Odor Identification Test as an Indicator of Idiopathic REM Sleep Behavior Disorder

Tomoyuki Miyamoto, MD, PhD,[1]* Masayuki Miyamoto, MD, PhD,[1] Masaoki Iwanami, MD,[1] Keisuke Suzuki, MD, PhD,[1] Yuichi Inoue, MD, PhD,[2] and Koichi Hirata, MD, PhD[1]

[1]*Department of Neurology, Center of Sleep Medicine, Dokkyo Medical University School of Medicine, Tochigi, Japan*
[2]*Japan Somnology Center, Neuropsychiatry Research Institute, Tokyo, Japan*

Abstract: Reduction of olfactory function in idiopathic rapid-eye-movement (REM) sleep behavior disorder (iRBD) is of the same magnitude as that found in patients with Parkinson's disease (PD) and dementia with Lewy bodies (DLB). We assessed olfactory function using the Odor Stick Identification Test for Japanese (OSIT-J) in 48 Japanese patients with iRBD, 21 with PD, and 34 with obstructive sleep apnea syndrome (OSAS). Possible score of the OSIT-J ranges from 0 to 12. OSIT-J scores were 4.9 ± 2.8 in patients with iRBD, 4.8 ± 2.8 in patients with PD, and 9.9 ± 1.4 in OSAS patients. An OSIT-J score of 8.5 was associated with a sensitivity of 88.2 and 85.3%, respectively, and specificity of 83.3 and 85.7%, respectively, in differentiating iRBD or PD patients from OSAS patients. Odor identification is impaired in Japanese patients with iRBD and PD. The results suggest that OSIT-J, which is a short and simple nonlexical olfactory identification test, can be useful as a clinical indicator for iRBD with Lewy body formation and is appropriate in the Japanese elderly population. © 2008 Movement Disorder Society

Key words: REM sleep behavior disorder; Parkinson's disease; Lewy body disease; olfactory dysfunction; Odor Stick Identification Test for Japanese (OSIT-J)

Dream enactment behavior is a core feature of rapid-eye-movement (REM) sleep behavior disorder. Idiopathic RBD (iRBD) was suggested to be a manifestation of an evolving synucleinopathy, such as Parkinson's disease (PD), dementia of Lewy bodies (DLB), and multiple system atrophy (MSA).[1] Lewy body pathology first affects the anterior olfactory nucleus and lower brainstem nuclei, including the dorsal motor nucleus (stage 1 according to Braak et al.), before involving the upper brainstem areas such as the locus ceruleus (stage 2) and substantia nigra (stage 3), and ultimately the cerebral cortex.[2] "Top-down" and "bottom-up" early stage symptoms have been observed in Lewy body-related α-synucleinopathies such as PD and DLB. Indeed, they may be the same disorder, but with different points of origin as noted by Langston.[3] In addition, neuropathologically, Lewy bodies were found in iRBD and distributed almost in the same manner as in PD.[1] Therefore, in PD, DLB, and iRBD, olfactory and autonomic dysfunctions are expected to occur early and to precede motor and/or cognitive manifestations.

Several simple methods have been developed to evaluate the ability to identify a variety of smells. The Brief University of Pennsylvania Smell Identification Test (B-SIT)[4–6] and Sniffin's Sticks[7,8] have been used to detect olfactory disorders in iRBD. However, these tests are not appropriate for Japanese without modification because some smells are unfamiliar because of cultural differences. In this study, we used the Odor Stick Identification Test for Japanese (OSIT-J),[9–11] developed specifically for Japanese and with confirmed efficacy, in patients with iRBD and PD. We investigated the frequency of olfactory disorders in these conditions and the utility of the OSIT-J as a supportive tool for their diagnosis.

TABLE 1. *Patient demographics*

	iRBD (n = 48)	PD (n = 21)	OSAS (n = 34)	P
Male/female	37/11	12/9	28/6	N/A
Age[a] (yr)	67.1 ± 6.8	63.9 ± 9.4	62.2 ± 6.7	0.012
MMSE[a]	28.3 ± 1.8	28.0 ± 1.9	28.6 ± 1.9	0.4933
Mean duration of disease[b] (yr)	6.7 ± 7.5	5.1 ± 4.5	N/A	0.5503

Data presented are mean ± SD, N/A = not applicable.
[a]One-way analysis of variance.
[b]Mann–Whitney U test.
iRBD, idiopathic REM sleep behavior disorder; PD, Parkinson's disease; OSAS, obstructive sleep apnea syndrome; MMSE, mini mental state examination.

