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Clinical practice guidelines for the management of olfactory dysfunction — Secondary publication☆

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ABSTRACT

Objective: To provide an evidence-based recommendation for the management of olfactory dysfunction in accordance with the consensus reached by the Subcommittee of the Japanese Clinical Practice Guideline for olfactory dysfunction in the Japanese Rhinologic Society.

Methods: Seven clinical questions (CQs) regarding the management of olfactory dysfunction were formulated by the subcommittee of the Japanese Clinical Practice Guideline for olfactory dysfunction. We searched the literature published between April 1990 and September 2014 using PubMed, the Cochrane Library, and Ichushi Web databases. The main search terms were "smell disorder," "olfactory dysfunction," "olfactory loss," "olfactory disturbance," "olfactory impairments," "olfaction disorder," "smell disorder," "anosmia," "cacosmia," and "dysosmia." Based on the results of the literature review and the expert opinion of the Subcommittee, 4 levels of recommendation, from A—strongly recommended to D—not recommended, were adopted for the management of olfactory dysfunction.

Results: Both oral and locally administered corticosteroids have been strongly recommended for patients with olfactory dysfunction due to chronic rhinosinusitis. Nasal steroid spray and antihistamine drugs have been moderately recommended for patients with allergic rhinitis. Although no drugs have been deemed to be truly effective for post-viral olfactory dysfunction by

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randomized-controlled trials (RCTs) or placebo-controlled trials, olfactory training using odorants has been reported to be effective for improving olfactory function. There is considerable evidence that olfactory testing is useful for differential diagnosis, prediction of disease progression, and early detection of cognitive decline in neurodegenerative diseases.

Conclusion: The Clinical Practice Guideline has developed recommendations for the management of various aspects of olfactory dysfunction.

1. Introduction

Olfaction is an important sensation for daily life. Not only is olfaction linked to the pleasure experienced during eating, but it is also essential for avoiding dangerous situations, such as fire and eating spoiled food. Therefore, olfactory dysfunction not only reduces the quality of life, but can also be life-threatening [1,2]. Recent work has reported that olfactory dysfunction is associated with neurodegenerative diseases, such as Alzheimer's disease and other cognitive disorders, as well as movement diseases, such as Parkinson's disease [3–6]. Although previous surveys have reported that the prevalence of olfactory dysfunction was 1–4% [7–10], more recent reports have demonstrated that more than 20% of the population suffer from olfactory dysfunction [11]. Therefore, it is important to establish and disseminate guidelines for the diagnosis and treatment of olfactory dysfunction.

Olfactory dysfunction is etiologically divided into three categories as follows: conductive dysfunction (e.g., airborne dysfunction caused by sinusitis and nasal allergy), sensorineural dysfunction (e.g., degeneration of the olfactory epithelium and nerves caused by viral infection and drug-induced impairment), and central dysfunction (e.g., disorder of the central nervous system caused by head injury, neurodegenerative diseases, and congenital anomalies) [12]. Since these different pathophysiological mechanisms require different treatments, appropriate and individual diagnoses are essential. Although many reviews and textbooks about olfactory dysfunction have already been published [13,14], no clinical practice guidelines for the diagnosis and treatment of olfactory dysfunction have been published.

On this basis, the Japanese Rhinologic Society (JRS) developed the Subcommittee of the Japanese Clinical Practice Guideline for the management of olfactory dysfunction. This clinical practice guideline reports the evidence-based recommendations for managing olfactory dysfunction in accordance with the consensus reached by the Subcommittee.

It should be emphasized that the recommendations for the clinical practice guidelines are not yet standard in terms of medical care and legal grounds, and that treatment should be decided based on individual clinical situations [15].

2. Users and subjects

The target clinician for this guideline is anyone who engages in the medical management of olfactory dysfunction. The target subjects for this guideline are adults and children with a diagnosis of olfactory dysfunction.

3. Literature search and evidence collection

The subcommittee of the Japanese Clinical Practice Guideline for the management of olfactory dysfunction raised 7 clinical questions (CQs) regarding the management of olfactory dysfunction.

