The relationship between intravenous olfactory test and taste disorder in patients with olfactory disorder

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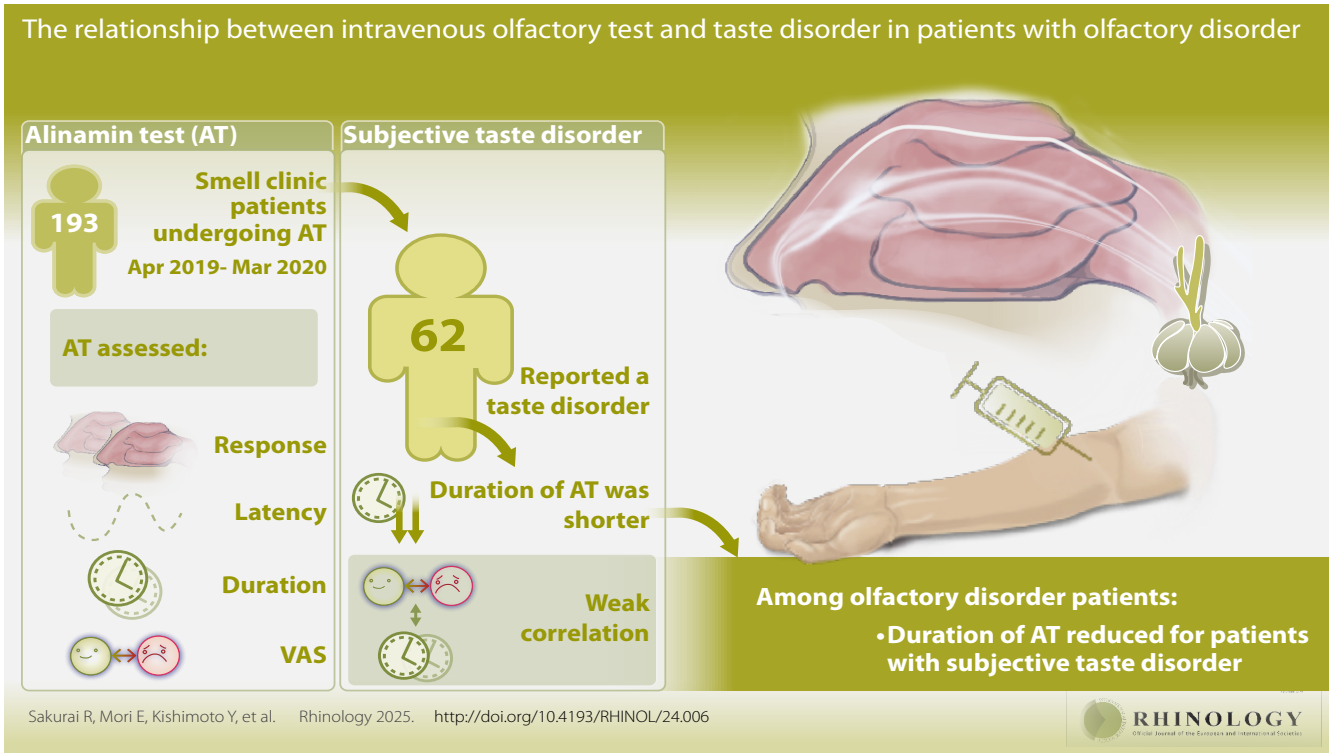

Abstract

Background: The intravenous olfactory test (alinamin test [AT]) is a retronasal olfactory assessment and may evaluate the flavour disorder; however, studies assessing whether AT accurately determines the severity of taste disorders are lacking. Our study aims to evaluate the relationship between AT and subjective taste disorders in the patiensts with olfactory disorder.

Methods: Between April 2019 and March 2020, 228 patients visited our smell clinic reporting olfactory disorders. Of these, 193 patients who underwent AT were included in this study. We evaluated the differences in AT response, latency time, and duration time between patients with and without subjective taste disorder. We also assessed the degree of subjective taste disorder experienced by patients using the visual analogue scale (VAS) and the correlation between latency and duration time of AT. To assess taste perception more broadly, we inquired about the presence of disorder using the term "taste" rather than "flavour," without focusing on any specific type of taste disorder.

Results: Of the included 193 patients, 62 reported awareness of a taste disorder. The duration time of AT was significantly shorter in patients with subjective taste disorder. A weak correlation was found between the VAS scores for subjective taste disorders and the duration time of AT.

