Prognostic Factors of Olfactory Dysfunction

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Objective: To determine appropriate counseling of patients with olfactory dysfunction.

Design: Retrospective analysis.

Setting: Interdisciplinary Center for Smell and Taste, University of Dresden Medical School, Technical University of Dresden.

Patients: A total of 361 males and 533 females, aged 11 to 84 years, who twice reported to the Interdisciplinary Center for Smell and Taste.

Main Outcome Measures: Residual olfactory performance, duration of olfactory loss until first assessment, presence or absence of parosmia or phantosmia, origin of olfactory loss, interval between assessments, age, sex, and smoking habits.

Results: Although 431 patients (48.2%) had functional anosmia at the first olfactory assessment, 444 (49.7%) had hyposmia, and 19 (2.1%) had normosmia; at the second assessment, 278 (31.1%) had functional anosmia, 496 (55.5%) had hyposmia, and 120 (13.4%) had normal olfactory function ($P < .001$). Changes in smell scores depended positively on the initial score and negatively on age and smoking habits. Normosmia was more likely to be restored in females and when residual olfactory function was relatively high. In contrast, the origin of dysfunction had no direct predictive value because it was mostly reflected by initial smell scores. However, in a sub-analysis omitting the initial olfactory performance as a potential predictor, the initial presence of parosmia was associated with a lower probability of anosmia as the final outcome.

Conclusion: The prognosis of olfactory dysfunction mainly depends on residual function, sex, parosmia, smoking habits, and age, whereas in this statistical model, origin plays only a second-line role, reflected in different degrees of initial olfactory loss.


L O S S O F O L F A C T O R Y A C U I T Y TO
the degree of anosmia is present in approximately 5% of
the population.\(^1,4\) In fact, it has been estimated for Aus-
tria, Switzerland, and Germany that approximately 80 000 people consult an oto-
rhinolaryngologist every year because of problems related to sense of smell.\(^5\)

Today’s treatment options for olfactory dysfunction are limited. Most improve-
ments appear to be owing to spontaneous recovery. However, many physicians may
not provide the patient with a prognosis of his or her olfactory loss. To increase the in-
formational basis for appropriate counseling of patients, we retrospectively ana-
alyzed prospectively collected olfactory function data of patients who sought treat-
ment at a specialized otorhinolaryngologic center at least 2 times. We focused our
analysis on factors that would provide information about the prognosis of olfactory
dysfunction, such as origin of olfactory loss, specific demographic factors, and the ini-
tial severity of olfactory dysfunction.

METHODS

PATIENTS

Study participants (Table) were 361 males and
533 females, aged 11 to 84 years, who had re-
ported to the Interdisciplinary Center for Smell and Taste of the University of Dresden Medical School, Technical University of Dresden, with concerns related to the sense of taste or smell. The origin of the concerns was determined on the basis of an exhaustive, standardized inter-
view, including questions for smoking status. In addition, all participants underwent thor-
ough otorhinolaryngologic examinations, in-
cluding nasal endoscopy. All participants under-
went detailed tests of orthonasal olfactory
function and retronasal or gustatory function whenever deemed necessary. Electrophysi-
ologic investigations using olfactory event-
related potentials and imaging of the head (com-
Threshold was defined as the mean of the last 4 of 7 staircase correct identifications triggered a reversal of the staircase. Odor dilution step. Two successive correct identifications or 1 incorrect odorant and 2 without odorant were presented at each alternative forced-choice task and a staircase paradigm starting liquid form, starting with a concentration of 4%. Using a 3-alanyl ethyl alcohol, presented in 16 successive 1:2 dilutions in the nostrils at a distance of approximately 1 to 2 cm.

Olfaction-related condition

URT infection 463 (51.8)
Trauma 211 (23.6)
Sinunasal disease 220 (24.6)

Diagnoses

At first assessment

Anosmia 431 (48.2)
Hyposmia 444 (48.7)
Normosmia 19 (2.1)
Parosmia 301 (33.7)
Phantosmia 151 (16.9)

At second assessment

Anosmia 278 (31.1)
Hyposmia 496 (55.5)
Normosmia 120 (13.4)

Abbreviation: URT, upper respiratory tract.

a Data are presented as number (percentage) of patients unless otherwise indicated.

Olfactory testing

The first olfactory assessment took place when the patient reported to the Smell and Taste Clinic for the first time. The second assessment followed at a mean (SD) interval of 1.3 (1.29) years (range, 0.083-8.83 years). Olfactory function was assessed bimonthly with the extended version of the Sniffin’ Sticks test (Heinrich Burghart GMBh, Wedel, Germany). In this validated test, odors are presented in felt-tip pens. For odor presentation, 1 pen at a time (cap removed) is placed in front of the nostrils at a distance of approximately 1 to 2 cm.

