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Long-term follow-up study of SWEDD patients with mild parkinsonian signs

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ABSTRACT

Background Whether scan without evidence of dopaminergic deficit (SWEDD) can be a reliable indication of a clinical entity of Parkinson's disease (PD) is controversial.

Objective To evaluate the proportion of SWEDD patients with mild parkinsonian signs who are classifiable as idiopathic PD.

Methods 32 SWEDD patients with unilateral or asymmetric finger tremor with a rest component and unilateral rigidity (Unified Parkinson's Disease Rating Scale (UPDRS)-III scores of 3-5) were enrolled. They underwent longitudinal examination by UPDRS-III, Mini–Mental State Examination (MMSE), smell test and ^{123}I-FP-CIT SPECT (DaTSCAN) at baseline (first DaTSCAN) and at follow-up (second DaTSCAN) after 27–83 months. Age-matched controls (n=112) also underwent MMSE and smell test.

Results At follow-up, 21 of 32 SWEDD patients (65.6%) showed significantly reduced specific binding ratios below the normal range, that is, positive DaTSCAN, sometimes with increased asymmetry index (n=11). Among these 21 patients, the mean (SD) UPDRS-III score at follow-up was significantly higher than that at baseline (5.5 (2.2) vs 4.0 (0.5)) (p=0.003). The mean (SD) MMSE scores in SWEDD patients (n=32) at baseline and follow-up were not significantly different compared with those in controls. Olfactory function both in SWEDD patients with positive and negative DaTSCAN was significantly impaired versus controls (p<0.001), although no significant difference was recognised between patients with positive (n=21) and negative (n=11) second DaTSCAN.

Conclusion The majority of SWEDD patients with mild rest tremor and rigidity could be classified as having idiopathic PD in this longitudinal and long-term follow-up study.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Scans without evidence of dopaminergic deficit (SWEDD) refers to patients clinically diagnosed with Parkinson's disease (PD) but showing normal DaTSCAN images. It remains controversial whether SWEDD should be categorized as a clinical entity of PD or rather a different disease entity.

WHAT THIS STUDY ADDS

⇒ This longitudinal and long-term follow-up study showed that the majority (65.6%) of SWEDD patients with unilateral or asymmetric finger tremor with a rest component and unilateral rigidity (UPDRS-III scores of 3−5) could be classified into the category of idiopathic PD, endorsing the arguments for a clinical entity of PD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further longitudinal and long-term follow-up studies are needed to evaluate whether SWEDD subjects, particularly those with mild parkinsonian signs (subtle or mild rest tremor and rigidity), are properly classified into idiopathic PD. Such investigations would also contribute toward disease-modifying therapies to be started earlier in the disease process and prevention clinical trials in the early stages of PD.

INTRODUCTION

The differential diagnosis of mild parkinsonism during its early stages still presents major challenges to clinicians. Both dopaminergic imaging using ^{123}iodine-labelled N-(3-fluoropropyl)−2β-carbomethoxy-3β-(4-iodophenyl) nortropane (^{123}I-FP-CIT) single photon emission CT (DaTSCAN) and dopaminergic imaging using ^{18}F-fluorodopa PET have been used as promising diagnostic tools to assess the progression of dopaminergic degeneration in early Parkinson's disease (PD),[1–3] because in early stages of PD, and even in preclinical stages, striatal dopamine transporter (DAT) binding is significantly reduced.[4] According to the Movement Disorder Society clinical diagnostic criteria for PD, a normal DaTSCAN is an absolute exclusion criterion that rules out PD.[5] In addition to detecting early degenerative parkinsonism, presynaptic dopaminergic imaging using DaTSCAN and ^{18}F-fluorodopa PET could differentiate neurodegenerative parkinsonism from other forms of parkinsonism. Moreover, several studies have demonstrated that decreased striatal DAT uptake is well correlated with symptom severity in PD.[6]

Among patients clinically diagnosed with early-stage PD who were enrolled in clinical trials or imaging studies for PD, approximately 2.0%–20% were found to have normal DaTSCAN images,[7–12] which are also referred to as scan without evidence of dopaminergic deficit (SWEDD).[11] In an earlier study by this

author, 15 out of 90 patients (approximately 17%) with subtle parkinsonian signs showed SWEDD.[12] The present study is a longitudinal, long-term follow-up study, in which a larger number of SWEDD patients with mild parkinsonian signs were examined with respect to clinical signs, Mini–Mental State Examination (MMSE) scores, smell test results and DaTSCAN imaging at two time points to clarify what proportion of such patients could be classified as having idiopathic PD.

