Nasal thallium-201 uptake in patients with parosmia with and without hyposmia after upper respiratory tract infection

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Background: In this study, we aimed to determine whether nasal thallium-201 uptake of the olfactory cleft and olfactory bulb (OB) differs between patients with parosmia with and without hyposmia after upper respiratory tract infection (URTI).

Methods: Twenty patients with parosmia after URTI were enrolled in this study (15 women and 5 men, 28 to 76 years old). Nasally administered thallium-201 migration to the OB, nasal thallium-201 uptake ratio in the olfactory cleft, and OB volume were determined in 10 patients with normal T&T olfactometry (Daiichi Yakuhin Sangyo, Tokyo, Japan) odor recognition thresholds ($\leq$2.0) who still complained of parosmia (parosmia group), and 10 patients with T&T odor recognition thresholds >2.0 (parosmia and hyposmia group).

Results: The nasal thallium-201 uptake ratio in the olfactory cleft was significantly higher in the parosmia group than in the parosmia and hyposmia group ($p = 0.0015$). Thallium-201 migration to the OB was not significantly different between the 2 groups ($p = 0.31$). The OB volume was significantly larger in the parosmia group than that in the parosmia and hyposmia group ($p = 0.029$); however, the mean OB volume in both the groups was lower than the normal threshold value in healthy individuals.

Conclusion: Our results signify the recovery of the olfactory epithelium; however, the olfactory neural projections to the OB and regeneration of OB were not complete in patients with parosmia with normal T&T recognition thresholds after URTI.

Key Words:
olfaction; sensory systems; nasal turbinate; molecular imaging; nuclear medicine; single-photon emission computed tomography; magnetic resonance imaging; odor recognition threshold; hyposmia

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Parosmia is a distortion of the sense of smell. In clinical settings, it is often not clear why few patients complain of parosmia after upper respiratory tract infections (URTIs) even after recovering from hyposmia. In addition, parosmia is most frequent during post-URTI as compared to other causes of olfactory dysfunctions.[1] However, the mechanism of post-URTI parosmia remains to be determined.

Nasally administered thallium-201 (^{201}Tl) migrates to the olfactory bulb (OB) 24 hours after ^{201}Tl administration in healthy individuals, as assessed by a combination of single-photon emission computed tomography (SPECT), X-ray computed tomography (CT), and magnetic resonance imaging (MRI).[2] The thallium-based olfactory imaging method is called "olfacto-scintigraphy." Nasal ^{201}Tl migration to the OB is reduced in patients with impaired olfaction due to head trauma, URTI, or chronic rhinosinusitis, which are the major causes of olfactory dysfunction, as compared to ^{201}Tl migration to the OB in healthy individuals.[3]

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TABLE 1. Patient characteristics

	Parosmia (n = 10)	Parosmia and hyposmia (n = 10)	*p*
Age (years), mean ± SD	61.4 ± 8.2	46.0 ± 11.9	0.003
Sex (female/male), n	8/2	7/3	1.0
Nonsmoker/smoker or ex-smoker, n	7/3	9/1	0.58

SD = standard deviation.

It has been shown that patients with impaired olfactory functions with qualitative disorders, such as parosmia, have smaller OBs than those without parosmia.[4] However, it is not clear whether patients with parosmia have larger OBs if olfactory function tests are normal. Here, we retrospectively determined whether nasal ^{201}Tl uptake analysis of the olfactory cleft and OB and OB volume differ between post-URTI patients with parosmia with and without hyposmia.

Patients and methods

Patients

Twenty patients with parosmia after URTI were enrolled in this study (15 women and 5 men; 28–76 years old). The characteristics of the included patients are shown in Table 1. All subjects were informed about the objective of the study and possible adverse effects (eg, allergic reactions to ^{201}TlCl and irritation of the digestive system), and written informed consent was obtained. Subjects were excluded if they were pregnant or lactating or had a history of kidney disease, liver injury, or other serious illnesses. The Medical Ethics Committees of our institution approved this study protocol (trial registration no. UMIN000023519).