METHODS

Patients and Control Subjects

A total of 112 patients were enrolled in this study at the sleep disorder clinic in our hospital between May 2007 and January 2008. Among these were 48 consecutive patients with polysomnography (PSG)-confirmed iRBD (37 males, 11 females), 34 consecutive patients with obstructive sleep apnea syndrome (OSAS) (28 males, 6 females; pretreatment, mean apnea hypopnea index (AHI) = 50.0 ± 24.2 events/hour; mean nocturnal O_2 saturation = 94.7 ± 2.5%; mean BMI = 27.1 ± 4.1kg/m^2), and 21 consecutive age-matched patients with PD who were under treatment (12 males, 9 females) (Table 1). The OSAS group was diagnosed as having OSAS without RBD or REM sleep without atonia by PSG and began CPAP with good efficacy.

IRBD was defined according to the criteria in the International Classification of Sleep Disorders second edition (ICSD, 2nd ed.).[12] Patient interviews focused on motor events during sleep associated with dreaming that may have included screaming, self-injuries, or injuries to their bed partner; patients' bed partners were interviewed to confirm the latter.

Clinical diagnosis of PD[13] was made by neurological specialists according to established consensus criteria. Also, all patients as assessed by a neurologist were without progressive supranuclear palsy, MSA, corticobasal degeneration, and other forms of atypical parkinsonism. PD patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr (H&Y) stage for evaluation of disease severity. Mean H&Y stage and UPDRS-III among PD patients were 2.2 ± 0.7 and 18.8 ± 8.8, respectively. With regard to medications, 12 patients were taking levodopa with decarboxylase inhibitor (L-dopa/DCI) and 17 patients were taking dopamine agonists with a mean equivalent L-dopa dose of 310.3 ± 219.0 mg/day.[14]

Cognitive function was evaluated by the Mini Mental State Examination (MMSE), with a score of less than 24 points indicative of dementia.[15] With regard to iRBD and PD, the Folstein MMSE was performed and its correlation with the OSIT-J score was examined.

Of the 112 patients, 9 were excluded from this study; 5 OSAS patients because of nasal disease and 4 PD patients with a MMSE score of less than 24. All included subjects were free from other conditions that can affect olfactory function such as usage of certain medications, nasal surgery, pulmonary disease, hormonal disorders, perennial allergies, or abuse of drugs or alcohol.

Data Collection and Analysis

Patients with iRBD underwent 1 night (8 hours) of polysomnographic recording in our sleep laboratory. PSG consisted of the use of a standard montage for scoring sleep stages: left and right oculograms, chin EMG, central (C3-A2, C4-A1) and occipital (O1-A2, O2-A1) EEG, and ECG. Sleep staging followed the recommendations of Rechtschaffen and Kales.[16] For the iRBD group, REM sleep was scored without the chin EMG criterion, thereby allowing for the maintenance of muscle tone during REM sleep. Recordings of oral and nasal airflow, thoracic and abdominal movements, and oximetry were made to detect apnea and hypopnea. Surface EMG recordings of the right and left anterior tibialis muscles were made to quantify leg movements. The scoring of arousal and periodic limb movements followed published guidelines.[17] Assuming that olfactory abilities in PD patients are not influenced by dopaminergic drugs, regular medications were not withdrawn.[18]

The OSIT-J (Daiich Yakuhin Sangyo Co. Ltd., Tokyo, Japan) is composed of 12 different odorants familiar to the Japanese population. Previously, the OSIT-J had included 13 odorants,[9–11] but the putrid odor was eliminated, leaving only 12 odors to be manufactured and supplied with the test. These odorants are described as condensed milk, cooking gas, curry, hinoki (Japanese cypress wood), India ink, Japanese orange, menthol, perfume, roasted garlic, rose, socks

smelling of sweat, and wood. Test odorants are micro-encapsulated in a melamine resin and incorporated within an odorless solid cream dispensed in a lipstick container. The cream is applied in a circle 2 cm in diameter to a 5.3 cm × 10.5 cm strip of paraffin paper. The paper strip is folded in two and rubbed together to release the odorant. Subjects open the folded paper in front of both nostrils and sniff. For each odorant, subjects are presented with a card showing four names of odors and are asked to select the odor presented. If the subject cannot choose one of the four, he or she must then respond by selecting one of two alternative answers: "detectable but not recognizable (unknown)" or "no odor detected (not detected)." The total number of correct answers for the 12 odorants presented, expressed as a percentage, is the OSIT-J score. In addition, because it requires no deodorizing filter or device, this test is feasible for use in outpatient clinics and at the bedside and can be completed within about 10 minutes.

