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Olfactory Training Is Helpful in Postinfectious Olfactory Loss: A Randomized, Controlled, Multicenter Study

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Objectives/Hypothesis: The aim of this study was to evaluate the effects of olfactory training (OT) on olfactory function in patients with persistent postinfectious olfactory dysfunction (PIOD).

Study Design: Randomized, single-blind, controlled, multicenter crossover study.

Methods: Twelve tertiary university medical centers participated. Investigations were performed at three visits (baseline, after 18 weeks, and after 36 weeks), including only subjects with PIOD of <24-months duration. At each visit, participants received detailed assessment of olfactory function. Seventy subjects trained with high concentrations of four odors for 18 weeks; the other half (n = 74) trained with low concentrations of odors. For the following 18 weeks this regimen was switched.

Results: After 18 weeks, olfactory function improved in the high-training group in 18 of 70 participants (26%), whereas only 11/74 improved in the low-training group (15%). In subjects with a duration of olfactory dysfunction of <12 months, olfactory function improved in 15/24 participants (63%) of the high-training group and in 6/31 participants (19%) of the low-training group ($P = .03$).

Conclusions: OT improves PIOD, and the use of odors at higher concentrations is beneficial to improvement. OT is a safe procedure and appears to be particularly useful in patients who start OT within 12 months after the onset of the disorder. OT is the first successful therapy regime in patients with PIOD.

Key Words: Olfaction, smell, postviral, hyposmia, anosmia, treatment, Sniffin' Sticks test.

Level of Evidence: 1b.

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INTRODUCTION

Approximately 5% of the general population are considered to be anosmic, and an additional 15% are considered to have hyposmia.[1] Upper respiratory tract infections (URTIs) are among the most frequent causes of olfactory deficits.[2–4] Fortunately, for postinfectious olfactory dysfunction (PIOD), high rates of spontaneous recovery have been reported in the literature. Hendriks[5] reported that spontaneous recovery occurs in 35% of the patients over a period of approximately 12 months. Duncan and Seiden followed 21 patients with PIOD using the University of Pennsylvania Smell Identification Test and found an increase of at least four points in 67% of participants after a mean follow-up of 37 months.[6] Additionally, they noted a correlation between the degree of improvement and length of follow-up in their patients.[6] In a retrospective series involving 262 subjects with a mean follow-up time of 14 months, Reden et al.[7] reported that 32% of PIOD patients experienced improvement of olfactory function, gauged with the Sniffin' Sticks test and indicated by an increase of at least six points in the threshold, discrimination, identification (TDI) score.[8] In a different study, Reden et al. reported clinically relevant improvement of olfactory function in 21% of the participants over a period of approximately 7 months. Hummel et al.[9] reported a short-term recovery rate of 6% to 8% within 4 months, using the same

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Burghart Messtechnik GmbH, Wedel, Germany provided the odor probes used for training.

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olfactory tests and definitions of success as Reden et al.[8] Thus, about one-third of PIOD patients exhibit improvement of olfactory function after 1 year.

To date there is no validated pharmacotherapy for PIOD, although attempts have been made to establish such treatment including trials with systemic and topical steroids,[10,11] vitamin B,[10] caroverine,[12] α-lipoic acid,[13] minocycline,[7] or acupuncture.[14] However, in a study on olfactory training (OT) in patients with PIOD, and traumatic and idiopathic olfactory dysfunction, Hummel et al. pointed out that structured short-term exposure to odorants over 12 weeks increased olfactory sensibility in 28% of participants (10 out of 36).[9] This study inspired the present work. The aim of this trial was to verify the efficacy of OT in PIOD.

MATERIALS AND METHODS

Study Design

This trial was performed as a randomized, single-blind, controlled, multicenter crossover study. The protocol was approved by the ethics committee of the medical faculties of participating institutions. All participants provided written informed consent. The trial was conducted in accordance with the Declaration of Helsinki, and was consistent with Good Clinical Practice and the applicable regulatory requirements.

The expected effect size of OT was at least 20%.[9] Because it is unclear whether success of OT depends on odor concentration, we decided to apply high- and low-odor concentrations in a crossover design.