To develop recommendations for these CQs, systematic reviews were performed. All members of the subcommittee of the Japanese Clinical Practice Guideline for the management of olfactory dysfunction, and a professional information specialist from the Japanese Medical Library Association, a non-profit corporation, cooperatively retrieved documents from 15th Oct. 2014 through to 16th Oct. 2014 by using an explicit search strategy. We searched for clinical practice guidelines, systematic reviews, RCTs, and comparative studies published between April 1990 and September 2014 using the PubMed, Cochrane Library, and Ichushi Web (the Japan Medical Abstracts Society website) databases. The main search terms were "smell disorder," "olfactory dysfunction," "olfactory loss," "olfactory disturbance," "olfactory impairments," "olfaction disorder," "smell disorder," "anosmia," "cacosmia," and "dysosmia."

4. Critical appraisal of the evidence

Members of the subcommittee of the Japanese Clinical Practice Guideline for the management of olfactory dysfunction reviewed the extracted articles detailed above. Two people were assigned for each CQ and they selected relevant articles to each CQ and collected relevant information. The subcommittee then assessed and summarized the information, and after achieving a consensus, coded the findings. The recommendation levels defined by the Medical Information Distribution Service (Minds), described below, were used to evaluate the efficacy of the treatment/examination in each CQ.

A: strong scientific evidence, and implementation of the treatment is strongly recommended;

B: scientific evidence, and recommended implementation of the treatment is moderate;

C: no scientific evidence, but implementation of the treatment is weakly recommended;

D: evidence suggests ineffectiveness or harm, and implementation of the treatment is not recommended.

5. Reviews before the release of the guideline

The draft guideline was externally evaluated and reviewed by both the JRS and the Oto-Rhino-Laryngological Society of

Japan. After making corrections according to feedback, the published guideline received public comments on the JRS website.

6. Standard olfactory testing in Japan

T&T olfactometer and intravenous olfactory tests have been used in Japan as an evaluation for patients with olfactory dysfunction. Because these tests are less well known in other countries, their methods and referent values will be introduced briefly.

T&T olfactometer is composed of five odors (β-phenylethyl alcohol, methyl cyclopentenolone, isovaleric acid, γ-undecalactone, and skatole; Table 1) and seven or eight graded series of concentrations (Fig. 1: Daiichi Yakuhin Sangyo, Tokyo, Japan). The odor detection threshold and odor recognition threshold are recorded on the olfactogram as shown in Fig. 2. The normal odor recognition threshold score of each nostril is 1.0 or less. The severity of olfactory dysfunction was categorized according to the mean T&T recognition thresholds, and patients were diagnosed with anosmia when the T&T recognition thresholds were 5.6 or greater (Table 2). The improvement in the T&T odor recognition threshold was judged according to the criteria of the Japanese Rhinologic Society (Table 3). Intravenous injection of thiamine Propyldisulfide (Alinamin) induces the sensation of a garlic-like odor, and Alinamin injection is widely used as one of the subjective olfactory tests in Japan. The mean of latency time and duration time in healthy volunteers are 8 s and 70 s, respectively. Nonresponders in the Alinamin test have been previously shown to have poor prognosis in the recovery of olfactory acuity.

7. Clinical questions and recommendations

7.1. CQ1: Is medical therapy effective in treating olfactory dysfunction caused by chronic rhinosinusitis?

Grade of recommendation: A

7.1.1. Local treatment of corticosteroids

Randomized, double-blinded, placebo-controlled trials of the efficacy of mometasone nasal spray in patients with nasal polyps have shown that olfactory scores improved significantly with mometasone compared to placebo after 1 month of treatment [16,17]. The adverse events included epistaxis and upper respiratory tract infection, none of which were serious. A prospective study reported that treatment with steroid nasal drops in the supine position with the head tilted back in patients with chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) improved the odor threshold and identification scores on the Connecticut Chemosensory Clinical Research Center (CCCRC) olfactory test [18]. Application of gelatin dressing combined with triamcinolone (10 mg/mL) at the olfactory cleft after endoscopic sinus surgery (ESS) has been reported to significantly improve threshold scores on the CCCRC test compared to those in a control group (gelatin dressing with saline) [19]. A prospective study in patients with CRSwNP compared the effects of fluticasone nasal spray for 8 weeks after

Table 1
Words expressing qualities of standard odors.

