°C until the assays were preformed. The concentration of CSF HVA was measured by injecting 80-microliter CSF samples into a high-performance liquid chromatography system equipped with 16 electrochemical sensors (CEAS Model 5500, ESA, Bedford, MA, USA), as described previously.(14)

PET imaging

^{11}C-CFT PET data acquisition: PET studies were performed at the Positron Medical Center, Tokyo Metropolitan Institute of Gerontology using a SET 2400W scanner (Shimadzu, Kyoto, Japan) in the three-dimensional scanning mode.(25) The ^{11}C-CFT was prepared as described previously.(26) Each subject received an intravenous bolus injection of 388 ± 75 (mean ± SD) MBq of ^{11}C-CFT. Each subject was then placed in the supine position with their eyes closed in the PET camera gantry. The head was immobilized with a customized head holder in order to align the orbitomeatal line parallel to the scanning plane. To measure the uptake of ^{11}C-CFT, a static scan was parallel to the scanning plane. To measure the uptake of ^{11}C-CFT, a static scan was performed for 75–90 min after the injection. The specific activity at the time of injection ranged from 7.1 to 119.6 GBq/μmol. The transmission data were acquired using a rotating ^{68}Ga/^{68}Ge rod source for attenuation correction. Images of 50 slices were obtained with a resolution of 2 × 2 × 3.125 mm voxels and a 128 × 128 matrix.

Analysis of ^{11}C-CFT PET images: Image manipulations were carried out by using the Dr. View software (version R2.0; AJS, Tokyo, Japan). The individual PET images

were resliced in the transaxial direction, parallel to the anterior–posterior intercommissural (AC–PC) line. Circular regions of interest (ROIs) were placed with reference to the brain atlas and individual MRI images. Five ROIs (diameter, 8 mm) were placed on the striatum on both the left and right sides in each of the 3 contiguous slices (the AC–PC plane, and regions 3.1 mm and 6.2 mm above the AC–PC line). Of the five ROIs, one ROI was placed on the caudate and four on the putamen. A total of 50 ROIs (diameter, 10 mm) were selected throughout the cerebellar cortex in five contiguous slices. To evaluate the striatal uptake of ^{11}C-CFT, we calculated the uptake ratio index by the following formula,(17, 18) as previously validated. (27, 28)

Uptake ratio index = (activity in the striatum – activity in the cerebellum)/(activity in the cerebellum).

Statistical analysis

Differences in the averages were tested using a Student's *t* test. Correlations between the two groups were assessed by linear regression analysis with Pearson's correlation test. *P* values < 0.01 were considered to indicate statistical significance.

RESULTS

The interindividual variability in the concentrations of CSF HVA in each group was relatively large (Figure 1A). CSF HVA concentrations in both the PD ($P < 0.01$) and NPD groups ($P < 0.01$) were significantly lower than that in the control group (mean ± 2SD, 36.0 ± 27.6), while no significant difference was observed between the NPS and control groups.

The striatal uptake of ^{11}C-CFT in the PD and NPD groups was below the normal range (mean ± 2SD, 2.68 ± 0.87; Figure 1B). In the PD group, CSF HVA concentrations were significantly correlated with the striatal uptake of ^{11}C-CFT ($r = 0.76$, $P < 0.01$). In the NPD group, although the difference in the two indexes was not statistically significant, the distribution pattern between the two indexes showed the same tendency as that in the PD group. However, in the NPS group, both CSF HVA concentrations and the striatal uptake of ^{11}C-CFT were within the normal ranges.

DISCUSSION

We evaluated the correlation between CSF HVA concentrations and nigrostriatal dopaminergic function by performing ^{11}C-CFT PET scans. ^{11}C-CFT PET scans showed that all patients with PD and NPD had the dysfunction of nigrostriatal dopaminergic system and all patients with NPS had normal function. The CSF HVA concentrations of all patients with PD and NPD were significantly lower than those of normal subjects, in accordance with previous studies.(5-12, 14, 15) Whereas, there was no significant difference in CSF HVA concentrations between normal subjects and patients with NPS. These results suggest that CSF HVA concentrations could reflect nigrostriatal dopaminergic function. However, in accordance with previous reports,(1-9, 13, 14) all groups showed large interindividual variability in CSF HVA concentrations and relatively wide overlaps among groups were found. Therefore, in clinical practice, measuring CSF HVA concentrations may be of limited value in the diagnosis of PD.