Study Centers

Ten otorhinolaryngology departments within tertiary medical hospitals plus the Institute of Pharmacology in Erlangen (Renner) in Germany participated: Universitätsmedizin Charité Berlin (Göktas, Holinski); University Hospitals of Cologne (Damm, Pikart, Vent); University of Halle-Wittenberg (Burkert); Smell and Taste Clinic of the University of Dresden Medical School (Hummel); University Clinics of Greifswald (Beule); University Hospital Mannheim (Frey); University of Jena (Reimann); University of Magdeburg and Sana Ohren-Klinikum, Haldensleben (Charalampakis); and University of Mainz (Haxel).

Study Protocol

At the first visit (V1, baseline, week 1), a thorough medical history was taken using a standardized case report form (CRF). In addition, a systematic otorhinolaryngological examination including endoscopy of the olfactory cleft was performed to exclude nasal pathologies. The diagnosis olfactory dysfunction was classified as postinfectious depending on the clinical findings and past medical history.

Olfactory testing was performed using the Sniffin' Sticks test (Burghart GmbH, Wedel, Germany).[2] Odorants were presented in felt-tip pens; for odor presentation the cap was removed by the investigator and the pen's tip was placed in front of the subject's nostrils. With this test battery, olfactory function was examined bilaterally for odor threshold, odor discrimination, and odor identification. The clinical evaluation of olfactory performance was based upon the composite TDI score represented by the sum of the scores from the three subtests.[2]

Inclusion criteria were persistent PIOD for at least 8 weeks but not longer than 24 months and age at study entry from 18 to 65 years.

Exclusion criteria were pregnancy, normosmia (TDI score >30.5), chronic rhinosinusitis, nasal polyposis, allergic or idiopathic rhinitis, post-traumatic olfactory loss, or other acute or chronic nasal diseases (e.g., acute viral infections), malignant tumors and/or oncology therapies (radiation, chemotherapy), and history of surgery on the nose or paranasal sinuses. Any patients using medication that may also have effects on the olfactory dysfunction (e.g., corticosteroids) were excluded.

At the second visit (V2, week 16–18) and the third visit (V3, week 32–37) participants were reexamined, which included an endoscopic reevaluation of the nasal cavities and testing with the Sniffin' Sticks. CRFs were completed concerning adverse effects due to OT, upper respiratory tract infections since the last visit or other events/treatments with potential (negative) impact on olfactory function (e.g., head trauma), parosmias/phantosmia, and changes of medication. Participants assessed the improvement or deterioration of ortho- and retronasal olfactory function and their OT activity in five-point ranking scales at the end of each training period.

Participants

Participants were either self-referrals or referred from an outside institution. A total of 171 subjects were included (109 women, 62 men). The mean age was 54.6 years (±9.6 years standard deviation [SD]; range, 24–65 years), the mean duration of olfactory dysfunction at the beginning of the study was 10.5 months (±9.8 months SD). Participants were randomized to an OT either with high odorant concentrations (high-training group: total n = 81, mean age: 54.6 years [±9.8 years SD], 29 male, 52 female, functional anosmia n = 31, hyposmia n = 50, TDI: 18.2 [±6.7 SD]) or low odorant concentrations (low-training group: total n = 90, mean age, 54.6 years [±9.5 years SD], 35 male, 55 female, functional anosmia n = 32, hyposmia n = 58, TDI: 17.5 [±6.9 SD]). Parosmia was present in 42.3% of participants at V1, and 13.3% had phantosmia.

One hundred forty-four participants completed V2 (high-training group: total n = 70, mean age: 54.5 years [±9.9 years SD], 24 male, 46 female; low-training group: total n = 74, mean age: 55.7 years [±8.1 years SD], 29 male, 45 female) and 126 patients V3 (high-training group: total n = 61, mean age: 55.4 years [±9.8 years SD], 20 male, 41 female; low-training group: total n = 65, mean age: 57.7 years [±8.0 years SD], 26 male, 39 female), respectively.

At V1 the two groups were not significantly different in terms of age, sex distribution, olfactory function (Table I), and duration of olfactory dysfunction.