METHODS

Control subjects

A total of 112 age-matched individuals between 67 and 92 years of age were selected from among non-neurological outpatients such as patients with controlled hypertension and dyslipidaemia, and community-dwelling healthy individuals as well. All control individuals had no cognitive impairment defined as MMSE score ≥25 in individuals of 65 years and under, and ≥24 in those over 65 years,[13] taking educational attainment into account.

Patients

A total of 32 SWEDD patients with mild parkinsonian motor signs (unilateral or asymmetric finger tremor with a rest component, and unilateral rigidity without bradykinesia) corresponding to Unified Parkinson's Disease Rating Scale (UPDRS)-III scores[14] of 3–5 from neurology outpatient clinics at four hospitals in Japan were enrolled. None of them subjectively complained of slowness of movement, nor objectively demonstrated bradykinesia. None of the patients had been treated with antiparkinsonian medication or had family history of PD. Two patients had rapid eye movement sleep behaviour disorder (RBD) diagnosed by the Japanese version of the REM sleep Behaviour Disorders Screening Questionnaire.[15]

No patient displayed signs suggesting any of those disorders causing parkinsonian signs such as essential tremor, vascular parkinsonism, drug-induced parkinsonism and atypical neurodegenerative parkinsonism (corticobasal syndrome (CBS), multiple system atrophy with predominant parkinsonism (MSA-P) and progressive supranuclear palsy (PSP)) by clinical investigation. Moreover, brain MRI (1.5 T) was performed in all patients to exclude cognitive impairment due to cerebral infarction, small vascular diseases, Alzheimer's disease, and vascular parkinsonism, and neuroimaging signs typical of CBS, MSA-P or PSP.

The SWEDD patients (n=32) underwent longitudinal examination with DaTSCAN twice, that is, at baseline (first DaTSCAN) and follow-up (second DaTSCAN) after an interval of 27–83 months (mean (SD): 52.4 (11.6)). The DaTSCAN images were evaluated by visual assessment of tracer binding[16] and by quantitative analysis calculating the values of the left and right specific binding ratio (SBR) and asymmetry index (AI).[17] The result of DaTSCAN imaging was defined as 'abnormal' when a reduced SBR,[17] an abnormally increased AI[17] or abnormal patterns[16] such as an egg shape (bilateral reduction of tracer uptake in the putamen and normal or almost normal uptake in caudate nuclei) (grade 2) or mixed-type pattern (normal or almost normal tracer uptake in bilateral caudate nuclei with asymmetrical tracer uptake reduction in the putamen of one side) (grade 3) was observed. The SBR reduction and an egg shape pattern are regarded as high evidence of PD,[16] which makes a PD diagnosis more probable or certain. Thus, in this study, the author defined a reduced SBR and/or abnormal patterns as positive DaTSCAN, and SWEDD patients with normal SBR and normal shape pattern (negative DaTSCAN) were longitudinally followed up for the evaluation.

The changes in the UPDRS-III scores, MMSE scores and smell test scores from baseline to follow-up were also evaluated.