All study procedures were approved by the Ethics Review Committee of Dokkyo Medical University. Each subject provided informed consent.

Statistical Analysis

The difference in the OSIT-J score among the iRBD, PD, and OSAS groups was evaluated by one-way analysis of variance (ANOVA) followed by post hoc Bonferroni correction. Spearman rank correlation test was used to evaluate whether age, disease duration, or MMSE was correlated with the OSIT-J score in patients with iRBD and whether age, disease duration, MMSE, UPDRS-III, or mean equivalent L-dopa dose was correlated with the OSIT-J score in those with PD. In the OSAS patients, we used the Spearman rank correlation test to determine whether age or MMSE was correlated with the OSIT-J score. Receiver operating characteristic (ROC) analysis was used to calculate the respective optimal cutoff values of the OSIT-J score for patients with iRBD, PD, and OSAS. All values are expressed as the mean ± SD. A P-value <0.05 was considered to be statistically significant. Statistical analyses were performed with Statistical Package for Social Science Software (Graphpad Prism, San Diego, CA and SPSS II Windows Ver 11.0, Japan).

RESULTS

The results of olfactory tests are presented in Figure 1. The total scores (accurate response rates) on the
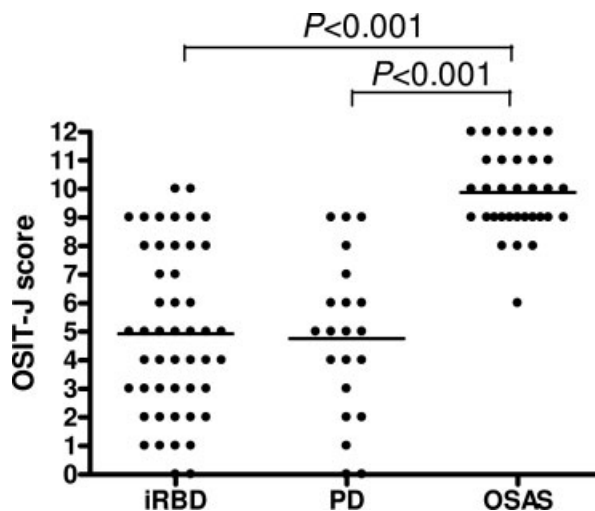

FIG. 1. Olfactory discrimination in patients with idiopathic REM sleep behavior disorder (iRBD), Parkinson's disease (PD), and obstructive sleep apnea syndrome (OSAS). Shown are scatter plots of individual scores for the odor stick identification test for Japanese (OSIT-J). Horizontal lines indicate mean levels.

OSIT-J were 4.9 ± 2.8 (41.1 ± 24.0%) in those with iRBD, 4.8 ± 2.8 (39.7 ± 23.1%) in those with PD, and 9.9 ± 1.4 (82.4 ± 11.9%) in OSAS patients. Scores were significantly lower in the iRBD ($P <$ 0.001) and PD ($P <$ 0.001) groups than in the OSAS group.

The OSIT-J score had no correlation with age (r = −0.204; P = 0.163), duration of illness (r = −0.275; P = 0.058), or the MMSE score (r = −0.005; P = 0.969) in iRBD patients nor with duration of illness (r = −0.098; P = 0.672), the MMSE score (r = 0.206; P = 0.368), UPDRS-III (r = −0.033; P = 0.885), or the mean equivalent L-dopa dose (r = −0.025; P = 0.911) in PD patients. No significant correlation was found between the OSIT-J score and the MMSE score (r = 0.266; P = 0.128) in OSAS patients. A significant correlation between age and OSIT-J score was observed in both PD (r = −0.705; P = 0.0004) and OSAS patients (r = −0.555; P = 0.0006).