Conclusions: Our results showed that among the patients with olfactory disorders, the duration time of AT was reduced for those with subjective taste disorders.

Key words: flavour disorder, intravenous olfactory test, olfaction disorders, taste disorders

Introduction

Among patients with olfactory disorders, some also suffer from taste disorders. These patients are primarily considered to have flavour disorders underlying the olfactory disorders. It can be predicted that most subjective taste disorders in patients with olfactory and taste disorders may result from flavour disorders [1]. Previous reports have shown that taste disorders due to olfactory disorders are often acute and occur after a common cold, whereas patients with idiopathic olfactory disorders complain less of taste disorders over time [2]. Flavour is considered a perception influenced by various sensory inputs originating from the oral cavity and closely linked to the sense of smell, particularly retronasal olfaction [3]. However, not all patients with olfactory disorders report subjective taste disorders, and the extent of olfactory perception, particularly retronasal olfactory dysfunction, may influence how patients perceive taste disorders. At present, the underlying mechanisms that determine the presence or absence of subjective taste disorder, including both taste disorder and flavour disorder, in patients with olfactory disorders are poorly understood. This is because the interaction of smell, taste, and flavour makes it difficult to assess taste disorders without the influence of other senses [4], and proper discrimination between olfactory and taste disorders is challenging due to the inherent limitations of the test, which can inadvertently stimulate the sense of taste.

One of the retronasal olfactory tests is the intravenous olfactory test, which is widely used as one of the subjective olfactory tests in Japan (Alinamin test; AT) [5, 6]. Other retronasal olfactory test methods are the retronasal olfaction test (ROT) and the candy smell test (CST) [7]. The standard method for retronasal olfactory test is to stimulate the retronasal olfaction by applying a test powder into the mouth while clipping the nose. The candy smell test makes use of different candies, each including a unique flavour, which stimulate retronasal olfaction by mouth. Since the ROT and CST stimulate retronasal olfactory by powder or candy in the mouth, they could stimulate tongue and taste itself [8, 9], thus it is difficult to distinguish the taste or flavour stimulation. In contrast, the intravenous olfactory test is that intravenous injection of thiamine propyl disulphide (Alinamin) induces the sensation of a garlic-like odour during exhalation through the nose. This is because when Alinamin is injected intravenously, it is released into the blood vessels of the airways, diffuses into the lungs, and is transported through exhalation to the olfactory cleft via the posterior nares. Therefore, it is extremely low to worry about stimulation of the tongue and taste itself.

It would be meaningful to investigate the relationship between the results of AT, which are considered to be able to assess pure retronasal olfactory sensation without stimulating the tongue or taste itself, and subjective taste disorders, as it may reveal the severity of olfactory disorder for the degree of taste disorder. However, no studies have examined the relationship between AT results and the degree of taste disorder in detail. Therefore, we investigated the relationship between the degree of subjective taste disorder with olfactory disorder and AT results.

Materials and methods

Study design and participants

This retrospective study was approved by the Ethics Committee of the Jikei University School of Medicine (Approval No. 35-244(11873)). We included patients who presented with olfactory disorder and underwent an intravenous olfactory test at the Department of Otorhinolaryngology, the Jikei University School of Medicine, between April 2019 and March 2020. All patients were asked if they had a taste disorder and provided a visual analogue scale (VAS) score for taste disorder at the first visit. The presence or absence of taste disorders was based on the responses to the questionnaire used at our hospital (Supplementary Material 1). We asked the patients as follows; "do you have taste disorder? – yes, or not" and "what is the degree of taste of the food" with answering for as VAS. We used the word "taste" to standardize the questions because it is difficult for human to distinguish between taste, flavour, and retronasal olfaction [10]. To assess taste perception more broadly, we inquired about the presence of disorder using the term "taste" rather than "flavor," without focusiong on any specific type of taste disorder.

Procedures

All patients underwent olfactory tests during their first visit. The following clinical information was collected: age (at the first visit), sex, duration of olfactory disorder, and serum zinc levels (at the first visit). To diagnose the causative diseases of olfactory disorders, all patients underwent nasopharyngeal endoscopy and sinus CT scan to detect the sino-nasal disease. An MRI was performed when we suspected neurodegenerative disease, a brain tumour, or when no cause was identified by alternative testing.

