Characteristics of olfactory dysfunction in patients with temporal lobe epilepsy

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A B S T R A C T

Objective: To determine the characteristics of olfactory dysfunction in patients with temporal lobe epilepsy (TLE).
Methods: Odor identification was assessed using the odor stick identification test for Japanese (OSIT-J, full score 12 points) in 65 patients with TLE and in 74 controls.
Results: The mean OSIT-J score was significantly lower in patients with TLE (mean ± SD = 8.1 ± 2.8; median = 9) than in the control subjects (mean ± SD = 10.6 ± 1.1; median = 11) (P < 0.005). Olfactory dysfunction (hyposmia/anosmia) was associated with bilateral seizure foci and older age of onset in TLE. Patients who underwent temporal lobectomy for hippocampal sclerosis did not show significant decline after long-term recovery. The Indian ink part of OSIT-J was useful for the detection of olfactory deficits in patients with TLE (sensitivity = 47%, specificity = 93%). Patients with TLE tended to have preserved olfactory ability for stimulating odors and for familiar odors of daily life.
Significance: We observed characteristic odor identification deficits for individual odors used in OSIT-J. Our study findings provide deeper insight into the underlying mechanism of olfactory function in patients with TLE and may be beneficial in the clinical management of these patients.

Olfactory dysfunction is observed in epilepsy and in neurodegenerative disorders such as Alzheimer’s disease (AD) and Parkinson’s disease (PD) [3–5]. In an earlier study, it was reported that anosmia/hyposmia is a biomarker for the early diagnosis of PD [5]. However, studies on the relationship between TLE and olfactory dysfunction are relatively limited, and determination of the clinical implication of this relationship is necessary.
Several smell identification tests have been developed to evaluate olfactory function. The University of Pennsylvania Smell Identification Test (UPSIT) and the Cross-Cultural Smell Identification Test are used in the United States, and the “Sniffin’ Sticks” test is used in Germany [6,7]. However, several odors used in these tests are unfamiliar to many Japanese individuals. The odor stick identification test for Japanese (OSIT-J) uses 12 odors, all of which have been confirmed as familiar to healthy Japanese individuals with normal olfaction, and the test has been validated as a useful evaluation tool for olfactory identification [8]. In a validation study of healthy subjects from the United States, it was reported that...
OSIT-J is effective for the identification of normal olfactory function [9]. This study is the first study to investigate the characteristics of olfactory dysfunction in patients with TLE using OSIT-J.

2. Materials and methods

2.1. Patients and control subjects

Between July 2018 and August 2019, we administered OSIT-J to 79 patients with TLE at Fukuoka Sannoo hospital located in Fukuoka, Japan. Of the 79 patients, 14 were excluded from the study. Of the 14 excluded patients, one had nasal disease, 12 had a history of smoking, and it was found after the test that one patient did not have TLE. Clinical diagnosis of TLE was made by epilepsy specialists based on comprehensive evaluation using the following criteria: (1) seizure semiology consistent with TLE, i.e., behavioral arrest, alteration of consciousness, orofacial automatisms, and manual automatisms; (2) interictal electroencephalography (EEG) and/or video-EEG showing temporal spikes or ictal EEG seizure pattern in the temporal region; and (3) no lesions other than temporal lobe lesions identified on magnetic resonance imaging (MRI). Bilateral TLE was defined as bilateral independent ictal onset on scalp or intracranial recordings.

The study group consisted of 65 patients with TLE aged 18–69 years (mean ± standard deviation [SD] = 40.3 ± 15.3 years; median = 36.0 years) (Table 1). Considering the age-related decline of olfactory function, patients who are 70 years old and above were excluded from the study. The laterality of TLE was right in 13 patients, left in 34 patients, bilateral in 13 patients, and unknown in 5 patients.

| Demographics | Value |
|--------------|-------|
| Gender       |       |
| Male         | 33 (51) |
| Female       | 32 (49) |
| Age (years)  |       |
| Range        | 18–69 |
| Mean ± SD    | 40.3 ± 15.3 |
| Median       | 36.0 |
| Seizure duration (years) |       |
| Range        | 2–54 |
| Mean ± SD    | 18.5 ± 13.9 |
| Median       | 14.0 |
| Mean monthly seizure frequency in the last year/month (median, range) | 6.0, 0–730 |
| History of febrile seizures, frequency |       |
| Present      | 14 |
| Absent       | 36 |
| Unknown      | 17 |
| Epilepsy etiology, n (%) |       |
| Hippocampal sclerosis/atrophy | 17 (26) |
| Frontal lobe | 4 (6) |
| Amygdala enlargement | 3 (5) |
| Febrile status epilepticus | 2 (3) |
| Brain tumor  | 0 (0) |
| Others       | 3 (5) |
| Unknown      | 36 (55) |
| Imaging      |       |
| Nonlesional  | 42 |
| Lesional     | 23 |
| Type of MRI lesion |       |
| HS           | 15 |
| Bilateral HS | 2 |
| Literality of the focus |       |
| Left         | 34 |
| Right        | 13 |
| Bilateral    | 13 |

Patients and control subjects were evaluated using OSIT-J [8,9]. Patients were administered standard dosages of typical anti-seizure medications (ASMs) at the time of the olfactory test.