Odor thresholds were obtained for the roselike odor phenyl ethyl alcohol, presented in 16 successive 1:2 dilutions in liquid form, starting with a concentration of 4%. Using a 3-alternative forced-choice task and a staircase paradigm starting at low phenyl ethyl alcohol concentrations, 1 pen containing a certain odorant and 2 without odorant were presented at each dilution step. Two successive correct identifications or 1 incorrect identification triggered a reversal of the staircase. Odor threshold was defined as the mean of the last 4 of 7 staircase reversals (reference ranges, ≥6 for males and ≥6.5 for females). Odor discrimination was determined with 16 triple sets of pens, 2 containing the same odorant and 1 containing a different one (for detailed listing of the odorants used, see Hummel et al), using a 3-alternative forced-choice task (reference range, ≥11 correct discriminations). Odor identification was determined with 16 odors (orange, peppermint, turpentine, clove, leather, banana, garlic, rose, fish, lemon, coffee, anise, cinnamon, licorice, apple, and pineapple), using a 4-alternative forced-choice task with presentation of a list of 4 descriptors for each pen (reference range, ≥12 correct identifications). The clinical evaluation of olfactory performance was based on the composite threshold discrimination identification (TDI) score represented by the sum of the scores from the 3 subtests. Pathological olfactory function was indicated by a TDI score of 30.5 or less, with the separation of hyposmia from functional anosmia at a TDI score of 15.5.

Statistical analysis

A patient with deteriorated olfactory function will probably be interested in the future change in olfactory performance and in the final olfactory diagnosis. Thus, target factors were (1) the numerical change in the TDI score from the first to the second assessment (ie, second minus first TDI scores); (2) a clinically significant change in olfactory diagnosis by 6 points, coded as −1 for worsening, 0 for changes of fewer than 6 points, and 1 for TDI score improved by 6 or more points; and (3) the final diagnosis number, coded as 1, 2, or 3, respectively, for the 3 diagnoses. Candidate factors were (1) mean (SD) TDI score at the first assessment, (2) duration of olfactory loss until the first assessment, (3) presence or absence of parosmia, (4) presence or absence of phantosmia, (5) origin of olfactory loss (eg, sinonasal disease [SND], trauma, or upper respiratory tract [URT] infection), (6) interval between first and second assessments; and demographic factors, including (7) age in years at first assessment, (8) sex, and (9) smoking habits.

Baseline values of olfactory function were compared for the candidate factors by means of univariate analysis of variance with post hoc α-corrected (Bonferroni) t tests, simple t tests, rank correlation (Spearman), or χ² statistics, as appropriate for the respective data. Candidate factors were submitted together to linear or binary logistic regression analysis (Stata/IC 10.1 for Linux; StataCorp LP, College Station, Texas). To increase the validity of the results, we repeated regression analyses for 1000 data sets created from the original data set by means of bootstrap resampling. Subsequently, the influence of factors identified by regression analysis as exerting significant effects on the target factors were assessed by means of analysis of variance, χ² statistics, or rank correlation. To adjust for different baseline TDI scores, the percent changes from the first to the second TDI assessments were analyzed in addition to the differences in TDI scores (ie, [second − first score]/[first score × 100]).

Baseline olfactory function

Reasons for olfactory loss were SND, head trauma, and URT infections. The olfactory function at the first assessment (Table) differed among origin groups (P < .001, χ² test). That is, although anosmia was equally associated with SND (30.6% of patients with anosmia had SND as the origin of their condition), trauma (34.3%) and URT infection (35.0%), hyposmia or normosmia was most frequently associated with URT infection (66.9% of patients with hyposmia and 78.9% of those with normosmia had this origin of olfactory dysfunction). Because they were closely related to the olfactory diagnosis, the mean (SD) initial TDI scores differed between origin groups (SND, 15.1 [6.0]; trauma, 14.1 [6.0]; URT infection, 19.0 [6.1]; analysis of variance: df = 2893, F = 2220.4, P < .001; post hoc α-corrected t tests; significant differ-
ences between infection and the other origins, \( P < .001 \), but not between SND and trauma, \( P = .24; \) **Figure**. Females had significantly, but only slightly better, mean (SD) initial TDI scores than males (17.4 [6.4] vs 16.1 [6.4]; \( P = .004 \)). Sex did not significantly differ with respect to age (mean [SD] age: males, 54.9 [13.4] years; females, 56.4 [11.8] years; \( t \) test for age, \( P = .08 \)), and age was not correlated with the initial TDI score (Spearman \( r = 0.0571 \), \( P = .09 \)). Finally, smokers (\( n = 76 \)) had the same TDI scores as nonsmokers (\( n = 818 \); \( P = .41 \)).