Smell test

A smell test was performed in all the SWEDD patients twice, that is, at baseline and follow-up and once in 112 age-matched controls, using an odor-stick identification test for Japanese (OSIT-J; Daiichi Yakuhin Sangyo, Tokyo) with 12 daily odorants familiar to Japanese individuals. The OSIT-J score was counted using three endpoints: the number of correct answers, responses of 'indistinguishable' (ie, detectable but not recognised) and responses of 'odourless' (ie, anosmia). Comorbid medical conditions such as chronic rhinitis and current heavy smoking (>20 cigarettes per day) were excluded. Moreover, since cognitive impairment and parkinsonism have synergistic effects on olfactory dysfunction[18] and patients with mild cognitive impairment show a high prevalence of parkinsonism,[19] SWEDD patients with amnestic cognitive dysfunction were ruled out by MMSE scores in the same way as the controls.[13]

Statistical analysis

The data are presented as the mean (SD). Disease duration was defined as elapsed months after the patients had first noticed motor symptoms, or, if the patients did not recognise any parkinsonian signs, since diagnosis had been confirmed by the doctor. Age, years of schooling and MMSE scores were compared between the control individuals and the SWEDD patients at baseline, using analysis of variance (ANOVA). The relative changes of UPDRS-III and MMSE scores in all the SWEDD patients between baseline and follow-up and those in the SWEDD patients with a positive DaTSCAN between baseline and follow-up were assessed by a paired-samples two-tailed t-test. The changes in age, years of schooling, UPDRS-III score and MMSE score between the SWEDD patients with positive and negative DaTSCAN at follow-up were assessed by ANOVA.

As for smell test, first, the three endpoints were compared between the controls and SWEDD patients at baseline using a model that included age and sex as covariates (analysis of covariance (ANCOVA)). Second, the relative changes between baseline and follow-up in SWEDD patients with a positive DaTSCAN were assessed by a paired-samples two-tailed t-test. The changes at

Table 1 Clinical and demographic data, and the mean change in UPDRS-III and MMSE in patients with SWEDD between first and second DaTSCAN

		SWEDD patients			
	Controls (n=112)	Baseline (n=32) (first DaTSCAN)	P value†	Follow-up (n=32) (second DaTSCAN)	P value*
Age, years	78.0 (7.0)	76.0 (7.1)	0.16	80.7 (7.1)	
Male/female	40/72	13/19		13/19	
Years of schooling	10.3 (2.6)	10.1 (2.8)	0.79	10.1 (2.8)	
Disease duration, months		2.8 (7.3)		52. 4 (11.6)	
UPDRS-III score (range)		3.9 (0.5) (3–5)		5.2 (2.0) (3–11)	<0.001
MMSE score	28.0 (1.3)	27.9 (2.0)	0.86	27.4 (2.5)	0.17

Data are shown as mean (SD).
*P values in UPDRS-III score and MMSE score of patients with SWEDD were assessed between the first and second DaTSCAN, using paired-samples two-tailed t-test.
†Analysis of variance, controls versus SWEDD patients at baseline.
DaTSCAN, ^{123}iodine-labelled N-(3-fluoropropyl)–2β-carbomethoxy-3β-(4-iodophenyl) nortropane (^{123}I-FP-CIT) single photon emission CT; MMSE, Mini-Mental State Examination; SWEDD, scan without evidence of dopaminergic deficit; UPDRS, Unified Parkinson's Disease Rating Scale.

follow-up between the SWEDD patients with a positive DaTSCAN and those with a negative DaTSCAN were assessed by ANCOVA with age, sex, MMSE, educational attainment, disease duration and UPDRS-III set as covariates. The data analysis was performed by using SAS statistical software, V.9.4 (SAS Institute). Significance was assumed at a p<0.05.

RESULTS

Age-matched control subjects

The demographic and clinical characteristics of the 112 age-matched controls are presented in table 1. The mean (SD) age was 78.0 (7.0) years (range 67–92). The mean (SD) age of the men (n=40) was 77.3 (7.1) years and that of the women (n=72) was 78.4 (6.9), revealing no significant difference between the sexes (ANOVA, p=0.39). The mean (SD) MMSE score was 28.0 (1.3), showing no significant difference between men (28.2 (1.6)) and women (27.9 (1.2)) (ANOVA, p=0.28). The mean (SD) educational attainment was 10.3 (2.6) years, revealing no significant difference between men (10.6 (2.9)) and women (10.1 (2.5)) (ANOVA, p=0.32).

