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A study on the prognostic significance of qualitative olfactory dysfunction

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Abstract We investigated the frequency and prognostic significance of qualitative olfactory dysfunction (parosmia, phantosmia) in a retrospective patient based study. A total of 392 patients with impairment of olfaction were tested at least two times for their olfactory function using the "Sniffin' Sticks". The mean interval between the first and the last test was 11 months. At the first visit 34% of all patients reported parosmia. Parosmia was most frequent in patients with postinfectious olfactory loss (56%), and less frequent in idiopathic, posttraumatic, sinunasal disease with frequencies of 10, 14, and 28%, respectively. In contrast, only 12% of all patients had phantosmias, with no significant differences between the patient groups. Improvement of olfactory function was found in 23% of all patients ($n = 90$). Pre-existing parosmia or phantosmia had no significant effect on recovery rate. Regarding qualitative olfactory dysfunction, 29% of those patients reporting parosmia reported relief of this symptom after an average of 12 months, whereas 53% of phantosmic patients lost phantosmia during the observation period. Although it has been suggested that olfactory distortion s could be regarded as an indicator of early recovery of decreased olfactory sensitivity, the current data indicate that occurrence of parosmia or phantosmia has little prognostic value. Phantosmia disappears at a faster rate than parosmia. These insights into qualitative olfactory dysfunction are regarded to be significant in the counseling of patients with olfactory loss.

Keywords Olfaction · Smell · Prognosis · Parosmia · Phantosmia

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Introduction

The sense of smell can be altered primarily in two different ways. One is the quantitative change in perception of odors. This could be either an increased or a decreased sensitivity towards olfactory stimuli, namely hyper- or hyposmia. Whereas hyperosmia seems to be a rare and relatively poorly understood phenomenon, hyposmia and anosmia are observed in approximately 16 and 5% of the population [1, 2], respectively, in elderly people even more often [3]. This deficit may be due to different pathologies, i.e., sinunasal diseases (inflammation of the nasal mucosa with or without nasal polyps), infections of the upper respiratory tract, head trauma or others, responsible for 72, 11, 5, and 12%, respectively, of cases of olfactory dysfunction [4].

Another, and possibly more significant alteration of the sense of smell relates to qualitative changes of olfaction. Many definitions have been used in the literature to describe these symptoms [5]. In our opinion the terms "parosmia" and "phantosmia" are best established to indicate distorted olfaction. "Parosmia" is defined as a sensation where an odorant is perceived differently than it used to smell, i.e., a distortion of an existing odor. In contrast, noticing a smell in the absence of an odor source is termed as "phantosmia", a

phantom smell. Qualitative olfactory dysfunctions are mostly reported as being malodorous. Therefore they have a major impact on the quality of life of most of the patients who experience parosmias or phantosmias [6]. These complaints seem to occur in 10–60% among patients with impaired olfaction [7–9]. Parosmias have been hypothesized to be a positive sign in terms of recovery of olfactory function [10].

Previous studies on the recovery rate of patients with quantitative olfactory problems demonstrated that approximately 32% of postinfectious, but only approximately 10% of posttraumatic patients improve over a period of 13 months [11]. Up to now little data exist as to how many of parosmic/phantosmic patients exhibit improvement of olfactory loss [7]. Thus, this retrospective study aimed to investigate the progress of qualitative olfactory disorders and—even more important—to study whether occurrence of parosmia or phantosmia contains information on the prognosis of olfactory dysfunction.

Patients and methods

Patients

All participants of this investigation presented themselves/were presented to the Smell and Taste Clinic of the Department of Otorhinolaryngology of the University of Dresden Medical School because of olfactory dysfunction. A total of 392 patients were included (236 women, i.e., 60%). The mean age was 57 years [range 17–83 years, standard error of means (SEM) 0.6]. All patients underwent a detailed ENT-examination including nasal endoscopy. Their history was recorded using a standardized procedure. Depending on the cause of disease the patients were divided into five groups: idiopathic (unknown etiology), postinfectious (following an infection of the upper respiratory tract), posttraumatic (following head injury), sinunasal (inflammation of the nasal cavity and/or sinuses; nasal polyposis), and other (e.g., neurodegenerative, toxic).

Olfactory testing

Olfactory function was assessed by means of the "Sniffin' Sticks" test kit, a validated psychophysical technique consisting of phenyl ethanol odor threshold testing, odor discrimination, and odor identification tests [12]. The results of the individual tests were summated to the so-called TDI-score (*T*hreshold, *D*iscrimination, and *I*dentification; with a maximum score of 48 points), which reliably indicates the degree of olfactory function. As defined previously [13], a score of 32 points or more indicates normosmia, a score between 16 and 32 points indicates reduced olfactory function in terms of hyposmia, and a score of less than 16 points indicates functional anosmia. An increase of more than 6 points between first and last visit was regarded as a clinically significant improvement, whereas a decrease of more than 6 points indicated deterioration of the sense of smell [14].