This is the first study that investigated the correlation between CSF HVA concentrations and nigrostriatal dopaminergic dysfunction. Regardless of relatively high

interindividual variability, CSF HVA concentrations in the PD group showed a considerably high correlation with the striatal uptake of ^{11}C-CFT. The NPD group with nigrostriatal dopaminergic dysfunction showed the same tendency as the PD group, although without significant correlation probably because of the small number of patients. On the other hand, the NPD group with normal nigrostriatal dopaminergic function showed normal ranges in both the HVA level and the striatal uptake of ^{11}C-CFT. Therefore, CSF HVA concentrations may be an additional surrogate maker for estimating the nigrostriatal dopaminergic function in patients with PD, in case that DAT imaging, which has been recognized as a standard maker for the diagnosis of PD, is unavailable.

It is important to note that the DAT images of patients with PD are unique; in the pre-symptomatic phase the reduction in the availability of striatal DAT was detected, presumably as a result of both the degeneration of nigral dopaminergic cells and the compensatory downregulation of DATs on the presynaptic site to maintain normal synaptic dopamine concentrations.(17-21) Furthermore, the striatal DAT availability declined at an annual rate of 5–10%.(19, 21, 29-31)

Considering our results and the unique characteristics of the DAT images, a possible explanation about the association between CSF HVA concentrations and the striatal uptake of ^{11}C-CFT is as follows (Figure 2). The first stage of the disease is a compensatory and asymptomatic phase. Along with the progression of nigrostriatal degeneration, the striatal DAT availability begins to decrease, as described earlier.(17-21) However, due to several compensatory mechanisms, including the downregulation of DATs and the upregulation of dopamine synthesis, the striatal dopamine concentrations are kept within the normal range.(32) As a result, CSF HVA concentrations are also kept in the normal range because CSF HVA is the major end-product of striatal dopamine metabolism. This phase would show relatively large intraindividual and interindividual variability in CSF HVA concentrations, as observed in subjects with normal nigrostriatal dopaminergic function, because of the reserve capacity for adjusting its levels. The second stage of the progression of the disease is an advanced and symptomatic phase. The compensatory mechanisms to maintain normal synaptic dopamine concentrations break down and the striatal dopamine and

CSF HVA concentrations begin to decrease with the reduction of DAT availability. In this phase, the intraindividual and interindividual variability in CSF HVA concentrations would gradually decrease because of a lesser capacity for adjusting its levels. Consequently, CSF HVA concentrations remain within a narrow range that corresponds to the remaining nigrostriatal dopaminergic function. In symptomatic patients with PD, CSF HVA concentrations correlate with nigrostriatal dopaminergic function. To verify this explanation, a study with larger number of patients is needed.

In conclusion, we found a significant correlation between CSF HVA concentrations and the striatal uptake of ^{11}C-CFT in patients with PD. Although we should remember that CSF HVA concentrations show large variability, CSF HVA concentrations may be an additional surrogate maker for estimating the remaining nigrostriatal dopaminergic function in patients with PD in case that DAT imaging is unavailable.

Acknowledgements

The authors thank Mr. Keiichi Kawasaki and Ms. Hiroko Tsukinari for their technical assistance. This study was supported by Grants-in-Aid for Neurological and Psychiatric Research (SM, YS, and K. Ishii) and Research for Longevity (SM, YS, and K. Ishii) from the Ministry of Health, Labor, and Welfare of Japan; for Scientific Research (B) No. 20390334 (K. Ishiwata) from the Japan Society for the Promotion of Science; for the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation, Japan (No: 06-46, K. Ishiwata); and for Long-Term Comprehensive Research on Age-associated Dementia from the Tokyo Metropolitan Institute of Gerontology (KK, SM, and K. Ishii).

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Table 1.