The control subjects were 74 healthy individuals (38 men and 36 women) aged 18–68 years (mean ± SD = 38.7 ± 15.1 years; median = 36.5 years) without epilepsy and with no family history of epilepsy.

All subjects with a history of recent upper respiratory tract infection, perennial sinus disease, smoking, hormonal disorder, perennial allergy, drug or alcohol abuse, neurodegenerative disorder associated with olfactory dysfunction, or other conditions that may affect olfactory function were excluded from this study.

The study protocol was approved by the International University of Health and Welfare Ethics Committee (study approval number: IUHW-775). Written informed consent was obtained from all participants.

2.2. OSIT-J

Odor identification was assessed using OSIT-J (Daiich Yakuhin Sangyo Co. Ltd., Tokyo, Japan) [8,9]. This test includes the following 12 odors familiar to the Japanese population: perfume, rose, condensed milk, Japanese orange, spicy curry, roasted garlic, sweaty smelling socks, cooking gas, menthol, Indian ink, wood, and Japanese cypress (hinoki). There are many odor identification tests that use odorants unfamiliar to the Japanese population. However, in the study by Kobayashi et al., the odors used were familiar to Japanese individuals, and the test kit was used to evaluate odor identification [8].

The odorants were packed in microcapsules mixed in a paste. The paste was hardened, shaped like a lipstick, and was referred to as an odor stick. Each odor stick was applied by the assessor in a circle 2 cm in diameter drawn on a thin 5.25 cm × 10.5 cm paraffin paper. The assessor then folded the paraffin paper in half, rubbed it three to five times to crush the microcapsules and released the odorant, and then passed it to a patient. Next, the patient opened the paraffin paper in front of the nostrils and sniffed the paper. The patient was then given six options: four odor names (of which one is correct), “not detected,” and “unknown.” The patient was first asked to choose the correct odor out of the four options. A suggestion to select “unknown” or “not detected” was made to the patient when there was difficulty choosing from one of the four odor names. “Unknown” indicated that the presented odorant was detected but not recognized. This procedure was repeated for each odorant.

The OSIT-J score is the total number of correct answers chosen for the 12 odors. Since this test does not require a deodorizing filter or device, it is practicable for use in outpatient clinics and at the bedside and can be completed within 10–15 minutes.

2.3. Statistical analysis

We collected patient data including gender, age, seizure duration, seizure profile, seizure frequency, and etiology. Differences in OSIT-J score between patients with TLE and the control subjects were evaluated using Mann–Whitney test. Kruskal–Wallis test was used to compare the differences in OSIT-J score between the control subjects and patients with right, left, or bilateral TLE. We performed post hoc analysis and multiple comparison using Mann–Whitney test and Bonferroni correction, respectively.

Using multiple regression analysis and Spearman’s rank correlation coefficient test, we evaluated factors that affect the OSIT-J score (e.g., age, age at epilepsy onset, duration of illness, seizure frequency before treatment and after treatment, MRI findings, previous surgery, TLE with hippocampal sclerosis (HS), number of
medications administered over the duration of the illness, and number of medications and individual ASMs administered).

We performed receiver operating characteristic (ROC) analysis to calculate the respective optimal cutoff values of OSIT-J score for patients with TLE, the control subjects, and patients with right, left, or bilateral TLE. Using Chi-square test, we evaluated the rate of selected answers for odorants between patients with TLE and the control subjects. Further, we compared OSIT-J scores of age categories using Mann–Whitney test. Participants in the second decade of life were less than five, and therefore we excluded them from the analysis.

We also used Kruskal–Wallis test and Mann–Whitney test to compare between control subjects and patients with HS who have or have not undergone surgery.

All data are expressed as mean ± SD. P-value <0.05 was considered statistically significant. Statistical analyses were performed using Statistical Package for Social Science software (SPSS statistics, version 25).