Details of the olfactory tests

The details of the olfactory tests performed in this study are as follows:

- Alinamin test: Following the injection of alinamin (prosultiamine, 10 mg, 2 mL, Takeda Pharmaceutical Company), its degradation products (propyl mercaptan with a garlic or onion-like smell) diffuse into the lungs after circulating in the bloodstream, are excreted in the exhaled air, reach the olfactory epithelium via the posterior choana, and stimulate olfactory neurons. Alinamin was injected into the patient's medial cubital vein at a constant rate for 20 s. The time from the start of the infusion until the smell was detected (latent time) and the time from smell to disappearance (duration time) were evaluated. The patient took one quiet nasal breath every 2 s and considered the odour to be gone when

it disappeared after 2–3 breaths. In healthy volunteers, the latency time was 8 s, and the duration was 70 s; therefore, the average values were 8 s or less and a duration of 70 s or more [11].

- T&T olfactometry: This is a standard olfactory threshold test in Japan wherein five types of olfactory substances (Rose; β-phenyl alcohol, Curry; methyl cyclopentenolone, sweaty socks or stool; isovaleric acid, peach; γ-undecalactone, and garbage; skatole) are used. Eight stages of -2–5 points with 10-fold dilutions were prepared. A point of 0 was the olfactory concentration in healthy adults. The patients sniffed each odour from the samples with the lowest (-2) concentrations. The concentration at which the odour was perceived was used as the detection and recognition threshold. If the patient could not perceive the odour, a score of 6 was assigned to each threshold (a score of 5 for methyl cyclopentenolone only). The average detection and recognition threshold was obtained by dividing the total score by 5. In the average recognition threshold, ≤ 1.0 was normosmia, ≤ 2.5 was mild olfactory disorder, ≤ 4.0 was moderate olfactory disorder, ≤ 5.5 was severe olfactory disorder, and ≥ 5.6 was anosmia from guideline criteria [11].

- Self-administered odour questionnaire (SAOQ): The questionnaire consists of 20 smell-related items: steamed rice, miso, seaweed, soy sauce, baked bread, butter, curry, garlic, orange, strawberry, green tea, coffee, chocolate, household gas, garbage, timber, sweat, stool, flower, and perfume. To complete the SAOQ, patients assigned a score to each odour item based on 4 levels: 2 points for 'strongly' smelling the odour, 1 point for 'weakly' smelling the odour, 0 points for 'not smelling it at all', and 'unknown' (no points assigned) [12-14].

- Open essence (OE): This is a card-type odour identification test. When opened, there are 12 types of twofold measurement cards, each with a particular odour. These odorants are described as Indian ink, wood, perfume, menthol, orange, curry, cooking gas, rose, cypress wood (Japanese cypress, 'hinoki'), sweaty-smelling socks, fried garlic, and condensed milk. Patients were instructed to select an answer from 6 choices, which included 'cannot identify', 'odourless', and names of 4 odours on the right side of the opened card (including 1 correct answer) [15]. The patient was considered normosmic if ≥ 8 of the 12 cards were correct. If ≤ 7 cards were correct, the patient was considered to have an olfactory disorder [16].

- VAS for an olfactory disorder or taste disorder (odour VAS/taste VAS): The left end of a 100-mm straight line indicated 'not smelling at all', whereas the right end indicated 'normally smelling'. The patients plotted their current olfaction and taste status in a straight line. The score was the distance from the left edge to the plotted point (0–100 points)[13, 14, 17, 18].

Exclusion criteria

Exclusion criteria were as follows:

- Less than 20 years of age at the time of the first visit.
- Cases in which questions about taste disorder were not aksed and the AT was not performed.

Outcomes

Major outcome

Among all patients with olfactory dysfunction, we investigated the relationship between the presence or absence of an AT response and the awareness of a taste disorder.

Minor outcome

In the group with AT response, we investigated the following items:

- The relationship between the latency and duration time (in seconds) of AT and the presence or absence of taste disorder.
- Correlation between the latency and duration time of AT (in seconds) and taste VAS.

Statistical analysis

The SPSS software version 24 was used for statistical analyses. All continuous variables were treated as nonparametric. The chi-square test was used for categorical variables, the Mann–Whitney U test was used for all independent continuous variables, and the Wilcoxon test was used for comparisons of paired continuous variables. Spearman's correlation coefficient was obtained for the correlation between continuous variables, and the strength of the relationship was expressed as r. Statistical significance was set at $p<0.05$.

Results

A total of 228 patients with complaints of olfactory disorders visited our outpatient department, of which 193 patients (85 females and 108 males, average age 54.49±1.10 years) underwent AT. Of these 193 patients, 62 were aware of taste disorders, and 131 were not; 142 responded to AT, and 51 did not. There was no relationship between the presence or absence of AT and subjective taste disorder.