Demographics of Patients and Control Subjects

	Subjects		Age	Duration	Striatal uptake of ^{11}C-CFT	CSF HVA
	N	M : F	(y)	(y)	(Uptake ratio index)	(ng/ml)
Parkinson's disease	21	11 : 10	72.9 ± 5.0	1.8 ± 1.3	0.94 ± 0.20	12.8 ± 9.35
Hoehn-Yahr 1	1	1 : 0	62	1	1.38	36.8
Hoehn-Yahr 2	8	4 : 4	71.6 ± 4.6	1.4 ± 0.9	1.03 ± 0.14	15.6 ± 9.4
Hoehn-Yahr 3	12	6 : 6	74.7 ± 3.9	2.1 ± 1.5	0.85 ± 0.17	8.9 ± 5.4
Non-Parkinson's disease	8	4 : 4	70.5 ± 7.7	1.6 ± 0.8	1.00 ± 0.19	16.4 ± 7.7
Non-parkinsonian syndromes	6	4 : 2	68.8 ± 6.3	4.5 ± 2.4	2.48 ± 0.28	31.9 ± 13.0
Control for PET study	8	5 : 3	62.3 ± 6.9		2.68 ± 0.44	
Control for CSF study	13	5 : 8	77.2 ± 8.2			36.0 ± 13.8

Data are expressed as mean ± SD.

N = number, CSF = cerebrospinal fluid, and HVA = homovanillic acid.

FIGURE LEGENDS

Figure 1. (A) The comparison of CSF HVA concentrations among the disease and control groups. Vertical bars represent mean ± SD. (B) Relationship between CSF HVA concentrations and the striatal uptake of ^{11}C-CFT. A solid line represents the regression line for the PD group. Linear correlation was significant ($r = 0.76$; $P < 0.01$). The grey bars beside the x- and y-axes represent the normal range (mean ± 2SD) for HVA (36.0 ± 27.6) and the striatal uptake of ^{11}C-CFT (2.68 ± 0.87). PD = Parkinson's disease, NPD = non-Parkinson's disease with parkinsonism, NPS = non-parkinsonian syndromes, C = controls, NS = not significant, CSF = cerebrospinal fluid, and HVA = homovanillic acid.

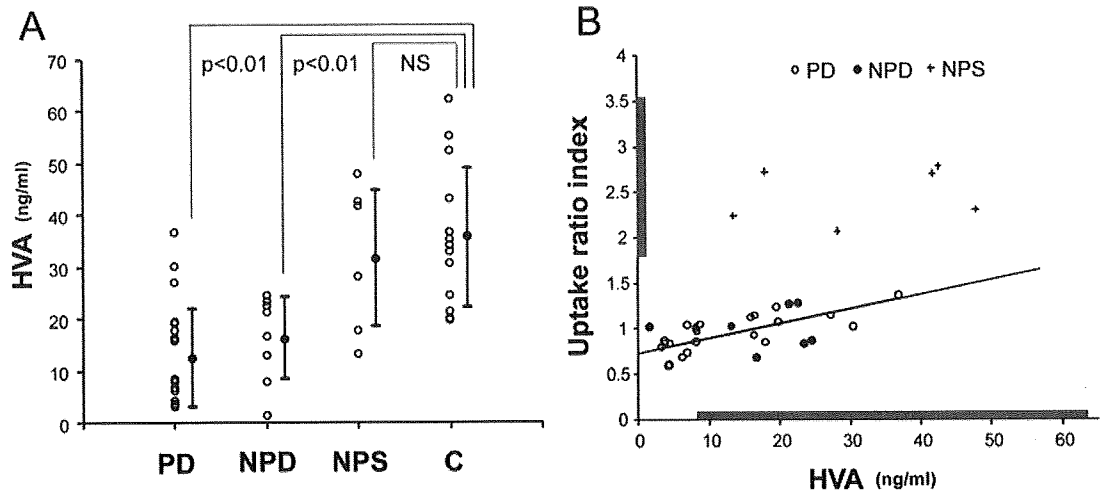
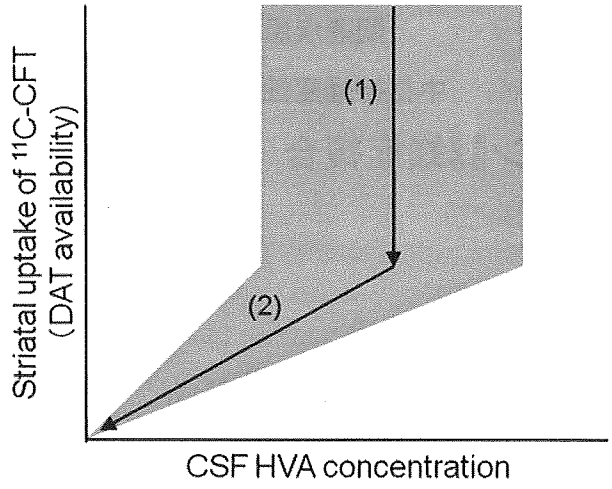