Next, the optimal cutoff value and sensitivity and specificity of the OSIT-J score in iRBD and PD patients were calculated. For differentiation of iRBD patients from OSAS patients with the cutoff value at 8.5, sensitivity and specificity were 88.2 and 83.3%, respectively, and positive and negative predictive values were 90.9 and 78.9%, respectively. For differentiation of PD patients from OSAS patients with the cutoff value at 8.5, sensitivity and specificity were 85.3 and 85.7%, respectively, and positive and negative predictive values were 78.3 and 90.6%, respectively. In

TABLE 2. *Discriminant analysis for the odor identification test in iRBD and PD compared with OSAS*

	Cutoff value	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Likelihood ratio	ROC AUC (95% CI)	SE	*P*-value
Compared with iRBD	8.5	88.2	83.3	90.9	78.9	5.28	0.932 (0.882–0.982)	0.026	<0.001
Compared with PD	8.5	85.3	85.7	78.3	90.6	5.96	0.935 (0.873–0.997)	0.031	<0.001

iRBD, idiopathic REM sleep behavior disorder; PD, Parkinson's disease; ROC AUC, receiver operating characteristic area under curve; SE, standard error.

addition, the likelihood and the area under the ROC curve were calculated (Table 2). With regard to the 12 odorants, correct answers were given by fewer than 40% of patients with iRBD for rose, Japanese oranges, condensed milk, cooking gas, wood, Japanese cypress "hinoki," and menthol (Table 3). Correct answers were obtained at relatively at high rates in iRBD and PD patients for curry, roasted garlic, and sweaty socks. Rose was the best discriminator with a sensitivity of 70.8% and specificity of 82.4% in iRBD. India ink was the best discriminator with a sensitivity of 81.0% and specificity of 83.3% in PD (Table 3).

Figure 2 shows the odor identification rate for each of the 12 odors in the OSIT-J among the OSAS subjects.

DISCUSSION

Evaluation by the OSIT-J revealed that olfactory dysfunction and a reduction in olfactory ability were observed more frequently in Japanese patients with iRBD and a Lewy body disease, such as PD, than in OSAS patients. Besides, to differentiate iRBD and PD from OSAS, the OSIT-J with a cutoff value of 8.5 yielded sensitivity of 88.2 and 85.3% and specificity of 83.3 and 85.7%, respectively. Therefore, a cutoff value of 8 was considered useful for differentiating iRBD and PD from OSAS. Another series showed that B-SIT may discriminate iRBD patients from healthy controls with a sensitivity of 61% and specificity of 83%.[6] The mean score of OSIT-J (4.9 ± 2.8) was much lower than that of B-SIT (7.1 ± 2.5) in iRBD patients and sensitivity was higher (88.2 vs. 61.0%). This is likely due to the presence of two additional answers in the OSIT-J (unknown and not detected) instead of the forced-choice paradigm of the B-SIT. If a forced-choice test presents only the choice of the correct answer without expressions of either "unknown" or "not detected," some subjects may not be able to select the choice that best describes their feelings. In such cases,

TABLE 3. *Odor item identification rates for iRBD and PD (%)*

	Correct answer		Wrong answer		Unknown		Not detected		Sensitivity		Specificity	
	iRBD	PD	iRBD	PD	iRBD	PD	iRBD	PD	iRBD	PD	iRBD	PD
Sweet odor												
Perfume	43.8	42.9	37.5	42.9	10.4	9.5	8.3	4.8	56.3	57.1	100.0	100.0
Rose	29.2	47.6	37.5	38.1	31.3	9.5	2.1	4.8	70.8	66.7	82.4	77.8
Japanese orange	37.5	19.0	39.6	76.2	16.7	0.0	6.3	4.8	62.5	81.0	67.6	66.7
Condensed milk	31.3	33.3	35.4	42.9	27.1	9.5	6.3	14.3	68.8	66.7	70.6	61.1
Spices												
Curry	72.9	71.4	16.7	14.3	8.3	4.8	2.1	9.5	27.1	28.6	100.0	100.0
Roasted garlic	52.1	42.9	27.1	42.9	16.7	9.5	4.2	4.8	47.9	57.1	94.1	94.4
Rotten, excrea												
Sweaty smelling socks	47.9	52.4	41.7	38.1	8.3	4.8	2.1	4.8	52.1	47.6	85.3	83.3
Gas, smoke												
Cooking gas	39.6	33.3	37.5	52.4	18.8	4.8	4.2	9.5	60.4	66.7	82.4	73.5
Wood, grass, herb												
India ink	41.7	19.0	16.7	28.6	25.0	23.8	16.7	28.6	58.3	81.0	88.2	83.3
Wood	31.3	33.3	27.1	23.8	22.9	14.3	18.8	28.6	68.8	66.7	52.9	47.2
Japanese cypress, "hinoki"	33.3	42.9	27.1	33.3	31.3	9.5	8.3	14.3	66.7	57.1	76.5	77.8
Menthol	33.3	42.9	22.9	28.6	35.4	23.8	8.3	4.8	66.7	57.1	88.2	91.7