Figure 1 (A to C) shows the causative diseases of olfactory disorders in all patients (n=193), a group of AT response (n=142) and a group of AT non-response (n=51). Sinusitis is the most common and post-infectious is the second in all patients. Sinusitis accounts for about half of causative disease in a group of AT response. Post-infectious is the most common and post-trauma

Table 1. Patient characteristics in the PACIFIC Cohort (analysis subset).

	AT response	AT non-response	P-value
Total number	142	51	
Patient background			
Age (years IQR)	52 (43-63)	64 (50-72)	0.000 *
sex (male/female)	66/76	19/32	0.324
Duration of illness (months IQR)	24 (5-60)	58.67 (6.5-60)	0.053
Zinc level (μg/dL IQR)	75 (67-83)	71 (64.25-79.75)	0.075
Presence or absence of taste disorder (presence/absence)	46/96	16/35	1.000
T&T olfactometer test			
Odour detection threshold (median IQR)	4.2 (2.4-5.65)	5.6 (4.4-5.8)	0.000 *
Odour recognition threshold (median IQR)	5.0 (3.1-5.8)	5.8 (5.7-5.8)	0.000 *
SAOQ (median IQR)	9 (2-20)	2 (0-5)	0.000 *
OE (median IQR)	5 (2-9)	1 (0-4)	0.000 *
VAS			
Odour VAS (median IQR)	14 (4-31.75)	15 (3-11)	0.013 *
Taste VAS (median IQR)	50 (22-83)	41.5 (12-73.5)	0.332

Abbreviations: AT, alinamin test; IQR, interquartile range; OE, open essence; VAS, visual analog scale; SAOQ, Self-administered odour questionnaire.
* means p-value is less than 0.05. There were significant differences in age, olfactory test (T&T olfactometer test, SAOQ and OE), and odour VAS. There were no significant differences in presence or absence of taste disorder and taste VAS.

is the second in a group of AT non-response. Table 1 shows the characteristics of patients who responded to AT and did not. Age was significantly younger in the group with AT response, and there were no significant differences in sex, disease duration, or trace element values (zinc). In addition, all olfactory tests (T&T detection threshold/recognition threshold, number of correct OE answers (whether food odours could be recognised), SAOQ score, and VAS score for olfactory dysfunction) showed significant differences. However, no significant differences were found in the taste VAS, indicating no relationship between the presence or absence of AT response and the degree of subjective taste disorder.

In the group of patients with AT response:

1) No significant difference was observed in the latency time of AT between patients with and without subjective taste disorders (18.62 vs. 16.81 seconds, p=0.875); however, the duration time was significantly shorter in patients with subjective taste disorder(42.76 vs. 62.65 seconds, p=0.012).

2) No correlation was found between the latency time of AT and the VAS score of subjective taste disorder (p=0.484, r=-0.062). However, a correlation was observed for the duration time(p=0.033, r=0.201).

Furthermore, since the degree of subjective taste disorder in patients with olfactory impairment were associated with the duration time of AT, we calculated the cutoff values in the presence of perceived subjective taste disorder and the duration time. Based on the ROC curve, a cutoff value of less than 36 seconds for the duration time was calculated using Youden's index with a sensitivity and specificity of 43.8% and 78.2%, respectively.

Discussion

Our study revealed two significant findings. First, there was no significant difference between the presence or absence of AT response and the awareness of taste disorder. Second, in the group that responded to AT, the duration time of AT was significantly shorter in the group with subjective taste disorder. A significant positive correlation was also observed between VAS scores for taste disorder and duration time of AT. In other words, the stronger the degree of subjective taste disorder, the shorter the duration time of AT.

We tend to confuse 'taste disorders' and 'flavour disorders'. When taste tests were performed on patients with olfactory disorders who had subjective symptoms of taste disorders, only 6% of the patients objectively had taste disorders [1, 19, 20]. Rozin reported that flavour perception differs from the five senses in that it is difficult to develop the ability to identify which sense is responsible for the perception, such as taste or odour [4]. One reason for this difficulty is that flavour is a cross-modal perception influenced by various senses, such as smell, taste, somatosensory perception, vision, and hearing [21]. Some studies have also reported that the brain activity regions that process each perception are similar, including flavour stimulation, unimodal stimulation by taste or smell, and bimodal stimulation by a mixture of taste and smell [3, 22, 23]. Contrarily, since we tend to use the term 'taste'