Figure 2. Schematic representation of the mechanism of CSF HVA reduction in patients with PD. (1) The nigrostriatal degeneration begins with a decrease in DAT availability, but due to several compensatory mechanisms, striatal dopamine concentrations (CSF HVA concentrations) are maintained within the normal range. There is a large variability with regard to CSF HVA concentrations. (2) The compensatory mechanisms break down and striatal dopamine concentrations (CSF HVA concentrations) begin to decrease along with the decrease in DAT availability. The variability in CSF HVA concentrations gradually becomes smaller. The grey zone represents the range of variability in CSF HVA concentrations to the striatal uptake of ^{11}C-CFT. DAT = dopamine transporter, CSF = cerebrospinal fluid, and HVA = homovanillic acid.



日本臨牀　67巻 増刊号4（2009年6月28日発行）別刷

パーキンソン病

—基礎・臨床研究のアップデート—

IV. 検査・診断

関連疾患

中枢神経変性疾患

パーキンソン認知症複合（グアム島，紀伊半島）

小久保康昌

関連疾患
中枢神経変性疾患

パーキンソン認知症複合(グアム島，紀伊半島)

Parkinsonism-dementia complex on Guam and the Kii peninsula

小久保康昌

Key words：パーキンソン認知症複合，筋萎縮性側索硬化症，紀伊半島，グアム島，タウ，TDP-43

はじめに

紀伊半島南部とグアム島は，筋萎縮性側索硬化症(amyotrophic lateral sclerosis: ALS)とパーキンソン認知症複合(parkinsonism-dementia complex: PDC)の世界的な多発地域として知られている(**図1**)．グアム島では，1970年代以降，ALSの発生率が劇的に減少したが，PDCは，いまだに一定頻度で新規発症患者が認められている．更に，近年は，Guam dementiaと呼ばれるAlzheimer病様の認知症のみを呈する新しい病型が増加している．また，紀伊半島やグアム島のALS/PDCの中枢神経系には，前頭側頭型脳葉変性症(FTLD)やALSで発見されたTDP-43が蓄積していることが判明した．

本稿では，このような新しい知見を含めて両地域のPDCに焦点を当てて概説する．

1. 歴史的経緯，疫学

グアム島：PDCが独立した疾患単位として初めて確立されたのは，1961年にMontefiore医療センターの平野らによって，詳細な臨床病理像が報告されたことによる[1,2]．当初，脳炎後パーキンソニズムと考えられたこの疾患は，大脳と脳幹におびただしい数のAlzheimer神経原線維変化が出現する神経変性疾患であることが明らかにされた．

PDCの年間発症率は，1960年代のグアム島において人口10万人あたり70人と極めて高頻度であったが，1970年代以降大幅な減少傾向にある．しかしながら，ALSの多発が2000年以降ほぼ消滅したのに対して，PDCについては減少はしたものの今なお高頻度に新規発症者が存在する．また，発症年齢は，10年を経るにつれて約5歳ずつ高齢化している．

近年，PDCの亜型として，Alzheimer病様の認知症のみを呈する新しい病型が，Guam dementiaとして注目を集めている．2,000人あまりの65歳以上のチャモロ人について検討した報告では，12.2％に認知症を認めたが，そのうちPDCは1.5％であったのに対して，Guam dementiaは8.8％と高頻度であった[3]．