Item	Compound name	Character of odors
A	β-Phenylethyl alcohol	Odor of rose, light sweet odor
B	Methyl cyclopentenolone	Burnt odor, caramel odor
C	Isovaleric acid	Putrid odor, sweaty odor, odor of long-worn socks
D	γ-Undecalactone	Canned peach odor, heavy sweet odor
E	Skatole	Odor of vegetable garbage, oral odor, aversive odor

Fig. 1. T&T olfactometer.

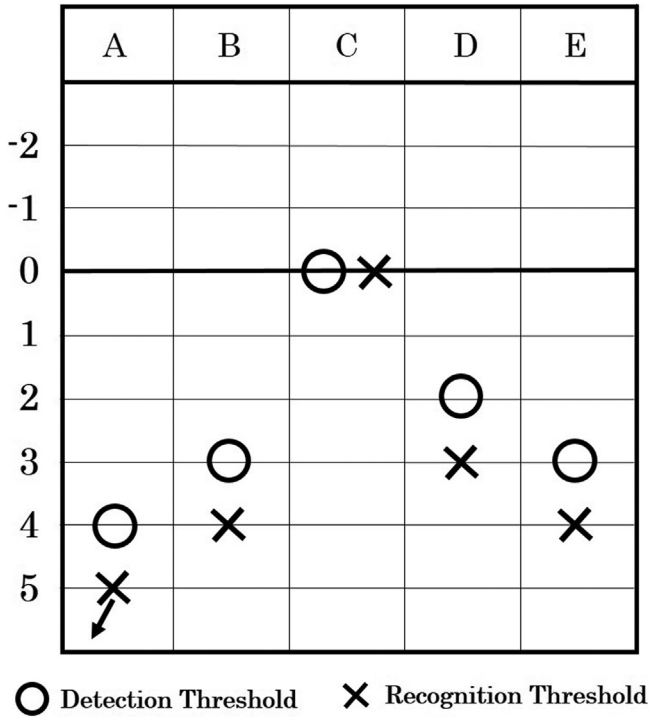

Fig. 2. Olfactogram by T&T olfactometer.

Table 2
The severity of olfactory dysfunction determined by average T&T odor recognition thresholds for five odors.

Recognition threshold	Severity of olfactory dysfunction
≤ 1.0	Normal
1.1–2.5	Mild hyposmia
2.6–4.0	Moderate hyposmia
4.1–5.5	Severe hyposmia
≥ 5.6	Anosmia

Table 3
Changes in patient odor recognition threshold according to criteria of the Japanese Rhinologic Society using a T&T olfactometer.

Category	Average recognition threshold changes after treatment
Cured	Patient odor recognition threshold achieved of ≤ 2.0
Improved	Patient odor recognition threshold decreased by ≥1.0 from pre-treatment condition
Worsened	Patient odor recognition threshold increased by ≥1.0 from pre-treatment condition
No change	All other cases

ESS (surgical group) and fluticasone nasal spray alone for 8 weeks (medical group); olfactory awareness scores and threshold and identification scores on the CCCRC test were significantly improved at 8 and 12 weeks after treatment in the medical group, albeit not as markedly as in the surgical group [20]. A randomized, double-blinded comparative study compared the effects of an oral leukotriene inhibitor and beclomethasone nasal spray on nasal symptoms after nasal endoscopic surgery [21]. At 1 year, symptom scores were improved in all patients. Improvements in nasal itching, post-nasal discharge, and headache were more marked in the leukotriene inhibitor group than in the fluticasone spray group, and improvements in olfactory dysfunction and nasal obstruction was more marked in the beclomethasone spray group.

