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Presence of Olfactory Event-Related Potentials Predicts Recovery in Patients with Olfactory Loss Following Upper Respiratory Tract Infection

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Objectives/Hypothesis: The aim of the present study was to evaluate the course of olfactory dysfunction in patients with olfactory loss following infections of the upper respiratory tract.

Study Design: Prospective cohort.

Methods: A total of 27 patients were included; each patient was evaluated twice. Psychophysical testing of olfactory function was performed with the Sniffin' Sticks test and chemosensory functions with event-related potential (ERP).

Results: At T1, 15 patients were considered hyposmic, 12 as anosmic. Accordingly, nine and 27 patients demonstrated olfactory ERP. At T2, 16 and 11 patients were considered as hyposmic and anosmic, and 11 demonstrated olfactory ERP. Analysis of variance did not show significant differences for any parameters between T1 and T2: threshold, discrimination, identification (TDI) scores at the Sniffin' Sticks and amplitudes and latencies of N1 and P2 in the ERP. However, seven patients demonstrated an increase of more or equal to six points at the TDI score, indicating significant improvement. Four of the seven patients had olfactory ERP at T1 (57%); of those patients who did not show improvement, five of 20 (25%) exhibited olfactory ERP. Thus, the presence of olfactory ERP predicts a positive evolution of olfactory function with a relatively high specificity of 83%.

Conclusions: The current findings clearly confirm earlier results on recovery rate of postinfectious olfactory loss. The new finding is that the presence of olfactory ERP at the first consultation is also a positive predictive factor of a favorable outcome in this disease.

Key Words: Smell, olfaction, olfactometer, magnetic resonance imaging, chemosensory event-related potentials, postinfectious.

Level of Evidence: 4

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INTRODUCTION

Postinfectious olfactory loss is characterized by a sudden loss of olfactory function during the course or following an infection of the upper respiratory tract (URTI).[1] In specialized centers, postinfectious olfactory loss is diagnosed in approximately one quarter of all patients.[2–4] However, when considering the entire patient population, postinfectious olfactory loss appears to be the cause in 11% of olfactory dysfunction.[5] It is typically found in women aged 50 years and older.[6,7] As treatment is far from being satisfying,[8–12] counseling of the patient is of primary importance.

Olfactory function is typically assessed in the clinic with psychophysical methods, separately for orthonasal and retronasal function, and with electrophysiological recordings (event-related potentials [ERPs]) following both olfactory and trigeminal stimulation.[13] Although clinical counseling is based on a thorough history plus validated and reliable psychophysical tests, the predictive value of electrophysiological responses is less clear. Interestingly, trigeminal event-related potentials are dependent of olfactory function, and might provide an additional gauge to the prognosis of the olfactory disorder.

The aim of the present study was to evaluate the course of olfactory dysfunction in patients with post-URTI olfactory loss using results from psychophysical

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TABLE I.
Descriptive Statistics of Measured Parameters.

	Mean	SD	Median	Minimum	Maximum	*P* Value*
Threshold T1	3.00	2.00	3.0	1.0	7.0	.382
Threshold T2	3.59	2.19	3.0	1.0	7.0	.072
Discrimination T1	7.26	2.80	7.0	2.0	12.0	.533
Discrimination T2	7.81	3.19	8.0	2.0	13.0	.285
Identification T1	6.52	2.39	6.0	2.0	10.0	.902
Identification T2	7.59	3.04	8.0	2.0	12.0	.811
TDI T1	16.7	5.76	17.0	6.0	26.0	.980
TDI T2	19.3	7.39	19.0	5.0	31.0	.578
Retronasal T1	10.4	3.49	10.0	5.0	17.0	.637
Retronasal T2	10.6	3.58	10.0	6.0	18.0	.474

*Kolmogorov-Smirnov test.
SD = standard deviation; TDI = threshold, discrimination, identification.

olfactory testing and chemosensory ERP recordings in order to predict recovery.

MATERIALS AND METHODS

Subjects

The study was conducted at the Department of Otorhinolaryngology of the Saint Luc University Hospital in Brussels. Diagnostic criteria for postinfectious olfactory loss included 1) history of post-URTI olfactory loss, 2) patency of the olfactory cleft at endoscopic examination, 3) evidence of olfactory dysfunction, and 4) exclusion of others causes of olfactory disorders (e.g., sinonasal disease). A total of 27 patients were included in this study (10 men, 17 women; age range, 22–74 years; mean age, 54.8 years).

None of the patients received any medical or surgical treatment during the study period, and each patient was evaluated twice (on average 8.6 months; range, 4–18 months).