このように，グアム島では，この50年間に発症率の減少と発病年齢の高齢化，そして臨床病型について劇的な変化が起こっている．これらの変化の要因としては，第二次大戦後の生活習慣や食生活の欧米化，背景人口の高齢化が大きく関与していると推定されている．

紀伊半島：1960年代の木村，八瀬らによる疫学調査によって，我が国の紀伊半島南部に

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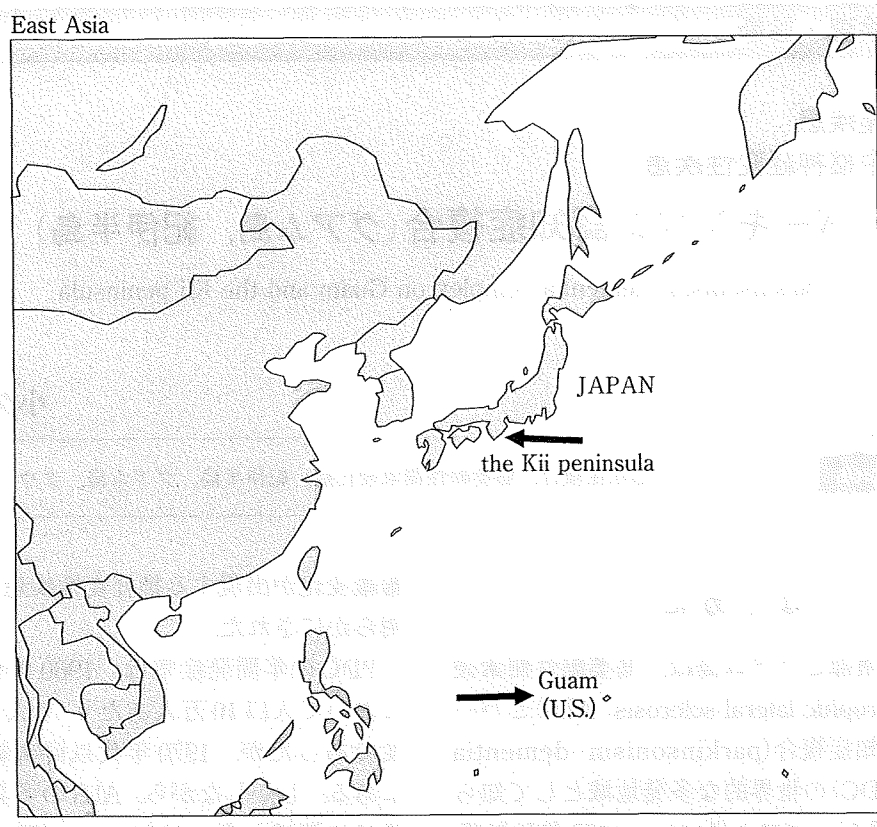

図1　西太平洋におけるパーキンソン認知症複合の多発地域

ALSの多発が実証された際に，認知症とパーキンソン症状を主体とする症例が存在することが見いだされていた．当時は，ALSに注目が集まっており，この疾患とグアム島のPDCとの関連については明らかにされなかったが，1990年代になり，Kuzuharaら[4]による臨床データの蓄積と初剖検例の報告によって，紀伊半島にもグアム島同様PDCが実在することが明らかになった．また，グアム島では，ALS，PDCともに発生率が激減したのに対して，1998年時点での三重県南部の多発地区におけるALSとPDC併せての年齢調整有病率は10万人あたり417.9と高率で，60年代の調査と比較しても減少が認められなかった[5]．発病年齢についてはグアム島同様，高齢化が認められている．

2. 臨　床　像

PDCの臨床像については，グアム島と紀伊半島で基本的な違いはないので，ここでは紀伊半島のPDCの臨床像について述べる[6]．

PDC症例の70％以上にALSもしくはPDCの家族歴がある．発症年齢は平均66.5歳で，男女比は，1：1.7と女性にやや多い．（グアム島では，3：1と男性優位）．