7.1.2. Oral corticosteroids administration

The efficacy of oral prednisolone in patients who do not improve with local treatment [22,23] and the usefulness of combined local treatment and oral prednisolone [24,25] have been reported. Oral prednisolone (40–60 mg/day for 10–14 days) has been reported to improve the mean olfactory recognition threshold in 83% of patients who did not respond to local treatments with betamethasone or beclomethasone [22]. Furthermore, some patients have been reported to experience an exacerbation of symptoms when oral prednisolone was discontinued, which indicates the need for oral steroids in maintaining improved olfaction [22]. In another study, odor identification function (Sniffin' Sticks test) did not improve with mometasone nasal spray (1–3 months) but improved significantly with oral prednisolone (starting at 40 mg/day with a gradual dose reduction, 21 days) [23]. A randomized, double-blinded, placebo-controlled trial in patients with CRSwNP showed that olfactory visual analogue scale (VAS) scores were significantly improved in the oral prednisolone group (25 mg/day for 2 weeks) compared to the placebo group, and that this improvement in olfactory function could be subsequently maintained with fluticasone nasal spray (26 weeks) [24]. One randomized controlled study was conducted to assess the effects of oral prednisolone (30 mg/day for 4 days, with gradual dose reduction by 5 mg/day every other day, for a total of 2 weeks) in patients with CRSwNP [25]. The treatment group showed significant improvements in olfactory test scores (Barcelona Small Test 24) and better maintenance of olfactory function with subsequent budesonide local treatment (12 weeks), compared to the control group.

Based on these reports, both local and oral steroids can be considered effective in treating olfactory dysfunction. Appropriate combinations of steroids and surgery appear to be even more effective than the administration of steroids or surgery alone.

7.1.3. Macrolides

Some reports have examined the use of erythromycin, clarithromycin, and roxithromycin for treating olfactory dysfunction caused by CRS. A randomized, placebo-controlled, double-blinded study of roxithromycin (150 mg/day for 3 weeks) in patients with CRS did not show any significant improvement in threshold and discrimination scores on the Sniffin' Sticks test after treatment [26]. Evidence for the direct effects of macrolide therapy on olfactory dysfunction appears to be insufficient.

7.1.4. Omalizumab

A randomized, double-blinded, placebo-controlled trial of omalizumab (anti-immunoglobulin (Ig)E antibody) was conducted in patients with CRSwNP presenting with bronchial asthma [27]. Omalizumab administered subcutaneously for 16 weeks (8 times every 2 weeks or 4 times a month based on serum total IgE concentration and body weight at the pre-treatment baseline) significantly improved the olfactory awareness score (loss of sense of smell) compared to the placebo group.

7.2. CQ2: Is endoscopic sinus surgery effective in treating olfactory dysfunction caused by chronic rhinosinusitis?

Grade of recommendation: B

A prospective study was conducted to compare the effects of a steroidal nasal spray after ESS (surgery group) and a steroidal nasal spray alone (conservative treatment group) [20]. Patients were matched by age, smoking history, and severity of obstruction. Both groups showed improvements in olfaction, although the remission rate was significantly greater in the surgery group (60%) compared to the conservative treatment group (20%). Most other reports have described observational studies with an olfactory dysfunction improvement ratio of 70% after surgery [19,20,28–40]. Of the 21 articles that examined the improvement ratio, 20 articles reported that surgery is effective for olfactory dysfunction, and only one article reported surgery as ineffective, with an improvement ratio of only 5.7% [30]. However, even that article showed a significant improvement in symptom and threshold scores after surgery.

Some factors associated with poor prognosis of surgical treatment and subsequent post-operative treatment in CRS to improve olfactory dysfunction include the following: male sex, older age (≥60 or ≥51 years old), long duration of olfactory

dysfunction, high circulating eosinophil count, complications (aspirin-induced asthma, bronchial asthma, and eosinophilic otitis media), history of sinus surgery, computed tomography score, absence of response to intravenous olfaction test, nasal polyps, post-operative recurrence of nasal polyps, smoking, degree of olfactory dysfunction, and low income [29,32,38,39].