The mean (SD) scores of correct answers, responses of indistinguishable and responses of odourless on the OSIT-J were 7.0 (1.7), 0.7 (1.2),and 0.2 (0.5), respectively (table 2). In men, the mean (SD) scores of these endpoints were 6.8 (1.5), 0.9 (1.2) and 0.2 (0.4), respectively, whereas in women they were 7.1 (1.7), 0.6 (1.1) and

Table 2 Comparison of the smell test results between controls and patients, and between the patient groups

		SWEDD patients		Positive DaTSCAN			Negative DaTSCAN	
Smell test	Controls (n=112)	Baseline (n=32) (first DaTSCAN)	P value†	Baseline (n=21) (first DaTSCAN)	Follow-up (n=21) (second DaTSCAN)	P value*	Follow-up (n=11) (second DaTSCAN)	P value‡
OSIT-J score								
Correct answers	7.0 (1.7)	4.3 (2.5)	<0.001	4.3 (2.6)	3.7 (2.1)	0.12	3.4 (2.2)	0.71
Responses of indistinguishable	0.7 (1.2)	2.5 (2.9)	<0.001	2.6 (3.0)	2.2 (2.2)	0.56	1.7 (2.0)	0.57
Responses of odourless	0.2 (0.5)	1.0 (1.6)	<0.001	0.9 (1.2)	1.3 (2.5)	0.37	1.9 (3.9)	0.61

Data are presented as mean (SD).
*P values in OSIT-J score of SWEDD patients with positive DaTSCAN (n=21) were assessed between the first and second DaTSCAN, using paired-samples two-tailed t-test.
†Analysis of covariance (ANCOVA), controls v. patients with SWEDD at baseline.
‡P values in OSIT-J score were assessed between the patients with negative second DaTSCAN (n=11) and positive second DaTSCAN (n=21) (ANCOVA, setting age, sex, MMSE, educational attainment, disease duration and UPDRS-III as covariates).
DaTSCAN, ^{123}iodine-labelled N-(3-fluoropropyl)–2β-carbomethoxy-3β-(4-iodophenyl) nortropane (^{123}I-FP-CIT) single photon emission CT; OSIT, odor-stick identification test for Japanese; SWEDD, scan without evidence of dopaminergic deficit.

0.2 (0.5), respectively, showing no significant difference in any endpoint between the sexes (ANOVA, p=0.29, p=0.20, p=0.45, respectively).

SWEDD patients at baseline (first DaTSCAN)

A total of 32 SWEDD patients with mild parkinsonian signs of rest tremor, postural tremor and rigidity without bradykinesia, having a mean (SD) UPDRS-III score of 3.9 (0.5), were studied. 24 patients (75%) did not subjectively recognise parkinsonian symptoms at the entry while 8 patients noticed rest tremor. The demographic and clinical characteristics of the SWEDD patients are presented in table 1. The mean (SD) age was 76.0 (7.1) years and was not significantly different from that of the age-matched controls (p=0.16). The mean (SD) disease duration was 2.8 (7.3) months. All patients showed normal SBR values and normal shape pattern by visual assessment, and two of them demonstrated abnormally increased AI (AI=28.2%, 22.7%, respectively).

The mean (SD) MMSE score was 27.9 (2.0), which was not significantly different from that of the controls (p=0.86). The mean (SD) educational attainment was 10.1 (2.8) years and was also not significantly different compared with the controls (p=0.79).

The mean (SD) scores of correct answers, responses of indistinguishable and responses of odourless on the OSIT-J were 4.3 (2.5), 2.5 (2.9) and 1.0 (1.6), respectively (table 2). Comparisons between the controls and the SWEDD patients showed statistically significant differences in every endpoint (p<0.001).

SWEDD patients at follow-up (second DaTSCAN)

The mean (SD) follow-up duration of disease in the 32 patients between the first and the second DaTSCAN was 52.4 (11.6) months. The demographic and clinical characteristics of SWEDD patients with the second DaTSCAN are presented in table 1. The mean (SD) age was 80.7 (7.1) years, showing no significant difference compared with controls (ANOVA, p=0.059). The mean (SD) UPDRS-III score was 5.2 (2.0), significantly higher than that at baseline (p<0.001).