3. Results

3.1. Total OSIT-J score

The mean OSIT-J score was significantly lower in patients with TLE (mean ± SD = 8.1 ± 2.8; median = 9) than in the control subjects (mean ± SD = 10.6 ± 1.1; median = 11) (P < 0.005) (Fig. 1A). We found clear differences in OSIT-J score between patients with right, left, or bilateral TLE and the control subjects (Fig. 1B). Statistically significant differences in OSIT-J score were observed between the control subjects and patients with left TLE (P < 0.0001), between the control subjects and patients with right TLE (P = 0.038), and between the control subjects and patients with bilateral TLE (P < 0.0001). We also found that 46.2% of patients with TLE and 8.2% of the control subjects had OSIT-J score <8.

Multiple regression analysis (β coefficient = −0.471, 95% confidence interval = −0.125 to −0.045; P < 0.0001) revealed that the OSIT-J score declined by 0.085 for every yearly increase in age (P = 0.000069) and declined by 0.794 when laterization changed (i.e., between left, right, and bilateral) (P = 0.0429).

OSIT-J score was found to have a negative correlation with age (ρ = −0.378; P < 0.005). Further, OSIT-J score was found to have no significant association with age at epilepsy onset (ρ = −0.160; P = 0.206), duration of illness (ρ = −0.169; P = 0.181), seizure frequency before treatment (ρ = 0.074; P = 0.562), seizure frequency after treatment (ρ = −0.101; P = 0.422), MRI findings (ρ = 0.130; P = 0.303), previous surgery (ρ = 0.023; P = 0.855), TLE with HS (ρ = 0.114; P = 0.366), and number of medications (ρ = −0.182; P = 0.146). No significant correlation was observed between OSIT-J score and any ASM administered. Fig. 2 shows the relationship between OSIT-J score and age category. Statistically significant dif-

Fig. 1. Odor stick identification test for Japanese (OSIT-J) scores. A: Comparison between patients with temporal lobe epilepsy (TLE, n = 65) and control subjects (n = 74); B: Comparison between patients with right (n = 13), left (n = 34), or bilateral TLE (n = 13) and healthy controls (n = 74). Patients with unknown seizure focus (n = 5) are not included. *P < 0.05, **P < 0.005, ***P < 0.0005, ****P < 0.0001.
ferences in OSIT-J score were observed in the fourth ($P = 0.039$), fifth ($P = 0.008$), sixth ($P = 0.001$), and seventh ($P = 0.002$) decades of life between patients with TLE and the control subjects. In contrast, no statistically significant differences in OSIT-J score were observed in the second ($P = 0.136$) and third ($P = 0.136$) decades of life between patients with TLE and the control subjects.

There were statistically significant differences in OSIT-J score between patients with HS (irrespective of surgical history) and the control subjects ($P = 0.001$). Mann–Whitney analysis revealed statistically significant differences in OSIT-J score between the control subjects and patients with HS who had no history of surgery ($P = 0.001$).

3.2. ROC curve and cutoff value

We performed ROC curve analysis to evaluate the usefulness of OSIT-J as a screening tool for TLE. For differentiation between patients with TLE and the healthy controls, a maximum area under the curve (AUC) of 0.808 was obtained when the cutoff value was set at 10.5. The cutoff value of 10.5 ($\phi = 0.516; P < 0.01$) yielded a sensitivity and a specificity of 81.5% and 62.1%, respectively (Fig. 3A), and positive and negative predictive values of 65.4% and 79.3%, respectively.

To evaluate the usefulness of OSIT-J as a screening test for bilateral TLE, we calculated its sensitivity and specificity. A cutoff score of 7.5 ($\phi = 0.374; P = 0.004$) yielded a maximum AUC of 0.736, a sensitivity of 69.2%, and a specificity of 75.0% (Fig. 3B).

3.3. OSIT-J score for individual odors

Fig. 4 shows the rates of correct answers to the 12 odors. The rates of correct answers to Indian ink (93% versus 52%; $P < 0.0001$), menthol (99% versus 75%; $P < 0.0005$), perfume (92% versus 66%; $P = 0.001$), wood (74% versus 45%; $P = 0.002$), Japanese cypress (77% versus 46%; $P = 0.002$), condensed milk (86% versus 62%; $P = 0.004$), rose (97% versus 82%; $P = 0.005$), cooking gas (74% versus 52%; $P = 0.012$), and roasted garlic (99% versus 88%; $P = 0.032$) were significantly lower in patients with TLE than in the healthy controls.

There were no significant differences in the rates of correct answers to spicy curry (97% versus 89%; $P = 0.154$), Japanese orange (84% versus 71%; $P = 0.068$), and sweaty smelling socks (93% versus 80%; $P = 0.057$) between patients with TLE and the control subjects.