初発症状は，精神症状で発症する場合とパーキンソン症状が先行する場合がある．精神症状としては，物忘れ，意欲低下，抑うつ症状があり，パーキンソン症状としては，動作緩慢，歩行障害，振戦がある．パーキンソン症状で発症した症例の中には，L-dopaに反応を示し，通常のパーキンソン病と区別のつかない経過を呈する場合がある．

病期の進行に伴って，次第にPDCの中核症状であるパーキンソン症状と様々な精神症状が顕在化してくる．パーキンソン症状としては，筋強剛，姿勢反射障害，無動を高頻度に認める．一部の症例では，振戦も認めるが，姿勢時振戦のこともあればパーキンソン病に特徴的な安静時振戦のこともある．

精神症状としては，記憶障害，見当識障害，

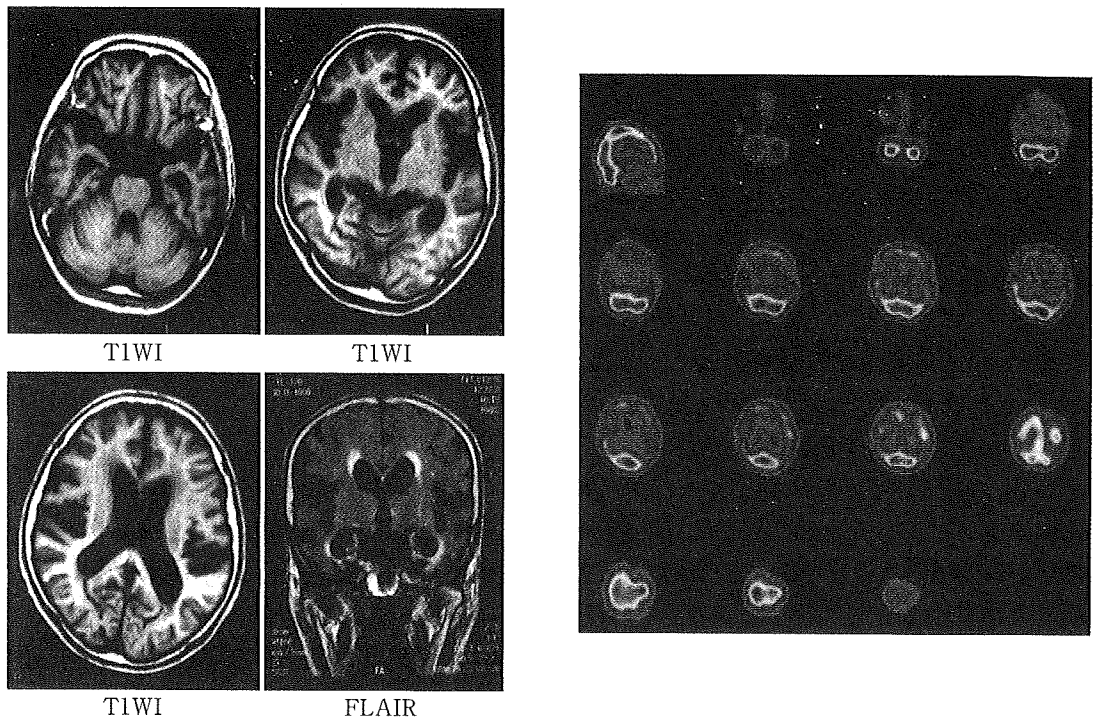

図2　紀伊半島のPDC症例のMRIと脳血流シンチ(文献[8]より引用)
前頭葉と側頭葉の萎縮と同部位の血流低下を認める.