**TEMPORAL CHANGES OF OLFACTORY FUNCTION**

Changes in TDI Score

Linear regression analysis identified the initial TDI score (\( P < .001 \); **Figure**), the presence of parosmia (\( P = .03 \)), age (\( P = .04 \)), and smoking habits (\( P = .04 \)) as significant factors modulating the numerical difference in TDI sum scores between the second and first olfactory assessments. However, parosmia failed to pass the post hoc \( t \) test (\( P = .20 \)). Changes in the TDI score depended negatively, although weakly, on the initial TDI score (Spearman \( r = -0.2236 \), \( P < .001 \)). In addition, changes in mean (SD) TDI score were significantly smaller in smokers (1.88 [5.67]) than in nonsmokers (3.72 [6.32]; \( t \) test, \( P = .02 \)). Age was weakly but significantly negatively correlated with the increase in TDI score between assessments (Spearman \( r = -0.067 \), \( P = .04 \)). When omitting the initial TDI score from the regression analysis, age (\( P = .01 \)) and smoking habits (\( P = .03 \)) were again identified as significant factors modulating the numerical difference in TDI sum scores between the second and first olfactory assessments. For the percent changes in TDI score, regression analysis found the initial TDI score (\( P < .001 \)) and age (\( P = .02 \)) to be significant predictors, and when omitting the first of the candidate factors, age (\( P = .003 \)) and smoking habits (\( P = .04 \)) were also found to be significant predictors. The predictions were in the same direction as for the difference changes in TDI scores.

Improvement in Olfactory Function

Clinically relevant improvement of olfactory function, defined as an increase in TDI score by at least 6 points, was observed in 263 patients (29.4%). Only 47 patients (5.3%) worsened significantly in their olfactory function, whereas no significant change was observed in 584 patients (65.3%).

Linear regression analysis identified that changes in TDI scores by a relevant degree (ie, by \( \geq 6 \) points) depended on the initial TDI score (\( P < .001 \)), smoking habits (\( P = .02 \)), the presence of parosmia (\( P = .04 \)), and the duration of olfactory loss until first assessment (\( P = .047 \)). However, the duration of the olfactory loss until first assessment and the presence of parosmia failed to pass the post hoc analysis (\( P = .20 \) and .49, respectively; \( \chi^2 \) tests). Of the remaining factors, significant change in TDI was negatively associated with initial TDI scores; that is, patients whose olfactory acuity worsened had initially higher TDI scores, whereas those who improved had the lowest initial scores (change of \( \geq 6 \) points: mean [SD] initial TDI score, 22.3 [5.8]; change of <6 absolute points: TDI score, 17.2 [6.6]; change of \( \geq 6 \) points: TDI score, 15.1 [5.4]; analysis of variance: \( df = 2893, F = 29.7, P < .001 \);
post hoc t tests: significant differences between all groups at P < .001). Of smokers, 9.2% worsened in their olfactory function and only 19.7% improved, whereas of non-smokers, only 4.4% worsened but 31.7% improved (P = .04; χ² test). When omitting the initial TDI score from the regression analysis, only smoking habits (P = .01) were identified as a significant factor modulating the numerical difference in TDI sum scores between the second and first olfactory assessments.

Final Olfactory Diagnosis

The initial distribution of olfactory diagnosis moved toward improvement at the second assessment (P < .001; χ² test for the diagnosis at the first vs that at the second assessment; Table). Linear regression analysis identified the initial TDI score (P < .001), sex (P = .006; Figure), and the duration of olfactory loss until the first assessment (P = .02) as significant factors affecting the final olfactory diagnosis. However, the duration of olfactory loss until the first assessment failed post hoc analysis of variance (P = .92). With respect to the final significant factors, the better the TDI score at the start of the assessment, the better the diagnosis at the end of the assessment (analysis of variance: df = 2893, F = 199.1, P < .001; mean [SD] initial TDI scores: final anosmia, 11.7 [4.1]; final hyposmia, 18.4 [5.4]; final normosmia, 22.8 [7.6]; post hoc t tests: significant differences between all groups at P < .001). Males had slightly worse final diagnoses than females as indicated by 38.1%, 54.0%, and 7.9% of the males but 23.3%, 65.1%, and 11.6% of the females having anosmia, hyposmia, or normosmia, respectively, as his or her final diagnosis (P < .001, χ² test). When omitting the initial TDI score from the regression analysis, sex (P = .001) and the duration of olfactory loss until the first assessment (P = .001) were again identified as significant factors modulating the numerical difference in TDI sum scores between the second and first olfactory assessments. In addition, the presence of parosmia was a further factor identified in the reduced regression analysis (P < .001). Patients who had parosmia at the initial assessment had slightly better final diagnoses. This was indicated by 36.3%, 54.0%, and 9.7% of the patients with parosmia, but 11.0%, 79.1%, and 9.9% of the patients without parosmia having anosmia, hyposmia, or normosmia, respectively, as their final diagnosis (P < .001, χ² test).