The mean (SD) MMSE score was 27.4 (2.5), showing no significant difference compared with controls (ANOVA, p=0.082) or with baseline (p=0.17).

The mean (SD) scores of correct answers, responses of indistinguishable and responses of odourless were 3.6 (2.1), 2.0 (2.1) and 1.5 (3.0), respectively. Comparisons between the controls and the SWEDD patients at follow-up showed statistically significant differences in every endpoint (ANCOVA, setting age and sex as covariates, p<0.001).

SWEDD patients with a positive DaTSCAN at follow-up

At follow-up, 21 of 32 SWEDD patients (65.6%) showed a significant decrease of putaminal SBR values below the normal range, that is, positive DaTSCAN. The demographic and clinical characteristics of SWEDD patients with a positive DaTSCAN (n=21) are presented in table 3. The mean (SD) age was 80.5 (7.7) years. The mean (SD) age of the men (n=9) was 77.3 (5.9) years and that of the women (n=12) was 82.9 (8.2) years, indicating no significant difference between the sexes (ANOVA, p=0.10). The mean (SD) disease duration was 51.6 (13.6) months. 11 of 21 SWEDD patients with a positive DaTSCAN, including 2 patients with increased AI at entry, revealed concurrently increased AI exceeding the reference value. By visual inspection, an abnormal shape pattern (a mixed type) was recognised in two patients (figure 1A,B).

The mean (SD) UPDRS-III scores at baseline and follow-up were 4.0 (0.5) and 5.5 (2.2), respectively, with the score at follow-up being significantly higher

Table 3 Clinical and demographic data, and the mean change in UPDRS-III and MMSE in SWEDD patients with positive DaTSCAN between first and second DaTSCAN, and in SWEDD patients at follow-up between positive and negative DaTSCAN

	Positive DaTSCAN			Negative DaTSCAN	
	Baseline (n=21) (first DaTSCAN)	Follow-up (n=21) (second DaTSCAN)	P value*	Follow-up (n=11) (second DaTSCAN)	P value†
Age, years	76.0 (7.6)	80.5 (7.7)		81.0 (6.1)	0.86
Male/female	9/12	9/12		4/7	
Years of schooling	9.7 (2.3)	9.7 (2.3)		11.0 (3.4)	0.20
Disease duration, months	3.6 (8.6)	51.6 (13.6)		54.1 (6.2)	0.57
UPDRS-III score (range)	4.0 (0.5) (3−5)	5.5 (2.2) (3–11)	0.003	4.5 (1.3) (3–7)	0.19
MMSE score	27.6 (2.0)	27.4 (2.5)	0.71	27.9 (2.3)	0.56

Data are shown as mean (SD).
*P values in UPDRS-III score and MMSE score of SWEDD patients with positive DaTSCAN were asssessed between the first and second DaTSCAN, using paired-samples two-tailed t-test.
†P values in age, years of schooling, disease duration, UPDRS-III score and MMSE score were assessed between SWEDD patients with positive DaTSCAN at follow-up and with negative DaTSCAN at follow-up, using analysis of variance.
DaTSCAN, ^{123}iodine-labelled N-(3-fluoropropyl)–2β-carbomethoxy-3β-(4-iodophenyl) nortropane (^{123}I-FP-CIT) single photon emission CT; MMSE, Mini-Mental State Examination; SWEDD, scan without evidence of dopaminergic deficit; UPDRS, Unified Parkinson's Disease Rating Scale.