7.3. CQ3: Is medical therapy effective in olfactory dysfunction caused by allergic rhinitis?

Grade of recommendation: B

7.3.1. Nasal steroid spray

Nasal steroid spray may improve olfactory function through inhibition of inflammation in the olfactory cleft [41], because there is a possibility that eosinophilia in the olfactory mucosa induces olfactory dysfunction [42]. In a randomized, placebo-controlled, double-blinded, crossover study, budesonide nasal spray significantly improved the olfactory detection threshold [43]. Another double-blinded, randomized study also demonstrated that mometasone furoate significantly improved odor identification, although olfactory detection did not change [44]. On the other hand, Stuck et al. conducted a randomized double-blinded trial, and showed that the olfactory detection threshold, but not odor identification, was improved by using a nasal steroid spray [45].

7.3.2. Antihistamines

A randomized double-blinded trial also demonstrated that antihistamine drugs significantly improved VAS scores of olfactory dysfunction [46]. In another randomized double-blinded trial, VAS scores of olfactory function were significantly improved with antihistamine drug treatment, but anosmia did not improve [47].

7.4. CQ4: Is medical therapy effective in treating post-viral olfactory dysfunction?

Grade of recommendation: C

Since post-viral olfactory dysfunction (PVOD) is a sensorineural olfactory dysfunction its recovery should require the regeneration of the olfactory epithelium/neural pathway. In Japan, several kinds of drugs, such as zinc sulfate, Kampo medicine, oral and intranasal steroids, vitamins, and adenosine triphosphate (ATP) have been used for the clinical treatment of PVOD. There were double-blind, randomized, placebo-controlled trials to test the efficacy of several drugs on PVOD, but none of the studies demonstrated statistically significant therapeutic effects. On the other hand, olfactory training using odorants has been reported to be effective in improving olfactory function in PVOD [48].

One important point to be considered is that previous studies examining the effects of medication on PVOD enrolled many patients with long-lasting olfactory dysfunction after onset. Therefore, information about whether such medication is effective for the treatment of PVOD soon after its onset is still limited. Another point to be considered is that PVOD shows some natural recovery [49,50]. Therefore, placebo-controlled studies are necessary to accurately evaluate the effect of drugs on PVOD.

7.4.1. Zinc

Zinc is a trace metal involved in enzyme activity, especially those involved in cell proliferation. Therefore, zinc has been considered essential to maintain the function of olfactory and taste organs in which the sensory cells are constantly regenerated. Zinc sulfate has long been used to treat olfactory and taste dysfunction, but there is no clear evidence about the effects of zinc on PVOD. In one double-blinded study, Zinc administration did not improve PVOD vs. a placebo group [51]. In a study by Aiba et al. 184 patients with PVOD were divided into three groups, as follows: (1) a group treated with zinc sulfate, (2) a group treated with a combination of intranasal steroid, vitamin B, and zinc sulfate, and (3) a group treated with a combination of intranasal steroids and vitamin B. There was no significant between-group difference in the improvement in olfactory function [52]. In another study, measured the serum concentration of zinc in patients with PVOD before the start of the treatment [53]. The authors reported that, in about half of the patients, the zinc concentration was within a normal range, while in the other half, it was below the normal range. The normal range group exhibited a greater improvement of olfactory function than did the low concentration group; within the low concentration group, patients treated with zinc exhibited a tendency for olfactory function to improve to a greater extent than those without zinc treatment.

7.4.2. Kampo medicines

The treatment of PVOD with tokishakuyakusan, a traditional Japanese medicine, greatly improved in olfactory function than that seen with intranasal steroid treatment [54]. Tokishakuyakusan has been shown to promote the production of neurotrophic factors and has been used as a supplementary medication for Alzheimer's disease [55]. Two other Kampo medicines, ninjin'yoeito and kamikihito, have also been used for the treatment of PVOD [55]. The administration with treated tokishakuyakusan or ninjin'yoeito to patients with PVOD who had not responded to intranasal steroids, improved 43% and 36% of patients, respectively [56].