Analysis of the total rate of answers revealed that patients with TLE chose more wrong answers (21%) than the control subjects (7%). Patients with TLE tended to choose wrong answers of odors, excluding the “not detected” option, more than the control subjects (Fig. 4).

There were significant differences in the rate of correct answers to menthol between patients with TLE of different lateralizations (i.e., right, left, or bilateral) ($\phi = 0.503; P = 0.017$) (Fig. 5).

No significant differences in total OSIT-J score were observed between patients with HS ($n = 48$) and those without HS ($n = 17$) ($P = 0.545$). However, patients with HS scored higher than those
without HS in the identification of cooking gas odor (76% versus 52%, \( \varphi = 0.309; P = 0.045 \)).

Of the 17 patients with HS, 12 underwent postoperative testing, while five did not undergo surgery. Patients with HS who underwent postoperative testing scored higher in the identification of Indian ink odor than patients with HS who did not undergo surgery (58% versus 0%; \( P = 0.044 \)).

No significant differences in OSIT-J score were observed between postoperative patients with TLE (\( n = 18 \)) and patients with TLE who did not undergo surgery (\( n = 47 \)) (\( P = 0.652 \)).

### 4. Discussion

#### 4.1. TLE and olfactory dysfunction

In this study, we found that, compared to healthy controls, patients with TLE had olfactory dysfunction. Recent meta-analysis of patients with epilepsy revealed that, of all forms of epilepsy, TLE and mixed frontal epilepsy had the strongest association with olfactory deficits [1]. The olfactory bulb transmits olfactory information as afferent input to the primary olfactory cortex, which includes the piriform cortex, periamygdaloid cortex, entorhinal cortex, and amygdala [10]. The primary olfactory cortex projects the olfactory information to secondary structures such as the hippocampus, thalamus, orbitofrontal cortex, and insular cortex for higher cortical processing [10]. The epileptogenic network may be variable in patients; however, in patients with TLE, it mainly consists of the temporal cortex, amygdala, hippocampus, and insular cortex. The significant overlap of the epileptogenic network and olfactory processing structures may explain the interictal dysfunction of olfaction.

#### 4.2. Epileptogenic focus and olfactory dysfunction: unilateral versus bilateral

In this study, it was found that OSIT-J scores were lower in patients with bilateral TLE than in patients with unilateral TLE. Difference in olfaction between patients with unilateral TLE and patients with bilateral TLE was investigated in only one previous study, and in that study, no difference was found between the two patient groups [11]. In contrast, in our study, we found that patients with bilateral TLE had lower olfactory performance than patients with unilateral TLE, and this finding was confirmed using a significant number of video-EEGs. Odor stick identification test for Japanese score, when substantially low, may be suggestive of bitemporal foci and is useful for patient management including pre-surgical evaluation.

Regarding patients with unilateral TLE in our study, no significant differences in OSIT-J score were observed between patients with right TLE and patients with left TLE. Previous findings regarding the relationship between seizure foci and olfactory dysfunction are conflicting. Low olfactory function was reported in patients with right focus [12–14], left focus [15,16], and no significant lat-

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**Fig. 4.** (A) Comparison of the answers of patients with TLE during OSIT-J (B) Comparison of the answers of healthy controls during OSIT-J.

**Fig. 5.** Comparison of the answers of patients with left, right, or bilateral TLE during OSIT-J.
eraly [11,17]. These conflicting findings may be due to differences in study method and confounding factors such as severity of epilepsy. Hemispheric dominance of olfactory function is yet to be investigated in patients with TLE.

4.3. Effect of patient age and epilepsy onset age on olfactory dysfunction

Our results showed that OSIT-J score had significantly negative correlations with patient age and epilepsy onset age, but not with duration of illness. These results are comparable to those of previous studies and meta-analyses [1,2]. The ability to detect unpleasant odors is relatively unaffected by age; however, the ability to detect pleasant odors tends to deteriorate with aging as reported in a study that used UPSIT [1]. The biological mechanism underlying the deterioration of olfactory function involves age-related olfactory nerve cell degeneration and changes in the selectivity of olfactory receptor neurons [2].

We propose a cutoff OSIT-J score of 10 or less for the detection of hyposmia in patients with TLE aged 60 and below. Our results showed a sensitivity of 81.5% and a specificity of 62.1% when the cutoff score was set to 10. Odor stick identification test for Japanese scores of 8 and above are usually considered normal in studies on PD [5]. The difference in cutoff value is related to the older age of patients with PD.