All procedures performed in this study involving subjects were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all the individual participants included in the study. This article does not contain any data of animal studies.

T&T olfactometry

In Japan, T&T olfactometry (Daiichi Yakuhin Sangyo, Tokyo, Japan) is a standard technique for estimating the olfactory thresholds; the normal odor recognition threshold score of each nostril is ≤2.0. The olfactory severities were categorized according to the mean T&T recognition thresholds, and the patients were diagnosed with anosmia when the T&T recognition thresholds were ≥5.6.[5] Each odorant was dissolved in mineral oil to form a graded series of concentrations and was then applied liberally on blotting papers followed by presentation to the patients using T&T olfactometry. The odor recognition threshold was estimated on the nasal side of ^{201}Tl administration.

Olfacto-scintigraphy and analysis of OB volume

For each subject, 0.3 mL of ^{201}TlCl (22 MBq) was administered unilaterally to the olfactory cleft, and SPECT-CT was performed 24 hours later. The data acquisition was undertaken using a dual-headed SPECT-CT hybrid system (Symbia T6; SIEMENS Healthcare Japan, Tokyo, Japan) equipped with low-energy high-resolution collimators. The data were acquired over 360 degrees with 90 projections (30 seconds per projection), 128 × 128 matrix (with 2.29 times zoom, pixel size 2.1 mm), and a 72-keV photopeak with a 30% main window and 7% sub-window on both sides. Data reconstruction was performed with 3D OSEM (9 subsets and 8 iterations), including attenuation and scatter correction (Flash 3D; SIEMENS Healthcare Japan).

The olfactory clefts were open in all the patients. Separate MRI images were merged with the SPECT-CT images. Nasally administered ^{201}Tl migration to the OB and the ratio of nasal ^{201}Tl uptake in the superior turbinate area to that in the olfactory cleft area (nasal thallium uptake ratio in the olfactory cleft) were determined. Experienced nuclear radiologists (J.T., K.O., and S.K.) who were blinded to the olfactory test data determined the regions of interest for the olfactory cleft area, the superior turbinate area, and the anterior skull base (OB area) on the ^{201}Tl SPECT–MRI fusion image. On 3 sequential fused images in coronal planes, the regions of interest were set manually on the olfactory cleft area to cover all the residual ^{201}Tl activity in the olfactory cleft including the superior and middle turbinate. Next, the oval regions of interest were set manually to delineate the superior turbinate and the OB on the side of the nasal administration of the tracer by referencing the MRI T2-weighted images.

Nasally administered ^{201}Tl migration to the OB was determined by the ratio of the total ^{201}Tl count in the OB region of interest to the total ^{201}Tl count in the olfactory cleft region of interest. Because the olfactory epithelium is mainly located in the superior turbinate, nasal thallium uptake ratio in the olfactory cleft was calculated as the ratio of the total ^{201}Tl count in the superior turbinate region of interest to the total ^{201}Tl count in the olfactory cleft region of interest. Experienced radiologists (N.W. and H.T.) who were blinded to the olfactory test data separately determined the volume of the OB by manual segmentation of 3.0-T MRI coronal slices (2-mm-thick, T2-weighted image) of the OB on the nasal side of ^{201}Tl administration. The change in the diameter at the beginning of the olfactory tract was used as the proximal demarcation of the OB. The means of the 2 radiologists' scores were used for analysis.

Statistical analysis

Mann-Whitney tests, Fisher's exact tests, and 2-tailed Spearman correlations were performed using Prism 6 software (GraphPad, San Diego, CAA). Values of $p < 0.05$ were considered significant.