Olfactory Training

OT was performed over two periods of 16 weeks. Participants exposed themselves twice daily to four odors (phenylethyl alcohol [PEA]: rose odor, eucalyptol: eucalyptus odor, citronellal: lemon odor, and eugenol: cloves odor). These four odorants were chosen[9] to represent primary odor categories claimed by Henning.[15] For OT, patients received four felt-tip pens (OT pens [OTPs]). They sniffed each odor for approximately 15 seconds and repeated this exercise once. Patients were asked to train in the morning and in the evening, resulting in a total of four expositions per day. They were asked to keep a diary where they rated overall olfactory abilities each Sunday (data not analyzed). At V1 participants received OTPs either with high or low odor concentrations. OTPs were returned after 16 weeks and replaced by OTPs with inverse odor concentrations (high vs. low concentration; low vs. high concentration). The group identity was blinded to the investigator to reduce experimental bias.

TABLE I.
Odor Thresholds, Odor Discrimination, and Odor Identification Before and After Olfactory Training.

		Group A, Low-Training Group, n = 74			Group B, High-Training Group, n = 70		
		Mean	SD		Mean	SD	
First training phase							
V1	TDI	17.54	6.90		18.20	6.71	
	Threshold	2.46	1.92		2.66	2.23	
	Discrimination	7.74	3.46		8.17	3.21	
	Identification	7.34	2.99		7.37	2.82	
				Δ			Δ
V2	TDI	20.32	6.46	2.78	21.24	7.29	3.04
	Threshold	3.22	2.26	0.76	3.21	2.37	0.55
	Discrimination	9.11	3.10	1.37	9.56	3.52	1.39
	Identification	8.05	2.86	0.71	8.37	3.02	1.00
		Group A, High-Training Group, n = 65			Group B, Low-Training Group, n = 61		
		Mean	SD		Mean	SD	
Second training phase							
V2	TDI	20.88	6.58		20.78	6.98	
	Threshold	3.42	2.32		3.07	2.36	
	Discrimination	9.22	3.03		9.32	3.40	
	Identification	8.32	2.80		8.27	2.95	
				Δ			Δ
V3	TDI	22.10	6.53	1.22	22.28	7.68	1.50
	Threshold	3.42	2.33	0.00	3.50	2.44	0.43
	Discrimination	10.02	2.93	0.80	9.93	3.43	0.61
	Identification	8.68	2.78	0.36	8.85	3.04	0.58
		Group A, Low–High-Training Group, n = 65			Group B, High–Low-Training Group, n = 61		
		Mean	SD		Mean	SD	
Complete training period							
V1	TDI	18.15	6.91		17.87	7.09	
	Threshold	2.60	1.96		2.82	2.37	
	Discrimination	8.02	3.54		7.90	3.23	
	Identification	7.54	3.01		7.15	2.91	
				Δ			Δ
V3	TDI	22.1	6.53	3.95	22.28	7.68	4.41
	Threshold	3.42	2.33	0.82	3.50	2.44	0.68
	Discrimination	10.02	2.93	2.00	9.93	3.43	2.03
	Identification	8.68	2.78	1.14	8.85	3.04	1.70

Δ = differences between measurements; SD = standard deviation; TDI = odor thresholds, discrimination, and identification score in the Sniffn' Sticks test; V1 = first visit, baseline; V2 = second visit after 18 weeks; V3 = third visit after 37 weeks.

In a pilot study, thresholds of odorants used for OT were obtained in 50 young, healthy women (age range, 20–25 years) using a single staircase, three-alternative forced choice paradigm.[2] Based on these results, a 0.0001% dilution (concentration at the 10th percentile in threshold tests of healthy volunteers) was used as concentration of odors in the OTPs for the low odorant concentration training group (low-training group). In the high odorant concentration training group (high-training group), PEA, eucalyptol, citronellal, and eugenol were used in neat concentrations in the OTPs.

Primary end point. The primary end point was set as the change of TDI scores at V2 compared to V1. Significant improvement was defined as improvement in more than 20% of participants (double the rate of spontaneous remissions within 16 weeks[9]). A clinically significant improvement of TDI scores was defined by an increase of at least six points.[7–9]

Secondary end points. Secondary end points were the change of ratings of ortho- and retronasal olfactory function.

Further end points. The outcome at V3 was determined by the number of participants who improved in TDI scores of at least six points. Further end points were the effects of OT on the Sniffin' Sticks subtests: olfactory threshold, odor identification, and odor discrimination. Correlational analyses were performed to investigate the potential role of

the age and the duration of PIOD on the improvement of olfactory function.