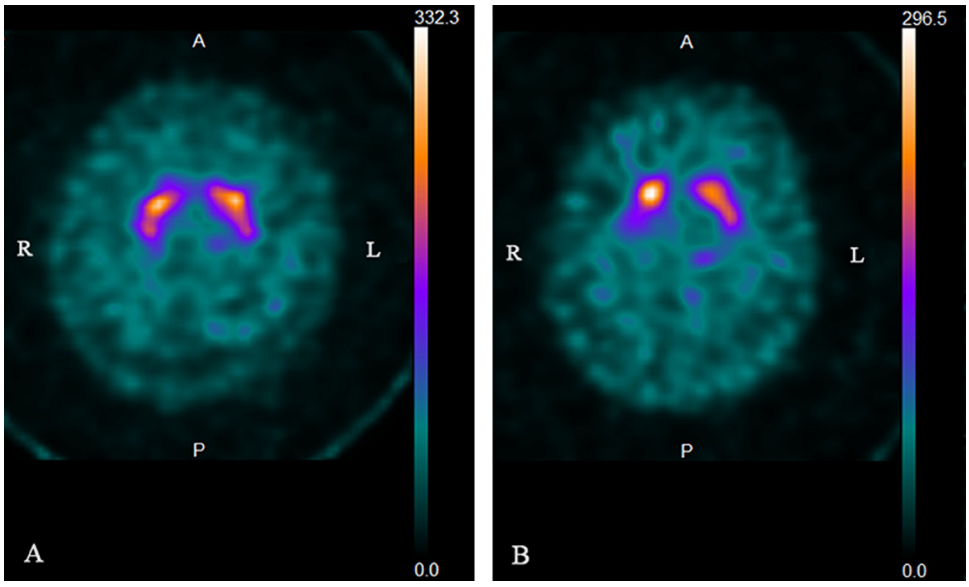

Figure 1 (A) A patient in their 50s with SWEDD with a UPDRS-III score of 4. The first DaTSCAN at entry showed normal tracer uptake (specific binding ratio (SBR): R, 5.72; L, 5.17; Avg: 5.45; asymmetry index (AI): 10.1% (normal range: <10.7%)). The pattern of uptake of DaTSCAN was almost normal by visual assessment. (B) The same patient in their 60s with a UPDRS-III score of 4 with a second positive DaTSCAN at a 51-month follow-up. A DaTSCAN image exhibited bilateral significant reduction of SBR (R: 4.23; L: 4.70; Avg: 4.49) and asymmetrical tracer uptake reduction dominantly in the right putamen by visual assessment, showing a 'mixed type' pattern (AI:11.4% (normal range: <10.8%)). DaTSCAN, ^{123}iodine-labelled N-(3-fluoropropyl)–2β-carbomethoxy-3β-(4-iodophenyl) nortropane (^{123}I-FP-CIT) single photon emission CT; SEWDD, scan without evidence of dopaminergic deficit; UPDRS, Unified Parkinson's Disease Rating Scale.

(p=0.003) (table 3). However, none of the patients subjectively had slowness of movement or difficulty in activities of daily life (ADL), nor objectively demonstrated obvious bradykinesia.

The mean (SD) MMSE score was 27.4 (2.5), showing no significant difference compared with controls (ANOVA, p=0.11) or with baseline (p=0.71) (table 3).

The mean (SD) scores of correct answers, responses of indistinguishable and responses of odourless were 3.7 (2.1), 2.2 (2.2) and 1.3 (2.5), respectively (table 2), revealing statistically significant differences in every endpoint compared with age-matched controls (ANCOVA, setting age and sex as covariates, p<0.001), although no significant difference was found compared with baseline (4.3 (2.6), 2.6 (3.0), 0.9 (1.2); p=0.12, p=0.56 and p=0.37, respectively) (table 2).

SWEDD patients with a negative DaTSCAN at follow-up

11 of 32 SWEDD patients (34.4%) did not have dopamine deficiency by second DaTSCAN imaging. The demographic and clinical characteristics are shown in table 3. The mean (SD) age was 81.0 (6.1) years, not significantly different compared with SWEDD patients with a positive DaTSCAN at follow-up (ANOVA, p=0.86). The mean (SD) age (years) of the men (n=4) was 76.8 (6.1) and that of women (n=7) was 83.4 (5.0), with no significant difference between them (ANOVA, p=0.80). The mean (SD) disease duration was 54.1 (6.2) months, showing no significant difference compared with SWEDD patients with a positive DaTSCAN at follow-up (p=0.57).