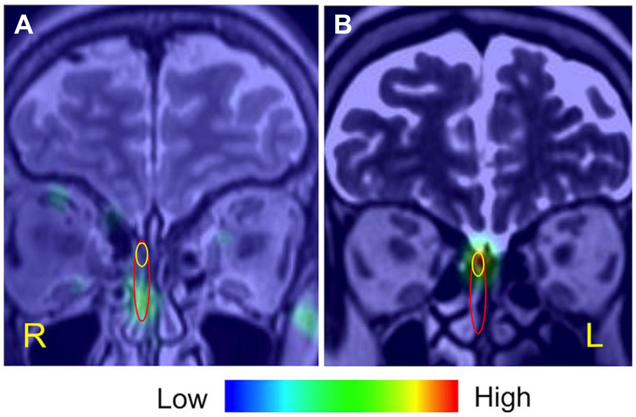

FIGURE 1. Representative images of olfacto-scintigraphy 24 hours after nasal administration of ^{201}Tl. (A) A 50-year-old female with post-URTI parosmia and hyposmia. (B) A 76-year-old female with post-URTI parosmia. Yellow circles indicate the superior turbinate area. Red circles indicate the olfactory cleft area. URTI = upper respiratory tract infection.

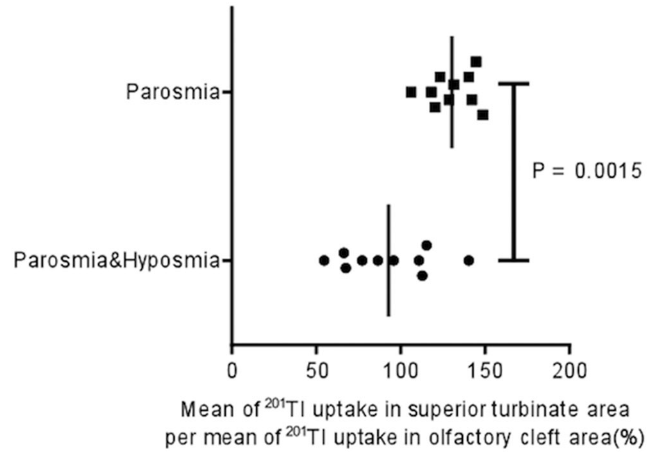

FIGURE 2. The nasal thallium uptake ratio in the olfactory epithelium was significantly higher in the parosmia group than in the parosmia and hyposmia group ($p = 0.0015$, n = 10 in each group).

Results

The T&T odor recognition thresholds in the subjects ranged from 0.2 to 5.8 (mean ± standard deviation [SD], 2.8 ± 1.9). Nasally administered ^{201}Tl migration to the OB, nasal thallium uptake ratio in the olfactory cleft, and OB volume were compared between 10 patients with normal T&T odor recognition thresholds (≤2.0) who still complained of parosmia (parosmia group) and 10 patients with T&T odor recognition thresholds >2.0 (parosmia and hyposmia group). The T&T odor recognition thresholds were significantly lower in the parosmia group than in the parosmia and hyposmia group ($p < 0.0001$). None of the subjects examined experienced major side effects following nasal administration of ^{201}Tl.

Representative images of olfacto-scintigraphy in a 58-year-old female with post-URTI parosmia and hyposmia and a 76-year-old female with post-URTI parosmia and normal T&T odor recognition threshold are shown in Figure 1. The nasal thallium uptake ratio in the olfactory cleft was significantly higher in the parosmia group than in the parosmia and hyposmia group (Fig. 2, $p = 0.0015$). On the other hand, thallium migration to the OB, which indicates the axonal connectivity of olfactory sensory neurons between olfactory epithelium and OB glomeruli, was not significantly different between the 2 patient groups ($p = 0.31$).

The OB volume was significantly larger in the parosmia group than in the parosmia and hyposmia group (Fig. 3, $p = 0.029$); however, the mean OB volume in both groups (31.2 mm^3 in the parosmia group and 22.6 mm^3 in the parosmia and hyposmia group) was lower than the normal value in healthy subjects (≥58 mm^3 for <45 years; ≥46 mm^3 for older subjects[5]). The nasal thallium uptake ratio in the olfactory cleft was significantly correlated with T&T odor recognition thresholds (Fig. 4, $p = 0.0023$, Spearman $r = -0.64$). The nasal thallium uptake ratio in the olfactory cleft did not significantly correlate with the OB volume, thallium migration to the OB, or age ($p = 0.18$, Spearman $r = 0.31$; $p = 0.50$, Spearman $r = 0.16$; $p = 0.08$, Spearman $r = 0.40$, respectively). The OB volume was significantly correlated with T&T odor recognition thresholds ($p = 0.024$, Spearman $r = -0.50$).