Data were obtained from 48 Japanese iRBD and 21 PD patients.
Sensitivity refers to the proportion of iRBD and PD patients who had an abnormal olfactory result.
Specificity refers to the proportion of OSAS subjects who had a normal olfactory result.
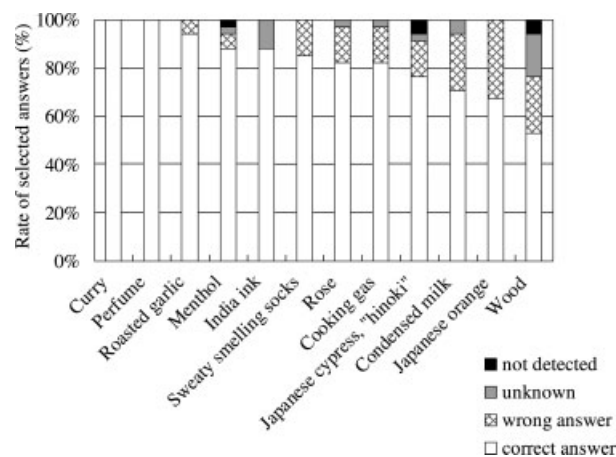iRBD, idiopathic REM sleep behavior disorder; PD, Parkinson's disease.

FIG. 2. Odor identification rate for each item on the OSIT-J in subjects with obstructive sleep apnea syndrome (n = 34). The odor identification rate was greater than 80% for each item. However, identification rates for four items, Japanese cypress, "hinoki" (76.5%), condensed milk (70.6%), Japanese orange (67.6%), and wood (59.5%), were reduced in subjects with OSAS.

the subject might choose an answer halfheartedly or too quickly, and thus reducing the accuracy of the test and the correlation between test results and subjective symptoms.[10] In the iRBD group, a rather large number of patients had only slightly decreased scores. This implies that olfactory dysfunction may appear prior to or closely following the onset of RBD because there was no relationship between the duration of iRBD and OSIT-J scores. On the other hand, Stiasny-Kolster et al.[8] reported that only 4 RBD patients in their series were classified as having normosmia according to the TDI score, but that 3 of the 4 had already presented with an increased olfactory threshold. Hence, an increased olfactory threshold is more sensitive than odor identification to differentiate iRBD or PD patients from OSAS patients.

The hypothesis was proposed that reduction of olfactory function in iRBD is of the same magnitude as in patients with Lewy body disease, including PD and DLB by Postuma et al.,[5] Fantini et al.,[6] and Stiasny-Kolster et al.[8] They noted a marked olfactory impairment in an RBD group compared with controls; however, they did not directly compare RBD with PD or DLB groups, but reviewed the literature to come to their conclusion.[5,6,8] Olfactory testing may discriminate PD patients from healthy controls with a sensitivity of 88% and specificity of 83%.[18] The deficit in PD contrasts with previous reports of preserved or only mildly reduced olfaction in patients with atypical parkinsonism such as tauopathies or MSA. Olfactory dysfunction, i.e., odor detection, discrimination, and