4.4. Effects of HS and surgical resection

In our study, no significant differences in OSIT-J score were observed between patients with HS and those without HS. In an earlier study, impaired olfactory function was reported in patients with HS [18]. In our study, of the 17 patients with HS, 12 had already undergone temporal lobectomy. In addition, no significant differences in OSIT-J score were observed between postoperative patients with HS and the control subjects. The improvement of olfactory function due to surgery may have offset the pre-existing olfactory deficits related to HS. This finding suggests that improvement of olfactory function may occur postoperatively as evidenced by the reduction in preoperative epileptic activity originating from the hippocampi and affecting temporal and frontal lobe structures.

In this study, the rate of “unknown” responses was lower in postoperative patients with HS than in all patients with TLE. This finding may be explained by the improvement of odor memory function due to surgery. The interval between pre- and post-surgical evaluations when worsening of olfaction was reported in postoperative patients is six months [19]. In our assessment, we used a mean postoperative duration of 4.7 years as the interval needed to regain olfactory ability by virtue of cortical plasticity.

In a previous study, the size and extent of surgical resection in patients were evaluated postoperatively [20]. The study reported that odor identification was similarly impaired regardless of surgical method and that the greatest impairment in nostril stimulation was observed ipsilateral to the resection. It was also reported that resection of the orbitofrontal cortex caused significant impairment of odor discrimination, hinting at the importance of the orbitofrontal region [20].

4.5. Individual odor identification characteristics

In this study, Japanese orange, sweaty smelling socks, and spicy curry were correctly identified by patients with TLE. In contrast, patients with TLE had significantly low identification accuracy to Indian ink, menthol, perfume, wood, Japanese cypress, condensed milk, rose, cooking gas, and roasted garlic (Fig. 4). Further, patients with TLE tended to preserve their identification of stimulating odors and may preserve their olfactory ability for familiar odors of daily life.

In our study, patients with TLE showed preserved ability to identify Japanese orange, spicy curry, and sweaty smelling socks. Preserved ability to identify spicy curry and sweaty smelling socks was also reported in patients with PD and in patients with AD [5,21,22]. It was reported that patients with nasal disorders such as chronic sinusitis had lower scores for the Japanese orange odor than for the other 11 odors tested [23]. In contrast, our patients with TLE correctly identified the Japanese orange odor. It was reported that patients with AD and patients with PD often misidentify the Japanese orange odor as apple odor [22].

The Indian ink part of OSIT-J was useful for the detection of olfactory deficits in patients with TLE (sensitivity = 47%, specificity = 93%). Olfactory deficits in the identification of the Indian ink odor are also reported in patients with PD. In two studies of patients with PD, it was reported that only 19% and 35% of patients correctly identified the Indian ink odor [24,25].

The highest specificity of the smell identification test for menthol for the prediction of TLE is 99%; however, as expected in our study, the sensitivity was found to be merely 25%. Menthol is reported to have a strong stimulating effect on the trigeminal nerve. In our study, we found that the smell identification test for menthol and Japanese cypress (hinoki) has high sensitivity and specificity for the prediction of bilateral TLE and may be useful in the assessment of the severity of epilepsy.

Olfactory deficits to cooking gas may be problematic for patients with TLE in their daily lives. Gas odors such as tert-butyl mercaptan and dimethyl sulfide are added to household gas to make gas leaks more detectable. In our study, 48% of the patients with TLE responded incorrectly to cooking gas odor, meaning that about half the patients with TLE may have olfactory deficits that place them at risk in cases of potentially dangerous gas leaks. Therefore, patients with TLE should be advised to install gas-leak alarms or to use induction cookers, instead of household gas cookers [26,27].

5. Limitations and future directions

No statistical adjustment can be made for any ASM because multiple ASMs were administered to the patients with TLE in different combinations. ASMs may affect olfaction; for instance, loss of ability to detect and recognize tastes and odors was reported in a boy during treatment with topiramate [28].

In our study, we did not investigate the effect of gender on OSIT-J score. In general, olfactory ability is slightly better in women than in men [2]. We adjusted the female-to-male ratio and believe that gender, as a factor, did not influence our results.

We could not compare test performance preoperatively and postoperatively for individual patients. Although there may be repeat-test effects on performance, such a comparison may reveal the effect of surgery on olfactory function.

6. Conclusions

Olfactory dysfunction is associated with bilateral seizure foci and older age of onset in patients with TLE. Significant decline of olfactory function was not observed in postoperative patients with HS after long-term recovery. In addition, our results showed that some patients had characteristic olfactory deficits for specific odors used during OSIT-J. Our findings provide deeper insight into the underlying mechanism of olfactory function in patients with TLE and may be beneficial in the clinical management of these patients.
Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Statement of compliance

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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