Discussion

We retrospectively determined whether nasal ^{201}Tl uptake analysis of the olfactory cleft and OB and OB volume differed between post-URTI patients with parosmia with and without hyposmia. The nasal thallium uptake ratio in the olfactory cleft was significantly higher in the parosmia group than in the parosmia and hyposmia group; however, thallium migration to the OB was not significantly different between the 2 groups. These results suggest that the recovery of the olfactory epithelium was present in the patients with parosmia with normal odor recognition thresholds.

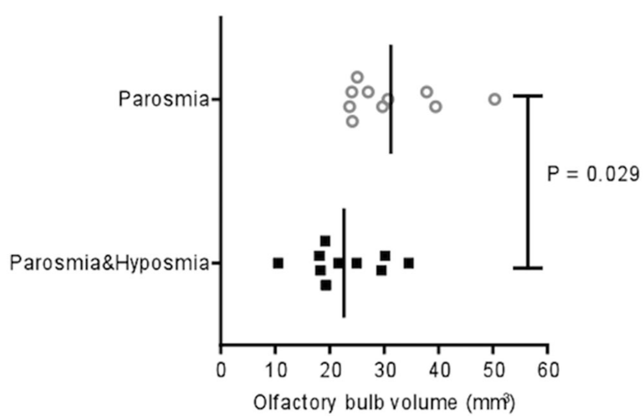

FIGURE 3. The OB volume was significantly larger in the parosmia group than in the parosmia and hyposmia group ($p = 0.029$, n = 10 in each group). OB = olfactory bulb.

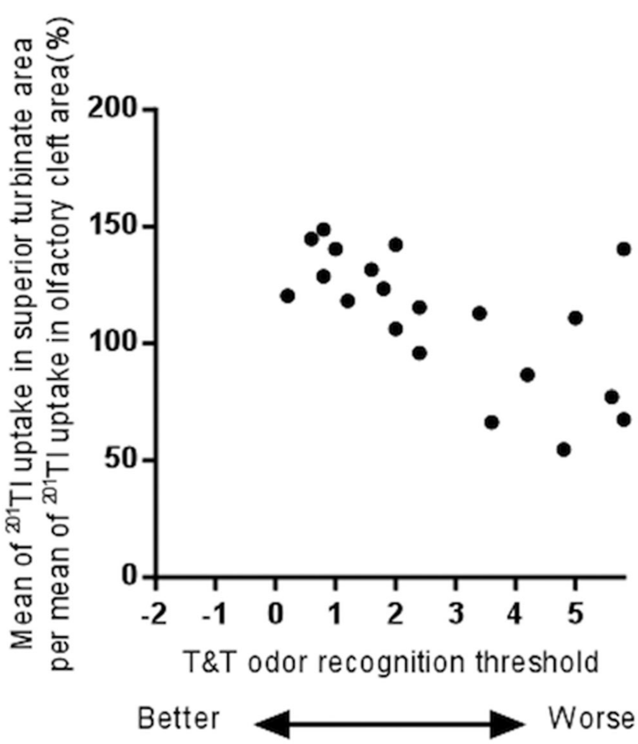

FIGURE 4. The nasal thallium uptake ratio in the olfactory cleft was significantly correlated with T&T odor recognition thresholds ($p = 0.0023$, Spearman $r = -0.64$, n = 20).

The axonal fibers of the olfactory sensory neurons were not fully recovered in subjects with and without hyposmia.