In addition, patients were interviewed about their complaints concerning olfaction, i.e., whether they experienced parosmias or phantosmias. Up to now there is no validated tool to objectively assess these subjective symptoms. Accordingly, patients were asked specific questions concerning their sense of smell, e.g., "does the coffee smell different from what it used to?" or "do you experience odorous sensations in the absence of an odor source?". Depending on the evaluation of this information patients were categorized as with or without parosmia or phantosmia.

The mean duration of disease before the patients' first investigation at the Department was 18 months (SEM 0.77). Patients underwent at least one follow-up investigation with a mean interval of 11 months (SEM 0.51).

Statistical analysis

For statistical analyses, SPSS (Statistical Packages for Social Sciences, version 12.0, SPSS Inc., Chicago, IL, USA) was used. Comparisons between first and last visit were performed using t-tests for paired samples. To compare results from patients with different causes of olfactory dysfunction analyses of variance were employed.

Results

In the majority of patients the olfactory deficit was caused by an infection of the upper respiratory tract (45%; $n = 176$). Other etiologies included head trauma in 20% ($n = 77$), sinunasal disease in 7% ($n = 29$), and another 7% of patients lost their ability to smell due to other diseases (see above). In 20% ($n = 81$) of the patients the etiology was unknown.

At the first visit 34% of all patients reported parosmia. Its frequency within the patient groups differed significantly, showing the largest fraction in the postinfectious group with 56% of the cases with parosmic complaints (χ^2 test: $P < 0.001$). Idiopathic, posttraumatic, and deficits related to sinunasal disease (SND) were accompanied by parosmia at a lower frequency

(10, 14, and 28%, respectively, Fig. 1). In contrast, only 12% of all patients suffered from phantosmia, with no significant differences between the patient groups (χ^2 test: $P = 0.69$; Fig. 2).

Overall, 23% of patients exhibited improvement of their olfactory ability by more than 6 points in the TDI-score after an average observation period of 13 months (SEM 0.96). Here, SND-related olfactory loss had the best prognosis, with 31% of patients out of this group exhibiting improvement, followed by 27% in the post-infectious group, 18% of the patients with idiopathic and posttraumatic olfactory loss, respectively, and 17% recovery in other cases.

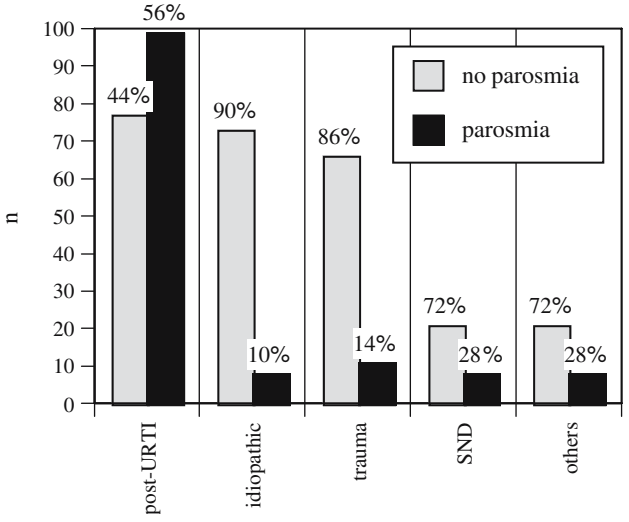

Fig. 1 Frequency of parosmia within different patient groups (*black bars* indicate the number of patients with parosmia, *gray bars* indicate the number of patients without parosmia), showing the largest fraction of parosmia in the group of patients with post-infectious olfactory loss (in number of subjects). The *numbers on top of each bar* indicate the percentage per group