Statistical Analysis

For statistical analyses, G*Power version 3.1.2 and Statistical Package for Social Sciences version 20.0 (SPSS, Inc., Chicago, IL) were used.[16] The results were given as mean ± SD or medians with interquartile ranges (IQR). Improvement of six points or more within the anosmic rage (TDI range, 1–15.5 points) was judged as random variation and evaluated as no change in the statistical analyses.

Sample size determination. The sample size calculation was based on the previous study,[9] reporting an effect size of 0.22 (no training group, 6% vs. training group, 28%) of OT in a 12-week period. Based on the latter observation, we assessed an effect size of about 0.24 in 16 weeks of OT. A sample size of 137 participants appeared to be adequate to study potential effects of the training procedure.

Comparisons were performed using *t* tests for independent samples and χ^2 tests. Comparison of subjective assessment of olfactory improvement was performed using the Mann-Whitney *U* test and the Wilcoxon test. Subjective assessments were expressed as medians with IQR. Analyses of variance (ANOVA) (repeated measures ANOVA design [rm-ANOVA]) were used for comparisons of olfactory function (within-subject factors: TDI, Sniffin' Sticks subtest [threshold, discrimination, identification]) between groups (between-subject factor: group [high-training, low-training]) obtained before and after OT (session: V1 vs. V2 vs. V3); age at diagnosis and duration of PIOD were used as covariates. Correlation analyses (Pearson or Spearman where appropriate) were performed to investigate the relation between changes of TDI scores and subjects' age, duration of PIOD, or number of new airway infections during the study.

The study was approved by the institutional review board of the medical faculty of the University of Cologne and by all local ethics committees of participating centers.

RESULTS

At V2, 6.2% of participants reported that they performed OT only occasionally. OT was carried out according to the instructions by 88.4% and at least more frequently by 5.4% of participants, respectively. The training interval was 18.4 weeks (±3.1 SD) between V1 and V2, and 18.3 weeks (±4.2 SD) between V2 and V3.

New infections of the respiratory tract were reported from 40.9% of participants of the high-training group and from 37.1% of the low-training group. A temporary negative impact on olfactory function was noted by 12 participants of the high-training group and by 13 of the low-training group. Reports of subjective deterioration of olfactory function at V2 were negatively correlated with the changes of TDI scores in the second training period (Spearman ρ −0.25, $P = .012$).

Temporary adverse effects due to OT were specified from six participants (8.1%) in the low-training group (1× inflammation of the right nostril, 1× hay fever symptoms, 2× burning in the nose, 1 mild depression, 1× parosmia) and of one (1.4%) of the high-training group (nosebleed). None of these problems led to discontinuation of the study. After the second training phase, one participant of the high-training group complained of temporary difficulties in swallowing at V3. All adverse events recovered completely without therapy.

Primary end point

At V2, olfactory function improved in the high-training-group in 18 of 70 participants (25.7%), whereas only 11 of 74 improved in the low-training group (14.9%). Three of 144 participants (high-training-group: 1.4%, low-training-group: 2.7%) exhibited deterioration of their olfactory function. The participants who profited from the OT showed an average increase of the TDI score of 9.1 (±2.6 SD) points. No significant difference was found between high- and low-training group in the χ^2 test ($P = .11$). Nevertheless, the primary end point of improvement in more than 20% of the participants was reached in the high-training group, whereas it was not reached in the low-training group.

At V3, an improvement of the TDI score was found in the low–high-training group in 30.8% and in the high–low-training group in 45.8% (χ^2 test: $P = .073$). Two of 126 participants of the low–high-training group (1.6%), but none of the high–low-training group worsened their olfactory function after 37 weeks OT.

Secondary end points. At V2, median assessment of improvement of olfaction was moderate improvement (IQR 1) in the high-training group and unchanged (IQR 1) in the low-training group for both the orthonasal ($P = .003$) and retronasal function ($P = .001$), respectively. At V3, rated olfactory function in daily life improved only in the group using the high-concentration OTPs from V2 (median no change, IQR 1) to V3 (median moderate improvement, IQR 1, $P < .001$) (Table II).

In terms of olfactory sensitivity rm-ANOVA revealed no significant differences for the between subject factor group (high- vs. low-training) comparing TDI scores, odor thresholds, odor discrimination, and odor identification at V1, V2, and V3, respectively (Table I).