意欲低下は必発で，抑うつ，多幸性，嗜眠傾向，幻覚を示す症例もある．特に，意欲低下や発動性の低下が最も特徴的で，おとなしく，じっとして動きの少ない，いわゆる皮質下性認知症を呈する．ほとんどの症例でbehavioral and psychological symptoms of dementia(BPSD)は認めず，FTD(frontotemporal dementia)に特徴的な常同行動や反社会的行動は示さないが，なかには徘徊を繰り返す例がある．

大部分のPDCに認められる運動ニューロン徴候は，認知症やパーキンソン症状を発症してから1–6年後に顕在化する．筋萎縮と筋力低下は，四肢筋萎縮や球麻痺として出現するのが一般的だが，呼吸筋麻痺を呈する場合もある．また，70％以上の症例に，腱反射の亢進やBabinski徴候といった錐体路徴候を認める．

その他の神経症状として，70％以上の症例に軽度の眼球運動障害を認めるが，進行性核上性麻痺に出現するような高度の垂直性眼球運動制限は出現しない．皮質基底核変性症にみられる症状の極端な左右差や肢節運動失行などの皮質症状は認めない．自律神経症状として，起立性または食事性低血圧を呈する症例がある．

グアム島のALS/PDCに認められる特異な網膜症が，紀伊半島の症例にも高率に合併する[7]．高齢発症の症例の中に，Guam dementiaのように認知症のみを示す例が存在するが，PDCであるかどうかは剖検例がなく不明である．

頭部CTおよびMRI(**図2**)[8]では，前頭葉と側頭葉の萎縮を認め，病期の進行とともに顕著となる．脳血流シンチでは，前頭葉と側頭葉に血流低下を認める．したがって画像所見は，前頭側頭型認知症に分類される．画像統計解析ソフトを用いたより詳細な脳血流シンチでの検討では，血流低下部位は，前頭側頭葉にとどまらず，頭頂葉，後頭葉，帯状回，尾状核，脳幹に及ぶ．MIBG心筋シンチグラフィは，病期の進行に沿って低下するので，心臓交感神経病変を伴っているものと考えられる．

3. 神経病理像

肉眼的には，前頭葉と側頭葉の萎縮が顕著で

ある．脳室拡大は著明で，海馬は萎縮し，黒質と青斑核の脱色素を認める．組織学的所見の特徴は，神経細胞脱落を伴った神経原線維変化(NFT)の出現とALS病変である．NFTは，海馬を含む側頭葉内側に顕著で，前頭葉や脳幹諸核にも多発する．ALS病変としては，脳幹と脊髄の錐体路変性，脊髄運動神経細胞の脱落，大脳運動領のBetz巨細胞の脱落を認める．脊髄にもNFTやタウ陽性病理を認める[4]．α-synucleinは，扁桃体を中心に脳幹や小脳に出現する[9,10]．FTLDと通常のALSに出現するユビキチン陽性封入体の主要成分として，2006年に同定されたTDP-43は，グアム島や紀伊半島のALS/PDCにも出現する[11,12]．TDP-43は，過剰リン酸化および断片化されており，ALS/PDCの病因に関与する新しいタンパク質として注目されている．

4. 病因，病態

これまでに提唱されている主な仮説として，遺伝素因説と環境要因説がある．

(1) 遺伝素因説：紀伊ALS/PDCにおいて，ALS，パーキンソン病，FTLDの原因となる21の候補遺伝子について検討したところ，いずれにも変異を認めなかった[13]．グアム島では，タウ遺伝子のSNP解析から，3種類のSNPsが疾患感受性遺伝子として報告されている[14]．

(2) 環境要因説：微量ミネラルや重金属の欠乏あるいは過剰説，ソテツに含まれる神経毒説，藍藻から産生されるbeta-methylamino alanine (BMAA)による神経毒説などがある．

ALS/PDCは，遺伝素因と環境要因の相互作用によって発症する多因子疾患と考えられる．著者らは，紀伊症例において酸化ストレスが病態に関与していることを報告した[15]．

5. 治療，予後

有効な治療法はなく，運動障害と精神症状は次第に進行し，末期には無言無動で屈曲拘縮を呈する．L-dopaは，一部の症例のパーキンソン症状に対して有効であるが，効果は一時的である．PDC症例の平均罹病期間は7年前後で，肺炎などの感染症が死因となる．

おわりに

紀伊半島とグアム島のPDCでは，タウ，α-synuclein，TDP-43といった神経変性疾患のkey proteinがoverlapして発現していること，遺伝素因と環境要因が特定の地域に濃厚に発現し，発症に至ることから，本症の発症要因の究明は，多くの孤発性神経変性疾患の原因解明の手がかりになりうると考えられる．

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