7.4.3. α-lipoic acid

After α-lipoic acid (600 mg/day) for 4.5 months were orally administrated to 23 patients with PVOD, the olfactory threshold, discrimination, and identification were evaluated. They found an improvement in the olfactory test score in 61% of patients, no change in 30%, and a worsening in 9% [57]. However, their subsequent double-blinded study did not confirm these results [58].

7.4.4. Vitamin A

In a double-blinded, randomized, placebo-controlled trial by Reden et al. [59], patients with PVOD received either vitamin A (10,000 U/day) or a placebo for 3 months. Olfactory function was evaluated using the Sniffin' Stick test, which was administered

5 months after the start of treatment. No significant between-group differences in the outcomes were found.

7.4.5. Minocycline

In a double-blinded, randomized, placebo-controlled trial, patients with PVOD received either minocycline (100 mg/day) or placebo for 3 weeks [60]. The olfactory tests were performed before and 7 months after the treatment. There were no significant between-group differences in patient outcomes.

7.4.6. Theophylline

Theophylline is a non-specific phosphodiesterase inhibitor and increases intracellular cAMP concentrations in neurons. In an open-label trial with 312 patients, including 97 patients with PVOD; after the administration of theophylline (200–800 mg/day), 50.3% of the patients with PVOD reported subjective improvement in olfaction [61]. Administration of pentoxifylline, another phosphodiesterase inhibitor, resulted in improvements in the olfactory threshold test in patients with sudden sensorineural hearing loss [62].

7.4.7. Steroids

After systemically administration of steroids to patients with CRS or PVOD, Patients with CRS showed significant improvements in olfactory recognition, while patients with PVOD did not [22]. However, the authors reported that some patients with PVOD did respond to the steroid treatment and showed an improvement in olfactory recognition, which suggests that steroids may be effective for acute, reversible stages of olfactory mucosal injury. Another group also administered steroids either systemically or intranasally in patients with PVOD [63]. There was no significant effect in the intranasal treatment group, while there was a significant improvement of olfactory scores after systemic steroid administration.

7.4.8. Olfactory training

Fifty-six patients with olfactory dysfunction, including 35 patients with PVOD were divided into two groups, as follows: patients in the olfactory training group performed olfactory training using four odorants (rose, eucalyptus, lemon, clove) twice a day for 12 weeks, and the control group did not perform such training [48]. The olfactory function of the two groups was evaluated using the Sniffin' Sticks olfactory test. The olfactory training group showed greater improvements in test scores than the control group [48]. The impact of an 8-month period of olfactory training was examined in patients with PVOD (n = 16). The patients exposed themselves to four different odors twice a day, and olfactory function was evaluated at baseline and again at 4 and 8 months after the start of training. Olfactory function was significantly improved at 4 months [64]. Thirty-nine patients with PVOD exposed themselves to suprathreshold concentrations of four odors over 32 weeks; overall, 31 patients (79%) showed an increased olfactory score at 32 weeks [65]. A recent randomized, single-blind, controlled, multicenter crossover study in Germany including 174 patients with PVOD demonstrated that olfactory training for 18 weeks improved olfactory function, and the use of odors at higher concentrations is beneficial to such improvements [66].

7.5. CQ 5: Are there any effective treatments for post-traumatic olfactory dysfunction?

Grade of recommendation: C

In Japan, prescriptions of Kampo medicines, zinc or vitamin preparations, topical or systemic steroids, and adenosine triphosphate are used to treat post-traumatic olfactory dysfunction. However, the efficacy of these medicines has not been supported by any studies with high levels of evidence, such as randomized-controlled trials. Several reports have indicated that olfactory training is effective in restoring olfactory function [67].

Post-traumatic dysfunction has the potential to recover spontaneously, and it is unclear to what degree spontaneous recovery affects the improvement rate. In order to fully investigate the efficacy of a medication, it is necessary to conduct randomized-controlled trials and evaluate therapeutic interventions at an early stage after injury.