identification, is known to be a common sign in PD. However, patients usually do not report this dysfunction spontaneously but it can be detected by special olfactory tests. Interestingly, olfactory abnormalities are reported in Alzheimer's disease (AD), but anosmia appears to be common in DLB but not in pure AD.[19] A Lewy body variant of AD had an increased prevalence of anosmia (65%) compared with "pure" AD (23%; odds ratio = 6.3).[20] These reports suggest that Lewy body disease and neurodegenerative diseases with an olfactory disorder share some common features. Thus, olfactory testing may be an additive, helpful and a simple nonlexical diagnostic instrument to support the discrimination of a Lewy body syndrome such as PD or DLB from healthy subjects or atypical parkinsonian syndrome such as tauopathies or MSA.[21–23] In humans, the primary olfactory area of the piriform cortex and the amygdala/entorhinal area and the secondary olfactory area of the orbitofrontal cortex and insular cortex were found to play a critical role.[24,25] Lewy bodies and Lewy neurites are frequently found in hippocampal structures, including the amygdala, in PD[2,26] and DLB.[27] In PD, the underlying mechanism for this observation may involve a disrupted mesolimbic pathway,[28] and involvement of the amygdala and hippocampus is important[29,30] as well as the olfactory bulbs.[31] As mentioned previously, the mesolimbic pathway is important in the pathogenesis of RBD[32] and is thought to be key to the pathogenesis of disturbed olfactory sensation and RBD. On the other hand, based on the kinds of odorants, strong smells of curry and sweaty socks were more accurately identified than other odorants by the iRBD and PD patients. It was shown that an uncomfortable smell activated brain areas unrelated to the olfactory tract in experiments on smells,[33] which may explain the difference.

Marked olfactory dysfunction occurs in PD at the earliest stage of the illness, affecting between 70 and 100% of patients and includes impairment in detection threshold, identification, and discrimination. Olfactory test scores correlate with the levels of dopamine transporter within the striatum of the brain of patients with early PD.[34] Conversely, 4 years from baseline, 7% of individuals with idiopathic olfactory loss had newly developed clinical PD symptoms, and, altogether, 13% of patients presented with abnormalities of the motor system relevant to PD.[35] As the olfactory system is impaired before the appearance of symptoms of motor dysfunction, olfactory impairment may be detected not only in very early stages of PD and overt RBD but also in the "premotor phase" in PD and "before dream enactment behavior" in RBD.

This study has some limitations. First, OSAS patients with a good response to CPAP therapy were selected as the control group, and this control group was slightly younger than the iRBD group. Second, the male-to-female ratio was not matched between the iRBD and OSAS groups. Olfactory functions are generally negatively associated with age and deteriorate in the elderly.[37] Olfactory functions are better in females than in males. In a study of B-SIT, the score was higher by one to two points in females than in males in all age groups.[37] Comparison of different generations and genders in a larger number of cases is warranted. Third, because PD patients were not de novo cases, it was not possible to rule out the potential influence of drug treatment on olfactory functions. Fourth, the lack of PSG in PD patients may have affected the results, because olfactory function might be differently affected in PD patients with RBD compared with PD patients without RBD.