The mean (SD) UPDRS-III score was 4.5 (1.3), not significantly different compared with SWEDD patients with a positive second DaTSCAN imaging (n=21) (p=0.19), or with the baseline value (paired-samples two-tailed t-test, p=0.070). None of the 11 patients had difficulty in ADL, nor demonstrated bradykinesia.

The mean (SD) MMSE score was 27.9 (2.3), showing no significant difference compared with SWEDD patients with positive DaTSCAN (p=0.56) or with baseline (paired-samples two-tailed t-test, p=0.14). The mean (SD) educational attainment was 11.0 (3.4) years, not significantly different compared with SWEDD patients with positive DaTSCAN (p=0.20).

The mean (SD) scores of correct answers, responses of indistinguishable and responses of odourless were 3.4 (2.2), 1.7 (2.0) and 1.9 (3.9), respectively, showing statistically significant differences in every endpoint compared with age-matched controls (p<0.001, p=0.002 and p<0.001 by ANCOVA, setting age and sex as covariates, respectively). No significant difference was shown in any endpoint compared with baseline (n=11) (4.4 (2.5), 2.2 (2.9) and 1.4 (2.2); p=0.11, p=0.67, p=0.60 by paired-samples two-tailed t-test, respectively), or with SWEDD patients with positive DaTSCAN (n=21) (p=0.71, p=0.57 and p=0.61, respectively) (table 2).

DISCUSSION

According to the previous reports,[7–12 20] the frequency of SWEDD among patients with parkinsonism varies from

approximately 2.0%–20%. Some follow-up studies have indicated that SWEDD cases do not develop abnormal DaTSCANs[11] or show minimal progression of dopaminergic denervation.[8] Moreover, a minority (12.5%) of SWEDD subjects with asymmetric rest tremor show reduced striatal uptake over long-term follow-up with DaTSCAN,[9] which contrasts with the result in this study showing a higher conversion rate to abnormal DaTSCAN in the patients with rigidity in addition to asymmetric finger tremor. SWEDD may not be early PD, but rather a different disease entity,[8] and true SWEDD cases seem extremely rare in degenerative parkinsonism.[10]

In contrast, a significant portion (approximately 17%—61%) of the patients evaluated as having SWEDD at baseline were later confirmed to have PD during the follow-up period,[21–23] demonstrating the progression of presynaptic dopaminergic degeneration. This suggests that SWEDD patients truly have dopaminergic degeneration despite their normal imaging results in the very early, minimally symptomatic stages of PD. Thus, there have been continuing controversies regarding whether SWEDD should be categorised as a clinical entity of PD because SWEDD is clinically heterogeneous.[24]

In healthy controls, the age-related decline in striatal DAT uptake by DaTSCAN has been reported as only 3.6%–9.6% per decade,[25–27] and another report found no significant decline in 6-((18)F)fluoro-L-dopa (FDOPA).[2] Additionally, in a Japanese multicentre database of healthy controls for DaTSCAN, the age-related decline in DAT availability was 6.3% per decade on average for both sexes.[17]

On the other hand, the rate of dopaminergic loss in PD is significantly greater than that of healthy controls, and DaTSCAN imaging provides a quantitative biomarker for the progressive nigrostriatal dopaminergic degeneration in PD.[25] Most follow-up studies showed an annual decline of the striatal DAT uptake ranging from 5% to 13% in an early stage of PD and a stable decline during the follow-up period.[2 26 28–31] Moreover, another study revealed that the subsequent decrease of DAT binding depends on the initial clinical stage of the patients with PD (Hoehn and Yahr stage I: −6.81%; stage II: −6.05%; stage III: −1.25%, respectively, per 15 months).[31]

In the current study, the author assessed the SWEDD patients with mild parkinsonian signs by clinical signs and a first DaTSCAN at baseline and subsequently evaluated the patients by regular neurological examination and a second DaTSCAN performed at an appropriate point at 27–83 months after the first DaTSCAN, and these assessments were carried out in line with the above-mentioned pace of decrease of DAT binding in PD.[2 26 28–31] In this study, 21 out of 32 SWEDD patients (65.6%) showed a significant reduction of putaminal dopaminergic uptake (SBR) below the normal range accompanied by significantly deteriorated motor symptoms of UPDRS-III, although the degree of the deterioration itself seems slight probably due to the short-term follow-up duration (a mean of 4.0 (1.4) years) or the very early stage of PD. In prodromal PD, the subjects who DAT image converted to DAT deficit showed essentially no change in UPDRS, whereas SBR values consistently declined.[32] 11 out of the 21 patients (52.4%) also revealed abnormally increased AI.