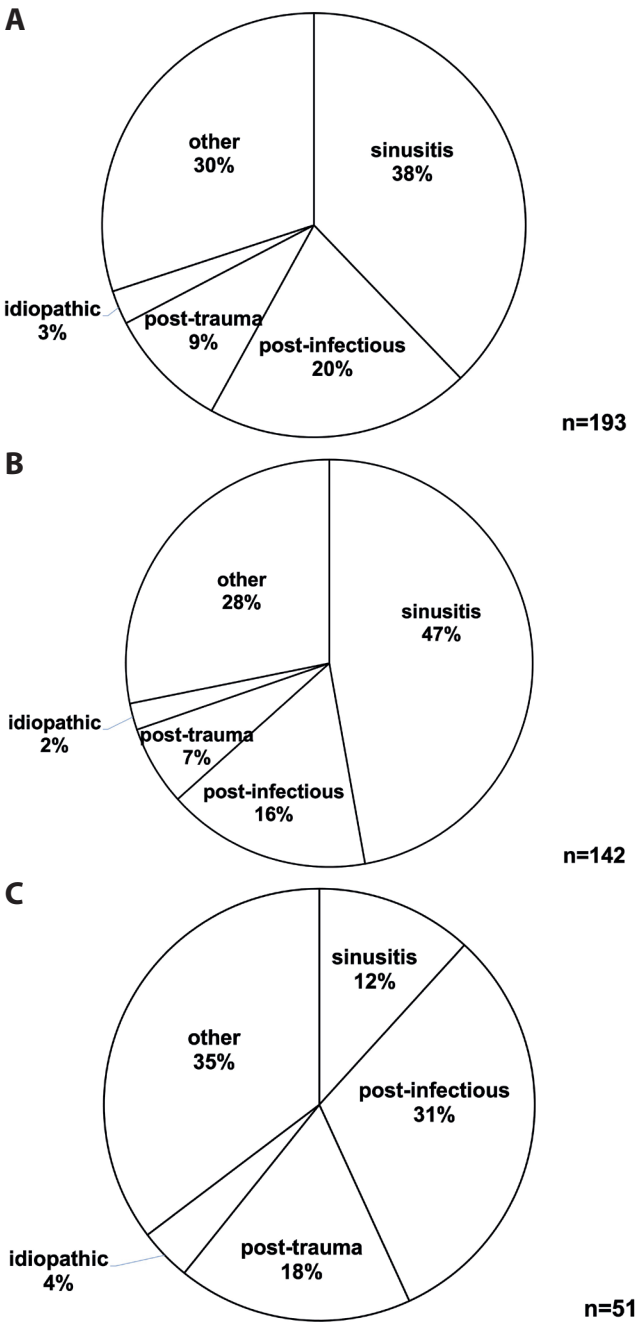

Figure 1. The causative diseases of olfactory disorder. 1-A: all patients (n=193), 1-B: a group of AT response (n=142), 1-C: a group of AT non-response (n=51). A) shows that sinusitis is the most common and post-infectious is the second in all patients. B) shows that sinusitis accounts for about half of causative disease in a group of AT response. C) shows that post-infectious is the most common and post-trauma is the second in a group of AT non-response.

for what is in the mouth [4], many sensations described as 'taste disorder' in patients with olfactory disorders may be a flavour disorder caused by an olfactory disorder.

Food-related retronasal olfaction is stimulated in the oral cavity almost simultaneously with the somatosensory perception of taste and mouth and influences the construction of the neural substrates of flavour perception after associative learning [3, 24, 25]. The alinamin used in AT has an odour reminiscent of garlic. Although it is difficult to rule out the influence of that associative learning, AT may reveal the rate and pathophysiology of flavour disorders caused by retronasal olfaction, or it may reveal the severity of an olfactory disorder for flavour disorders caused by retronasal olfaction.

AT is considered a retronasal olfactory test. When alinamin is injected intravenously, it undergoes hydrolysis into vitamin B1 and side-chain propyl mercaptan [26]. Propyl mercaptan is released into the blood vessels of the airways, diffuses into the lungs, is transported through exhalation to the olfactory cleft via the posterior nares, and activates olfactory sensory neurons (OSN). This activation directly induces OSN axonal responses, and the orbitofrontal cortex, entorhinal cortex, hippocampus, insular cortex, hypothalamus, piriform cortex, amygdala, and anterior cingulate cortex are activated by olfactory stimuli to sense odours [27]. The average time of AT values was a latency period of 8 s or less and 70 s or more.