REFERENCES

1. Gagnon JF, Postuma RB, Mazza S, et al. Rapid-eye-movement sleep behaviour disorder and neurodegenerative diseases. Lancet Neurol 2006;5:424–432.
2. Braak H, Del Tredici K, Rüb U, et al. Staging of pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197–211.
3. Langston JW. The Parkinson's complex: parkinsonism is just the tip of the iceberg. Ann Neurol 2006;59:591–596.
4. Doty RL, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). Laryngoscope 1996;106:353–356.
5. Postuma RB, Lang AE, Massicotte-Marquez J, et al. Potential early markers of Parkinson disease in idiopathic REM sleep behavior disorder. Neurology 2006;66:845–851.
6. Fantini ML, Postuma RB, Montplaisir J, et al. Olfactory deficit in idiopathic rapid eye movements sleep behavior disorder. Brain Res Bull 2006;70:386–390.
7. Kobal G, Hummel T, Sekinger B, et al. "Sniffin' sticks": screening of olfactory performance. Rhinology 1996;34:222–226.
8. Stiasny-Kolster K, Doerr Y, Möller JC, et al. Combination of 'idiopathic' REM sleep behaviour disorder and olfactory dysfunction as possible indicator for synucleinopathy demonstrated by dopamine transporter FP-CIT-SPECT. Brain 2005;128:126–137.
9. Hashimoto Y, Fukazawa K, Fujii M, et al. Usefulness of the odor stick identification test for Japanese patients with olfactory dysfunction. Chem Senses 2004;29:565–571.
10. Kobayashi M, Nishida K, Nakamura S, et al. Suitability of the odor stick identification test for the Japanese in patients suffering from olfactory disturbance. Acta Otolaryngol 2004;124 (Suppl 553):74–79.
11. Saito S, Ayabe-Kanamura S, Takashima Y, et al. Development of a smell identification test using a novel stick-type odor presentation kit. Chem Senses 2006;31:379–391.
12. American Academy of Sleep Medicine. International classification of sleep disorders, 2nd ed.: Diagnosis and cording manual. Westchester, IL: American Academy of Sleep Medicine; 2005. p 148–152.
13. Hughes AJ, Daniel SE, Kilford L, et al. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.
14. Vingerhoets FJG, Villemure JG, Temperli P, et al. Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow-up. Neurology 2002;58:396–401.
15. Bleecker ML, Bolla-Wilson K, Kawas C, et al. Age-specific norms for the mini-mental state exam. Neurology 1988;38:1565–1568.
16. Rechtschaffen A, Kales A, editors. A Manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles: UCLA Brain Information Service/Brain Research Institute; 1968.
17. Coleman RM. Periodic movements in sleep (nocturnal myoclonus) and restless legs syndrome. In: Guilleminaut C, editor. Sleeping and waking disorders: indications and techniques. Menlo Park, CA: Addison Wesley; 1982. p 265–295.
18. Tissingh G, Berendse HW, Bergmans P, et al. Loss of olfaction in de novo and treated Parkinson's disease: possible implications for early diagnosis. Mov Disord 2001;16:41–46.
19. McShane RH, Nagy Z, Esiri MM, et al. Anosmia in dementia is associated with Lewy bodies rather than Alzheimer's pathology. J Neurol Neurosurg Psychiatry 2001;70:739–743.
20. Olichney JM, Murphy C, Hofstetter CR, et al. Anosmia is very common in the Lewy body variant of Alzheimer's disease. J Neurol Neurosurg Psychiatry 2005;76:1342–1347.
21. Doty RL, Stern MB, Pfeiffer C, et al. Bilateral olfactory dysfunction in early stage treated and untreated idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1992;55:138–142.
22. Doty RL, Gilbe LI, McKeown DA, et al. Olfactory testing differentiates between progressive supranuclear palsy and idiopathic Parkinson's disease. Neurology 1993;43:962–965.
23. Wenning GK, Shephard B, Hawkes C, et al. Olfactory function in atypical parkinsonian syndromes. Acta Neurol Scand 1995;91:247–250.
24. Zatorre RJ, Jones-Gotman M, Evans AC, et al. Functional localization of human olfactory cortex. Nature 1992;360:339–341.
25. Poellinger A, Thomas R, Lio P, et al. Activation and habituation in olfanction—an fMRI study. Neuroimage 2001;13:547–560.
26. Harding AJ, Stimson E, Henderson JM, et al. Clinical correlates of selective pathology in the amygdala of patients with Parkinson's disease. Brain 2002;125:2431–2445.
27. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. Brain 2002;125:391–403.
28. Doty RL, Deems DA, Stellar S. Olfactory dysfunction in parkinsonism: general deficit unrelated to neurologic signs, disease stage, or disease duration. Neurology 1998;38:1237–1244.
29. Westermann B, Wattendorf E, Schwerdtfeger U, et al. Functional imaging of the cerebral olfactory system in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2008;79:19–24.
30. Masaoka Y, Yoshimura N, Inoue M, et al. Impairment of odor recognition in Parkinson's disease caused by weak activations of the orbitofrontal cortex. Neurosci Lett 2007;412:45–50.
31. Scherfler C, Schocke MF, Seppi K, et al. Voxel-wise analysis of diffusion weighted imaging reveals disruption of the olfactory tract in Parkinson's disease. Brain 2006;129:538–542.
32. Iranzo A, Graus F, Clover L, et al. Rapid eye movement sleep behavior disorder and potassium channel antibody-associated limbic encephalitis. Ann Neurol 2006;59:178–181.
33. Savic I. Imaging of brain activation by odorants in humans. Curr Opin Neurobiol 2002;12:455–461.
34. Siderowf A, Newberg A, Chou KL, et al. [99mTc]TRODAT-1 SPECT imaging correlates with odor identification in early Parkinson disease. Neurology 2005;64:1716–1720.
35. Haehner A, Hummel T, Hummel C, et al. Olfactory loss may be a first sign of idiopathic Parkinson's disease. Mov Disord 2007;22:839–842.
36. Hawkes C. Olfaction in neurodegenerative disorder. In: Hummel T, Welge-Lüssen A, editors. Taste and smell. An update (Adv Otorhinolaryngol). Basel: Karger; 2006. p 133–151.