7.5.1. Kampo medicine

Tokishakuyakusan treatment improved olfactory test scores (using T&T olfactometry) in 41.7% of patients with post-traumatic olfactory dysfunction [68]. In another study, 7 patients with post-traumatic olfactory dysfunction were treated with kamikihito; 1 patient recovered, 5 patients improved, and 1 patient showed no change [69].

7.5.2. Zinc

Ninety-five patients with post-traumatic olfactory dysfunction were divided into three groups based on the method of treatment as follows: zinc sulfate only, combination of zinc sulfate and the usual therapy (topical corticosteroids and systemic vitamin B complex), or the usual therapy. Patients who were administered zinc sulfate demonstrated significantly higher improvement rates than those who received the usual therapy [52]. In another study, 22 patients with post-traumatic olfactory dysfunction were treated with zinc sulfate, tokishakuyakusan, and vitamin B12 complex; 5 patients recovered, 5 patients improved, 10 patients showed no change, and 2 patients showed an exacerbation of symptoms [70].

7.5.3. Steroids

Some case studies have reported the efficacy of topical or systemic steroids. A total of 108 patients with post-traumatic olfactory dysfunction were treated with topical steroids, and the improvement rate was 25% [71]. In another, 12 patients with post-traumatic olfactory dysfunction were treated with topical betamethasone; 1 out of 12 patients showed an improvement in the olfactory test score. Five patients were also treated with topical dexamethasone, and 3 out of the 5 patients showed an improvement [72]. In another study, 116 patients with post-traumatic olfactory dysfunction were treated with systemic prednisolone (15 mg × QID for 3 days, tapered every 3 days),

and the olfactory threshold improved in 19 patients [73]. Patients with post-traumatic olfactory dysfunction were treated with topical betamethasone, and the improvement rate was 28.6%. In this report, the improvement rate between patients who were administered steroids and those administered tokishakuyakusan was compared, but no significant differences were observed [54].

7.5.4. Vitamin A

In a double-blinded, placebo-controlled study, vitamin A at a dose of 10,000 IU per day was administered to 52 patients with olfactory loss, including 19 patients with post-traumatic olfactory loss, for 3 months. No significant improvement, as evaluated by the olfactory test scores (the Sniffin' Sticks test) was observed 5 months after the initial test [59].

7.5.5. Olfactory training

A prospective study with 38 patients with post-traumatic olfactory dysfunction was performed to investigate the effect of olfactory training [67]. The training group underwent olfactory training for 5 min twice daily using the following four odorants: phenylethyl alcohol (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (cloves). Compared to the control group, the training group had significantly higher olfactory function scores, as measured by the Sniffin' Sticks test at 16 weeks. The improvement rates of both groups were 33% and 13%, respectively.

7.6. CQ 6: Can olfactory dysfunction contribute to the prediction of early diagnosis of neurodegenerative diseases?

Grade of recommendation: A

There is considerable evidence that olfactory testing is useful in differential diagnosis, prediction of disease progression, and early detection of cognitive loss in neurodegenerative diseases. Objective olfactory dysfunction is an early sign and common symptom of Parkinson's disease, and olfactory deficits may precede clinical motor signs. For example, some asymptomatic relatives of patients with Parkinson's disease have been found to exhibit olfactory dysfunction that can predict the future development of Parkinson's disease [74]. Indeed, olfactory dysfunctions are considered as biomarkers of a preclinical diagnosis of Parkinson's disease and for its differentiation from other forms of parkinsonism [75–78]. Severe hyposmia is a prominent clinical feature that predicts the subsequent development of Parkinson's disease [79–81]. Olfactory testing may therefore be a useful screening tool to detect those at high risk for the development of Parkinson's disease in later life [79,82]. Idiopathic hyposmia in relatives of patients with Parkinson's disease is also associated with an increased risk of developing clinical Parkinson's disease [81,83]. In another study, enlarged substantia nigra hyperechogenicity was the most frequent baseline sign in individuals developing Parkinson's disease compared to healthy controls, followed by the occurrence of mild parkinsonian signs and hyposmia [84]. Olfactory deficits in Parkinson's disease are not stationary by the time the motor phase is entered but continue to progress over time. The olfactory deficits in Parkinson's disease have also been found to correlate with both motor and non-motor features [85,86]. Another study found that early Parkinson's disease is associated with frequent and severe olfactory deficits that are correlated with disease severity, symptom duration, and single photon emission computed tomography [76]. Therefore, hyposmia may be useful as a marker of disease progression, at least in the early disease stages.