Psychophysical Testing of Olfaction Performance

Psychophysical testing of olfactory function was performed with the validated Sniffin' Sticks test.[14] Odors are presented to the patients in felt-tip pens. For birhinal stimulation, the pen's tip is placed approximately 2 cm in front of both nostrils. This test encompasses three different approaches. First, the odor threshold is assessed with n-butanol with stepwise dilutions in a row of 16 felt-tip pens. Second, patients are asked to discriminate odors 16 times. Third, a row of 16 odors is presented to the patients together with a list of four verbal descriptors that are used by the subjects to identify individual odors. To judge olfactory function, results from testing of odor threshold (T), odor discrimination (D), and odor identification (I) are added together as a total TDI score. For healthy subjects, the TDI score at the 10th percentile is 30.3 for ages from 16 to 35 years, 27.3 for ages from 36 to 55 years, and 19.6 for patients >55 years. Functional anosmia (addressed further in the text as anosmia) is diagnosed if the TDI score is <16. With a TDI score between 16 and normal age-related value, patients are considered hyposmic. Retronasal olfactory performances were evaluated with a row of 20 different odors intraorally presented following a standardized method as well.[15]

Chemosensory ERP

Chemosensory function was also assessed with chemosensory, late near-field ERP elicited with relatively specific olfactory and trigeminal stimuli. In many clinical situations, electrophysiological responses are usually interpreted as being present or not, which is heuristically determined.[16] The frequency spectrum of the chemosensory ERPs is 2 to 8 Hz. Most labs use a sampling frequency of 250 Hz, low pass filtering of 20 to 40 Hz, and high pass filtering in the range of 0.01 Hz. Recording sites are usually located in the midline in clinical circumstances (positions Fz, Cz, and Pz of the international 10/20 system), referenced to linked earlobes. For averaging, typically 10 to 30 records are used. The number of artifact-free recordings must be >60% in order to allow analysis. The pretrigger period is 500 ms and post-trigger sampling is 1,500 to 2,000 ms (refer to Rombaux et al.[16]).

The outlet piece of the olfactometer was placed in the right nostril just behind the nasal valve (2–4 mm from the nares).

Statistical Analysis

Data were tested for deviations from normal distribution using the Kolmogorov-Smirnov test. Analyses of variance were then applied if no deviation was found. Onset of olfactory loss was considered as T0, interval between onset and first clinical evaluation as T1, and second evaluation as T2. Statistical work with analysis of variance was applied to 13 parameters: scores for odor threshold, discrimination, identification, TDI, and retronasal odor identification, olfactory and trigeminal event related potentials; N1 and P2 amplitudes; and latencies at position Cz.

Sex, age, and intervals between T0 and T1, and between T1 and T2 were considered as covariates. Pearson correlation coefficients were calculated, and correlations with $P < .0083$ were considered to be significant (Bonferroni correction of 0.05 level with factor 6 because of six comparisons).

RESULTS

On average, male patients were 57.9 years old (standard deviation [SD], 10.4; median, 59.5; minimum, 36; and maximum, 74 years); female patients were 52.9 years old (SD, 12.8; median, 59; minimum, 22; and maximum, 68 years). Descriptive statistics of measured parameters are described in Table I.

At T1, 15 patients were considered as being hyposmic and 12 as anosmic. Accordingly, nine and 27 patients demonstrated olfactory and trigeminal ERP, respectively, at T1. At T2, 16 and 11 patients were

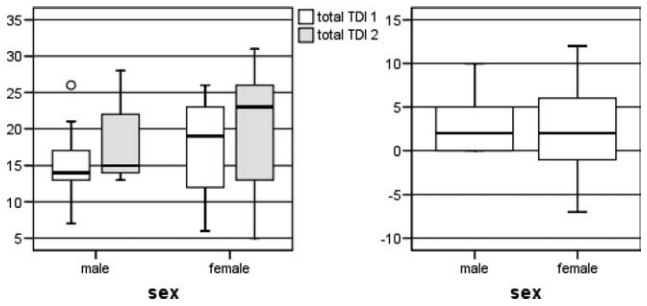

Fig. 1. Boxplot of total TDI scores, values at time points 1 and 2 (left) and patientwise differences between the two evaluations (right).

considered as hyposmic and anosmic, respectively, and 11 and 27 patients demonstrated olfactory and trigeminal ERP, respectively. Analysis of variance with threshold, discrimination, identification, total TDI score, and retronasal scores as repeated measures, sex as a factor, and intervals 1 and 2 and age as covariates did not show significant differences for any parameter. There was no significant interaction between the parameters named above (shown for the TDI score in Fig. 1 between males and females).

Correlations between TDI scores and retronasal scores at T1 and T2 were significant; T1, $r = 0.547$, $P = .003$; T2, $r = 0.755$, $P = .0001$ (Fig. 2).

Seven patients demonstrated an increase of more or equal to six points at the TDI score between T1 and T2, indicating significant improvement of olfactory function at an individual level. Among these seven patients, four (57%) had olfactory ERP at T1 and five at T2. Of those patients who did not show any improvement, 25%(5/20) exhibited olfactory ERP at T1. Thus, with a relatively low sensitivity of 44% the presence of olfactory ERP predicts with a relatively high specificity of 83% a positive evolution of olfactory function (Fig. 3).