There are 2 main hypotheses for the mechanisms of parosmia: a peripheral theory and a central theory.[6,7] The peripheral theory that proposes the inability of abnormal olfactory neurons to form a complete picture of the odorant is supportive for our results showing the immature regeneration of the olfactory sensory neurons. The inability of the axons to accurately rewire the OB has been shown in mice with olfactory nerve resection.[8] The immature regeneration of the olfactory sensory neurons in patients with post-URTI parosmia may inhibit the regeneration of glomeruli in the OB and the correct guidance of olfactory sensory nerve axons to specific targets in the OB.

In this study, we have shown a reduction in OB volume in patients with parosmia with and without hyposmia as compared to the normal OB volume as previously reported.[4] Specifically, for healthy subjects <45 years old, the OB should have a minimum volume of 58 mm^3, and for healthy subjects >45 years old, the OB should have a minimum volume of 46 mm^3 (Rombaux et al.[4]). We referred to these findings, which correspond to European populations, because there is no report of OB volume in healthy Japanese populations.

However, the OB volume was significantly larger in patients with parosmia without hyposmia as compared to that in patients with parosmia and hyposmia. The degeneration of glomeruli in the OB has been shown in rats after reversal of olfactory nerve lesions.[9] The degeneration of glomeruli in the OB may be present in patients with post-URTI parosmia, even after the odor recognition threshold is recovered in these subjects.

Furthermore, we showed the significant correlation between T&T odor recognition thresholds and the nasal thallium uptake ratio in the olfactory cleft. These results suggest that ^{201}Tl may be a useful olfactory neuronal tracer for the precise evaluation of odor recognition ability in patients with parosmia. Nonetheless, clinical studies with larger subject cohorts are necessary to confirm the usefulness of olfacto-scintigraphy in routine clinical imaging of patients with parosmia.

In this study, we did not evaluate whether the patients had a lower olfactory threshold on the side opposite of the studied side. In the right nostril (studied side), we compared all factors of the olfactory nerve and OB. Furthermore, all subjects in this study had parosmia. Thus, the olfactory threshold of the left nostril would likely not influence the results of this study. In addition, throughout the follow-up period (17.5 ± 11.2 months) of this study, all subjects continued to experience parosmia. Therefore, we could not determine the usefulness of olfacto-scintigraphy to predict the recovery of patients with parosmia.

OB volume was also significantly correlated with T&T odor recognition thresholds in patients with parosmia. Our results showing the correlation between olfactory function and OB volume are in accordance with a previous report of another olfaction test known as "Sniffin' Sticks."[10] However, it may be difficult to determine whether the subjects have normal odor recognition thresholds only by MRI because the OB volume of the patients with parosmia is smaller than the normal values in healthy subjects.

Patients with parosmia with mental illness could hardly select the correct choices for odors in olfactory function tests. Patients with predominant negative symptoms of schizophrenia tend to evaluate odors in a significantly more pleasant way.[11] A significantly higher rate of parosmia/phantosmia symptoms is also reported by patients with severe depression as compared to those with minimal to moderate depression.[12] Olfacto-scintigraphy can be applied when the OB volume estimated on MRI images is small and the scores of olfactory function tests are unreliable in patients with parosmia coupled with mental illness to determine whether these patients have a normal odor recognition threshold. However, this is only recommended for cases in which the patient understands the usefulness and possible side effects of olfacto-scintigraphy (eg, allergic reactions to ^{201}TlCl and irritation of the digestive system) and provides written informed consent.

Finally, questionnaires regarding daily life problems have been shown to be useful for investigating parosmia.[13] In this study, we could not assess the correlation between nasal thallium uptake rate and scores of questionnaires for olfactory disorders because these questionnaires are not available in Japanese. Furthermore, we did not quantify parosmia in the subjects using previously established scoring systems.[14] To score the degree of parosmia is not standard in Japan. We would like to adapt the scoring systems in future studies.

Conclusion

Our results signify the recovery of the olfactory epithelium; however, the olfactory neural projections to the OB and regeneration of OB were not complete in patients with parosmia with normal T&T recognition thresholds after URTI.

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