On the other hand, 11 out of 32 SWEDD patients (34.4%) demonstrated no reduction of striatal DAT uptake by follow-up DaTSCAN, which probably implies that their stages of parkinsonian signs were too early for reduction of striatal DAT uptake to be detected even by DaTSCAN, because bradykinesia, compared with rigidity, is more closely related to a significant correlation with DAT activity, whereas the severity of neither rest tremor nor action tremor correlates well with striatal DAT binding among the motor symptoms of PD.[29] Moreover, striatal DAT binding in PD may reflect dopaminergic activity rather than the loss of substantia nigra neurons because the number of substantia nigra neurons is not associated with striatal DAT binding in PD.[33 34] At the symptom onset of PD, the loss of presynaptic DAT in the putamen was substantially greater in younger patients compared with older patients, but the rate of progression of the transporter loss was significantly slower in younger patients, suggesting that older PD patients have less efficient compensatory mechanisms.[35] The rate of decline of DAT binding during the very early phase of PD could be considerably slower than in the clinical stage.[36] Thus, in this study, a normal DaTSCAN in old patients with mild parkinsonian signs with SWEDD could represent false-negative imaging cases in the very initial stage of the disease because compensatory downregulation of DAT in the early stages of PD may be less efficient in older-onset patients than in younger-onset patients,[37] although the author could not entirely exclude the possibility that SWEDD subjects with normal DaTSCAN at follow-up study may not be in the early stage of idiopathic PD but rather may have a different disease entity. These inconsistencies may reflect methodological limitations as well as the heterogeneity in patient populations.

In connection with cognitive function, SWEDD subgroups have been shown to possess similar cognitive symptoms irrespective of their final clinical diagnosis.[38] Moreover, some patients with idiopathic PD with SWEDD demonstrated early cognitive decline, suggesting that patients with SWEDD may be at even greater risk for cognitive decline than patients with DaTSCAN-positive early-stage PD.[39] In this study, MMSE scores both at baseline and follow-up in SWEDD patients showed no significant difference compared with those in age-matched controls, and moreover, no significant difference was observed between SWEDD patients at baseline and follow-up, probably because of the early stages of the disease or the short period of follow-up.

In relation to the smell test, patients with parkinsonism and SWEDD had normal olfaction or significantly milder olfactory dysfunction as compared with patients with PD.[21] On the other hand, the smell test indicated a high probability of PD in 85.3% of PD patients as opposed

to only 23.8% of patients with SWEDD.[40] In this study, olfactory function in SWEDD patients was significantly impaired at every endpoint compared with age-matched controls. These findings seem to be reasonable because the majority of SWEDD patients in the current study eventually converted to PD as confirmed by DaTSCAN imaging, and olfactory impairment is an early and more common symptom in PD compared with SWEDD.[40]

In conclusion, the majority (65.6%) of SWEDD patients with mild rest tremor and rigidity in this study could be classified as cases of idiopathic PD by a follow-up DaTSCAN. Because the frequency at which subjects with SWEDD are determined to be converted to PD by final assessment should depend on the length of periods of follow-up study, further longitudinal and long-term follow-up studies by clinical and DaTSCAN investigation covering larger samples of SWEDD subjects are needed to evaluate whether SWEDD subjects, particularly those with subtle or mild parkinsonian motor signs, are properly classified into idiopathic PD. Such investigations would also contribute toward disease-modifying therapies to be started earlier in the disease process and prevention clinical trials in the early stages of PD.

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