Improvement of olfactory acuity was most likely in young nonsmokers with severely restricted olfactory performance. Clinically relevant improvement of olfactory loss was most likely in nonsmokers with a low TDI score at the time of reporting to the clinic. However, normal olfactory function at the second assessment was most likely in females with initially better TDI scores. Olfactory function at the first visit was the strongest predictor of development of olfactory function, as previously reported,12-16 with a dependence, however, on the kind of prognosis.12-16 When simple improvement in olfactory acuity is of interest, higher initial scores predict lower improvement. By contrast, when normal olfactory function is of interest, higher initial scores are associated with higher probability of normosmia.

It is widely recognized that women outperform men in olfactory tests.17 In this study, sex did not result in a difference at the initial diagnosis of olfactory loss, but females improved more. Also, the fact that age and smoking status are negative predictors of olfactory function is not surprising.4 However, the lack of importance of the origin of olfactory loss for its prognosis disagrees with the common perception that olfactory function is more likely to be recovered when it was lost because of a URT infection than because of head trauma. Indeed, separate analysis of improvement in olfactory function for its origin resulted in significant effects. That is, the numerical changes in TDI score depended on the origin of olfactory loss (analysis of variance of the mean [SD] differences between the second and first TDI scores: df = 2893, F = 34.9, P < .001; SND, 5.8 [7.6] points; trauma, 0.9 [4.9] points; infection, 3.3 [5.8] points; percent changes from the first TDI score: F = 32.2, P < .001; SND, 52.3% [75.8%]; trauma, 11.8% [43.6%]; infection, 25% [45.8%]; α-corrected post hoc t tests: P < .05 for all groups). The origin of olfactory loss was also significantly related to clinically relevant improvement or worsening of olfactory function (P < .001, χ² test). It was furthermore significantly different between groups of final diagnosis (P < .001, χ² test). Although 61.6% of the patients with trauma had anosmia at the final diagnosis, this was the case in only 30.4% and 17.5% of the patients with SND or URT infection, respectively. On the other hand, normal olfactory function at the second assessment was seen in 19.5% of the patients with SND, 15.3% of the patients with URT infection, but only 2.8% of the patients with trauma as the origin of their olfactory loss. Nevertheless, multivariate statistical analysis failed to identify origin as a significant predictor of the development of olfactory function after it had been decreased or lost. A possible reason for this apparent discrepancy was the interdependence of initial olfactory function and its origin. However, when omitting the initial diagnosis from the candidate factors, origin still failed to provide a statistically significant prognostic factor. Thus, consistent with the literature,11 the origin of olfactory loss appears to play a smaller role in recovery of olfactory function than intuitively perceived. Sex, age, smoking, and possibly the presence of parosmia, which could indicate regenerative processes,9 are more relevant prognostic predictors.

In conclusion, we show that the prognosis of olfactory dysfunction primarily depends on residual function and secondarily on sex, smoking habits, age, and parosmia, whereas in this statistical model, origin of olfactory loss plays only a second-line role, reflected in different degrees of initial olfactory loss.

Submitted for Publication: April 19, 2009; final revision received July 9, 2009; accepted July 19, 2009.

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Author Contributions: Both authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hummel. Analysis and interpretation of data: Hummel and Lotsch. Drafting of the manuscript: Hummel and Lotsch. Critical revision of the manuscript for important intellectual content: Hummel and Lotsch. Statistical analysis: Lotsch. Study supervision: Hummel.

Financial Disclosure: None reported.

Funding/Support: The work was supported by the Interdisciplinary Center for Neuroscience Frankfurt (Dr Lotsch).

Previous Presentation: A subset of these data, including less than half the number of patients, has been published previously by Reden J, Mueller A, Mueller C, et al. Arch Otolaryngol Head Neck Surg. 2006;132(3):265-269.

Additional Contributions: Bettina Hauswald, MD, Volker Gudziol, MD, Mareike Trittin, MD, Simona Negoias, MD, Franziska Krone, and Monika Roesner helped with acquisition and preparation of the data.

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