In this study, we expected that patients with robust olfactory disorders, to the point of olfactory deprivation, would be more likely to experience flavour disorder and consequently be more likely to perceive subjective taste disorder. However, there was no significant difference between the presence or absence of AT response and the perception of subjective taste disorder. One reason for this may be that the patients with no AT response tended to have a longer disease duration. Flavour is a cross-modal perception [21], and flavour perception may be compensated over time. Another factor is the different distribution of causative diseases, with a higher percentage of conductive olfactory disorders in the group with AT reaction and sensorineural olfactory disorders in the group without response.

In the group with AT response, we found a relationship between the duration time of AT and subjective taste disorder. Based on the ROC curve results, if the AT duration time was longer than 36 s, there was a high possibility that the patient was not aware of the taste disorder. In other words, if the duration exceeds 36 s but the patient perceives a taste disorder, the possibility of a taste disorder rather than a flavour disorder due to olfactory influences should be considered.

One reason for the shortened duration may be reduced olfactory fatigue (olfactory adaptation). Olfactory adaptation is associated with cyclic adenosine monophosphate (cAMP)-sensitive channels [28, 29]. The cAMP concentration in the saliva and nasal mucus in patients with olfactory taste disorders is lower than in healthy patients [30]. Based on these findings, olfactory adaptation is more likely to occur when cAMP concentration is reduced, and adaptation may occur earlier in patients with flavour disorder. In clinically, there are patients who perceive an odour but it disappears in an instant, and the evaluation of the

duration time of the AT may be also useful in quantitatively capturing the symptoms of such patients. Another possible reason for the shortened duration is that neuropathy causes a decrease in the number of olfactory cilia, resulting in an excess of odour molecules relative to the number of cilia. In addition, neuropathy may raise the temperature of the olfactory epithelium and interfere with the response mediated by the second messenger-independent pathway related to membrane fluidity [31]. In the past, patients who underwent laryngectomy also responded to this test; therefore, considering routes other than the posterior choana is crucial [32].

Our study has certain limitations. First, we could not distinguish between true taste disorders such as the problems with taste receptors or transmission pathways and flavour disorders because we did not perform taste tests for patients with olfactory and subjective taste disorders. However, since odour has a taste-enhancing effect, we cannot rule out the possibility that olfactory disorders can cause taste disorders, making it difficult to identify pure taste disorders in patients with olfactory disorders. Second, the AT test used in this study is a psychophysical examination; hence, it is not objective. However, it may be possible to obtain objectivity by comparing the duration time of AT with the active areas and degree of brain activity using functional MRI. Third, that this study was not examined the outcome of AT by causative disease due to the small number of patients.

Conclusion

Our results showed that among the patients with olfactory disorders, the duration time of AT was reduced in those with subjective taste disorders. The duration time of AT is related to olfactory adaptation, and our results suggest that the possibility to olfactory adaptation may be one reason for patients with olfactory disorders who complain of taste disorders.

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None.

Authorship contribution

EM designed the study and the main conceptual ideas. RS wrote the manuscript. YK, HT, NY, YT, MN, RSM, and MT collected the data and worked on the manuscript. NO supervised the project. All authors discussed the results and have approved the final manuscript for submission.

Conflict of interest

The authors declare no conflicts of interest.

Ethics

Study approval statement: This study design was approved by the ethics committee of Jikei University School of Medicine (Approval No. 35-244(11873)).

Consent to participate statement: All study participants were given the opportunity to opt out.

Data availability

The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request.

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SUPPLEMENTARY MATERIAL

Supplementary Material 1. Questionnaire sheet.

Age:
Sex: Male/Female
Occupation:

1. How bad is your sense of smell?
   1. not at all
   2. almost no smell, faintly noticeable when approached
   3. strong smell, mostly noticeable when approached
   4. a little weak
   5. normal odour
   6. too sensitive, too strong

2. Do you have fluctuating symptoms of olfactory disorder?
   1. none
   2. gradually getting worse
   3. gradually getting better
   4. changing (intraday, daily)

3. Do you have any allergies?
   1. no
   2. asthma (pediatric asthma, bronchial asthma, aspirin asthma, other)
   3. Allergic rhinitis, pollen allergy
   4. other ( )

4. Do you have any taste disorder?
   No Yes

5. Do you smell differently from before?
   No Yes

6. Do you smell, even when there is no odour?
   No Yes