Among older persons without cognitive impairment, difficulty in identifying odors has been found to predict subsequent development of mild cognitive impairment in Alzheimer's disease [87]. In patients with mild cognitive impairment, olfactory identification deficits, particularly with a lack of awareness of olfactory deficits, may have clinical utility as an early diagnostic marker for Alzheimer's disease [88].

7.7. CQ7: Are steroids effective in the treatment of olfactory dysfunction?

Grade of recommendation: B

A short course of systemic steroids should be prescribed for olfactory dysfunction due to CRSwNP. Topical steroids should be prescribed for olfactory dysfunction due to allergic rhinitis and CRSwNP. The long-term use of high-dose topical steroids should be considered as a risk for pituitary-adrenal suppression. There is limited evidence for the use of steroids in the treatment of olfactory dysfunction caused by other etiologies, such as post-infectious, post-traumatic, and idiopathic olfactory dysfunction.

One systematic review [89] and two randomized placebo-controlled double-blinded trials [24,25] demonstrated that olfactory test scores significantly improved after treatment with oral steroids in patients with CRSwNP. In these studies, oral prednisolone or prednisone was administered at a dose of 15 mg–50 mg, which was gradually tapered over a period of 2–3 weeks. The frequency of adverse events was low. However, in one study, suppression of the pituitary/adrenal system and a decrease in bone metabolism occurred transiently during steroid administration [89]. Thus, evidence for the efficacy of oral steroids for olfactory dysfunction is limited to short-term administration, and no long-term administration studies on their efficacy and safety have yet been conducted.

Three randomized controlled trials have reported that nasal spray steroids improve olfactory test scores of patients with olfactory dysfunction due to allergic rhinitis [44,45,47], and two randomized controlled trials have demonstrated that nasal spray steroids can improve subjective olfactory symptoms in patients with olfactory dysfunction due to CRSwNP [16,17]. There were no serious adverse events due to nasal spray steroids, and no suppression of the pituitary/adrenal system. Nasal spray steroids are recommended as a remedy for olfactory dysfunction secondary to sinonasal disease. A high dose of topical steroids, 0.1% betamethasone nasal drops, has been used in Japan for patients with olfactory dysfunction. However, it has been reported that pituitary-adrenal suppression occurred in 61–68% of patients with olfactory dysfunction due to the use of

steroid nasal drops for more than two months [90,91]. That said, in these studies, adrenal cortisol production recovered about one month after stopping steroid treatment.

Regarding olfactory dysfunction caused by other etiologies, including post-infectious, post-traumatic, and idiopathic olfactory dysfunction, there is limited evidence for the efficacy of steroid treatment. In a randomized controlled trial of patients with post-infectious and idiopathic olfactory dysfunction, nasal spray steroids did not improve olfactory test scores [92]. In three case studies [93–95], oral steroids resulted in an improvement in olfactory test scores. However, these studies did not use control groups for comparison. It is therefore difficult to determine whether the recovery of olfaction was due to spontaneous recovery or the effect of treatment.

Disclosure statement

This study was funded by The Japanese Rhinologic Society (JRS). The JRS is an independent academic organization that receives no sponsorship or funding from specific organizations or businesses. Furthermore, the JRS received no funding for the preparation of the present guidelines from any businesses, which includes businesses representing the pharmaceutical industry.

Conflicts of interest

The authors report no conflicts of interest. Members of the committee with a conflict of interest were excluded from the drafting of any part of the guideline to which the conflict of interest is applicable. Companies that provided non-personal financial conflicts of interest to members of the Committee of the Clinical Practice Guideline during the production of this guideline are listed as follows:

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