When investigating changes within categories anosmia, hyposmia, and normosmia, anosmic participants decreased from 36.3% at V1 to 21% at V2 and to 15.3% at V3. The percentage of hyposmic participants increased from 63.7% at V1 to 72.6% at V2 and 75.8% at V3; 6.5% became normosmic at V2 and 8.9% at V3. No significant differences were found between the two training groups at V3.

We observed a negative relationship between the duration of PIOD and the changes of TDI during the first OT period ($r = -0.19$, $P = .033$, Fig. 1). When focusing only on subjects with a duration of olfactory dysfunction of <12 months, olfactory function improved in 15 of 24 participants (62.5%) of the high-training-group and in six of 31 participants (19.4%) of the low-training group (χ^2 test: $P = .03$).

DISCUSSION

For the first time, effects of a structured OT have been studied in postinfectious olfactory dysfunction in a randomized, controlled investigation. After 18 weeks of training, olfactory test scores were significantly improved in more than a quarter of the high-training group, and more than half of the participants using the high-concentration OTPs reported at least a moderate improvement of olfactory function. These results became

TABLE II.
Subjective Reports of Olfactory Function in Daily Life.

	Deterioration	No Change	Moderate Improvement	Marked Improvement	Total Recovery
Changes of orthonasal olfactory function, %					
V2, n = 128					
High-training group*	0	33	53	13	0
Low-training group†	4	54	34	7	0
Total group	2	45	43	10	0
V3, n = 120					
Low-training group	2	38	47	14	0
High-training group†	0	35	42	21	2
Total group	1	37	44	18	1
Changes of retronasal olfactory function, %					
V2, n = 122					
High-training group*	0	39	43	18	0
Low-training group†	0	68	26	6	0
Total group	0	55	34	11	0
V3, n = 114					
Low-training group	2	37	39	22	0
High-training group†	0	40	40	18	2
Total group	1	39	39	20	1

Results show percent of variations of subjective assessment of olfactory function in daily life at V2 (after 18 weeks of OT) and V3 (after 37 weeks of OT).
*Significant differences between the high-training group and the low-training group in the Mann-Whitney *U* test; $P < .01$.
†Significant differences within the groups performing first the low-odor training and then crossing over to the high-odor training in the Wilcoxon test; $P < .001$.

even more pronounced when focusing on patients with olfactory dysfunction for <12 months.

Due to high rates of spontaneous improvement of PIOD, any successful treatment must generate beneficial effects that occur more frequently than spontaneous recovery. Spontaneous remission rates were reported to vary from 6% to 67% in the literature, depending on the duration of follow up.[5–9] The rates of spontaneous remission of PIOD gauged by validated smell tests in previous series[6–9] (Fig. 2) appear to follow a linear progression of spontaneous improvement of PIOD over time. The course of recovery found for the high–low-training group seems to be different compared to spontaneous recovery, whereas this is less pronounced for the low–high-training group.

Although exact mechanisms of OT are unknown, it may be assumed from research in animals[17–19] and humans[9,20,21] that repeated exposure to an odorant may modulate regenerative capacity of the olfactory mucosa.

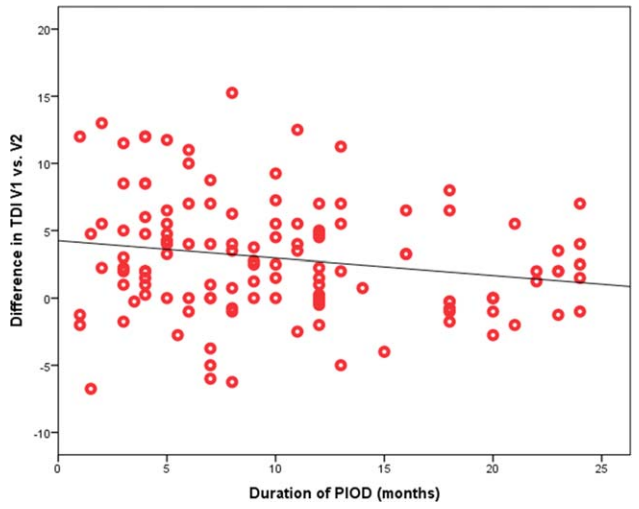

Fig. 1. Scatter plot of the duration of olfactory dysfunction at V1 and change of odor thresholds, discrimination, and identification score in the Sniffn' Sticks test (TDI) scores between V1 and V2 (difference V2 − V1). V1 = first visit, baseline; V2 = second visit after 18 weeks. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