Those patients who showed an improvement were mostly in the hyposmic range at T1, with only one patient being in the anosmic range. The status of normosmia was only reached by one patient.

DISCUSSION

The current study produced the following three major findings: 1) on an individual basis, there is a significant improvement of olfactory function in patients with postinfectious olfactory loss in 7/27 (26%) of patients over a period of approximately 9 months; 2) recovery to normosmia is a very rare finding, occurring in this study only in 4% of the patients (n = 1); and 3) orthonasal hyposmia in combination with olfactory ERP at T1 seems to be related to a higher chance of olfactory recovery.

The sudden onset of olfactory loss associated with upper respiratory tract infection typically affects middle aged women (starting from an age of 50 years) and is combined with severe, but frequently incomplete loss of olfactory function. Functional anosmia is present in 36% to 53% of the cases, and hyposmia in 47% to 64% of the cases.[3,4] In addition, parosmia is described by at least 15% of the patients.[6] Our study confirms earlier results

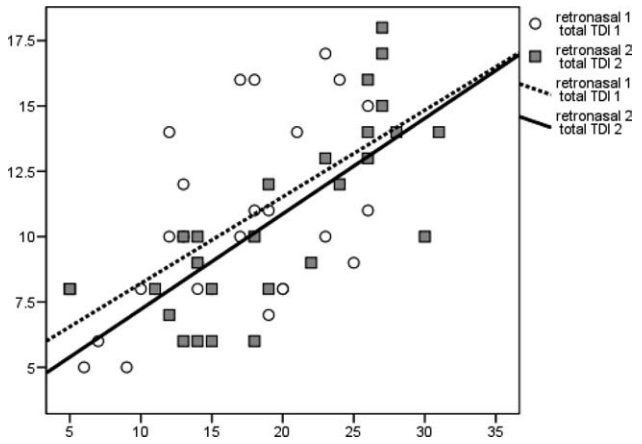

Fig. 2. Plot of total TDI scores at time points (x axis) against retronasal scores (y axis) at time points 1 and 2.

from patients with postinfectious olfactory loss with more hyposmic than anosmic patients at T1 and T2.

Postinfectious olfactory loss is believed to be due to damage of olfactory receptor neurons.[17] Pathophysiology of the disorder is not yet understood, but it might be related to either a toxic attack of the neuroepithelium from the viruses or dysfunction of perireceptor events. Biopsy studies of the neuroepithelium have revealed that olfactory epithelia of patients with postinfectious olfactory loss exhibit a large area of cicatrization, decreased number of cilia on the olfactory receptor neuron, and replacement of sensory epithelium with respiratory epithelium.[17] Such damage to the periphery is believed to also be reflected in the volume of the olfactory bulb.[18,19]

The most salient finding of the present study is that the presence of olfactory ERP seems to be a predictor of recovery of the sense of smell. Specifically, olfactory ERP were present in four out of the seven patients exhibiting individual recovery. Previous research established a correlation between olfactory sensitivity and presence or absence of ERP.[20] In addition, work by Welge-Lussen indicated that olfactory ERPs become visible only when a certain degree of brain area has been activated, which shows a relation to olfactory processing.[21] Thus, presence

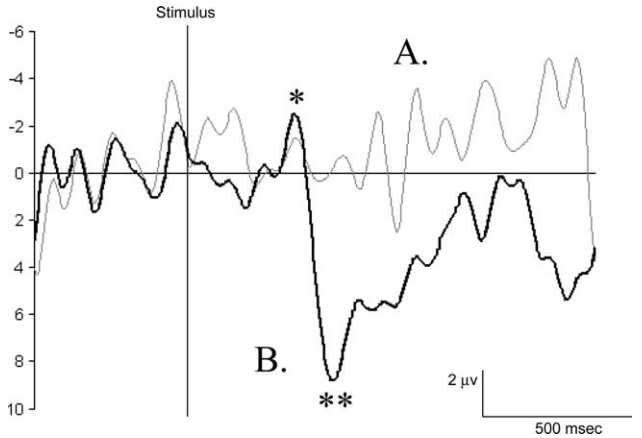

Fig. 3. Olfactory event related potentials (OERP) at T1: (A) patient without OERP. (B) patient with OERP. * = N1; ** = P2.

of olfactory ERP appears to indicate a certain maturity of the olfactory system. Patients with olfactory ERP have a higher likelihood to recover compared to patients who do not show olfactory ERP.

CONCLUSION

The current findings clearly confirm earlier results. Patients with post-URTI loss of olfactory function might recover, as in this example of approximately a quarter over a period of 8 months. Also, as has already been noticed, only a small number of patients reach the status of normosmia. Importantly, however, the present results establish as a new result that presence of olfactory ERP at the first consultation is also a positive predictive factor of a favorable outcome.

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