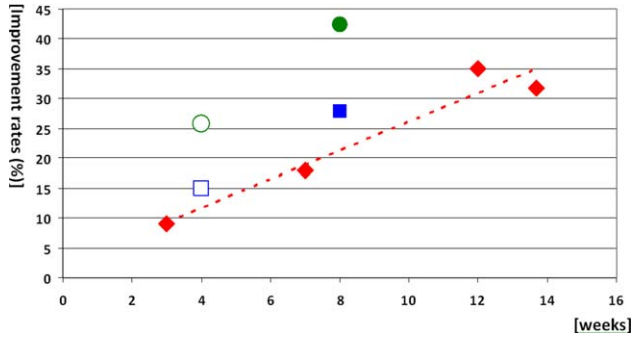

Fig. 2. Spontaneous improvement and improvement rates with olfactory training in postinfectious olfactory dysfunction (PIOD). Rhombuses: spontaneous improvement rates of PIOD adapted from the literature with a linear trend line.[6–9,13] Squares: improvement rates in the low-high-training group at V2 (open squares) and V3 (filled). Circles: improvement rates in the high-low-training group at V2 (open circles) and V3 (filled circles). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE III.
Average TDI Changes in Different Age Groups.

	TDI Difference Between Results at the 3 Visits		
Age Group, yr	Visit 2 (V2–V1)	Visit 3 (V3–V2)	Difference V3–V1
	Low-training group	High-training group	
<40	2.45	0.50	2.44
41–50	1.75	1.20	2.62
51–60	3.39	1.92	5.66
>60	2.89	0.60	3.15
	High-training group	Low-training group	
<40	2.06	3.50	3.50
41–50	1.87	0.63	2.94
51–60	3.67	1.51	4.31
>60	3.89	1.94	5.86

TDI = odor thresholds, discrimination, and identification score in the Sniffn' Sticks Test; V1 = first visit, baseline; V2 = second visit after 18 weeks; V3 = third visit after 37 weeks.

The regeneration of olfactory receptor neurons decreases with age, leading to a reduced number of olfactory receptor neurons.[22,23] Reden et al. reported a negative correlation between the patients' age and the rate of recovery.[8] A high recovery rate was found in patients under 40 years old (47%) and less recovery in patients over 69 years old (7%); this rate was 33% to 35% for patients in an age range from 40 to 69 years.[8] In our study population, only 6% were younger than 40 years and age over 65 years was an exclusion criterion. Therefore, it is not unexpected that we did not find a significant correlation between recovery rate and age. This is also illustrated in Table III.

In line with the literature[8] we found a negative correlation between recovery rate and duration of the disease (Fig. 1).

The recovery rates following high odor concentration training estimated previously (28%, 12 weeks)[9] were confirmed by the present study (high-training group: 26%, 18 weeks). In the low-training group, rates of improvement (≈15%) were 50% higher than spontaneous remission rates expected from the previous literature (≈10%).[7,9] This may be due to the fact that low odor concentration OTPs used in this series still exhibit a treatment effect thereby exceeding the effect of a true placebo. Thus, even a low concentration of odors used for OT seems to influence the recovery rate; it may also be possible that sniffing itself might have a positive effect on recovery. More research is necessary to understand these effects of OT, which may not only relate to changes at the olfactory epithelium, but also to modulations at the level of the central olfactory system,[9,21] or changes in the cognitive processing of olfactory information. Specifically, although it was not planned within the context of this multicentric study, future studies are needed that will follow up on patients to see if the improvement of olfactory function is permanent or not.

As an interesting outcome, we observed that about 40% of the participants suffered from UTRIs within each 18-week period. Half of these participants reported a deterioration of olfactory function due to this new infection, and reinfection was negatively correlated to the changes of TDI scores. Therefore reinfection after initial PIOD seems to be an important independent factor potentially deciding the natural course of the disease.

CONCLUSION

Olfactory training is a safe procedure without major side effects, increasing the recovery rates of PIOD, particularly in patients who start OT within the first 12 months after the onset of the disease.

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