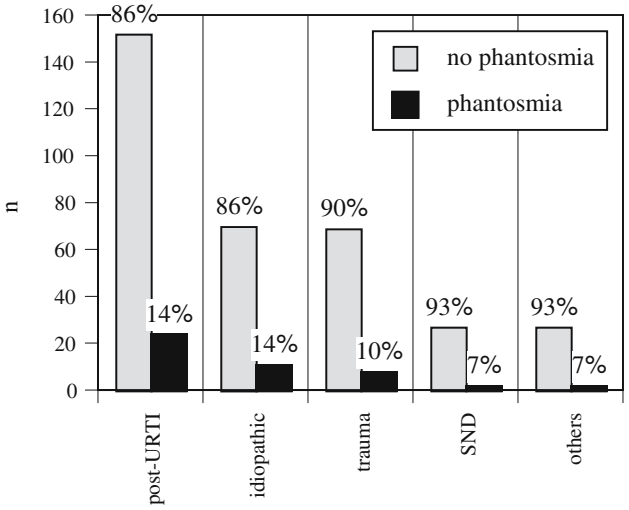

Fig. 2 Frequency of phantosmia (in number of subjects) within different patient groups (*black bars* indicate the number of patients with phantosmia, *gray bars* indicate the number of patients without phantosmia), with no difference between the groups of patients. The *numbers on top of each bar* indicate the percentage per group

Patients exhibiting parosmia were mostly hyposmic (71% of parosmic patients), 22% were functionally anosmic and the rest was normosmic. In contrast, with phantosmic patients a large portion was functionally anosmic (43%), while 53% of the patients with odor phantoms were hyposmic (Fig. 3).

Regarding the influence of qualitative dysfunction on the degree of quantitative improvement neither parosmia nor phantosmia seemed to have a significant impact on the change of the TDI-score between the two visits. The numbers were 2 (SEM 0.4) and 2.4 (SEM 0.5) points, respectively, for mean changes in non-parosmic and parosmic patients ($P = 0.58$), and 2.1 (SEM 0.4) and 1.8 (SEM 1.1) in non-phantosmic and phantosmic patients ($P = 0.78$), respectively.

In patients with parosmia ($n = 134$) 28% exhibited an improvement of olfactory function (phantosmia [$n = 47$] 30%), of those without parosmia 21% did so (22% without phantosmia). These differences did not reach the level of statistical significance (χ^2 test: $P = 0.11$ and $P = 0.23$). Progress rates are shown in detail in Figs. 4 and 5.

Twenty-nine percent of patients with parosmia reported disappearance of the symptom after a mean duration of 11.9 months (SEM 0.9). Out of 47 patients with phantom smells 53% lost this complaint after the same mean observation period.

Discussion

Results of the present study indicate that (1) parosmia and phantosmia appear most frequently in olfactory

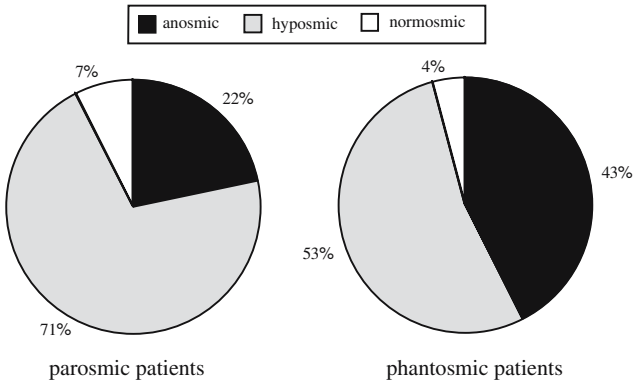

Fig. 3 Olfactory function of parosmic patients ($n = 134$) and phantosmic patients ($n = 47$), showing that in the group of phantosmic patients anosmia occurs twice as often as in the group of parosmic patients

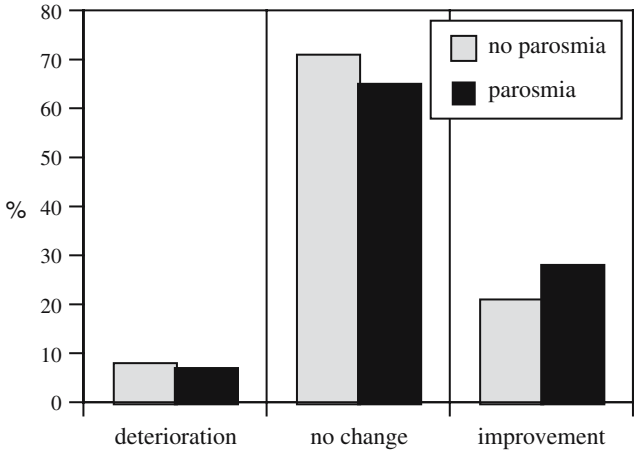

Fig. 4 Change of olfactory function in patients with parosmia ($n = 134$). *Black bars* indicate the percentage of patients with parosmia, *gray bars* indicate the percentage of patients without parosmia. Data are presented separately for subgroups of patients exhibiting improvement, deterioration or no change of olfactory function over an average observation period of 11 months. Improvement rate was not influenced by the presence or absence of parosmia [$\chi^2(df = 1) = 2.4$; $P = 0.11$]

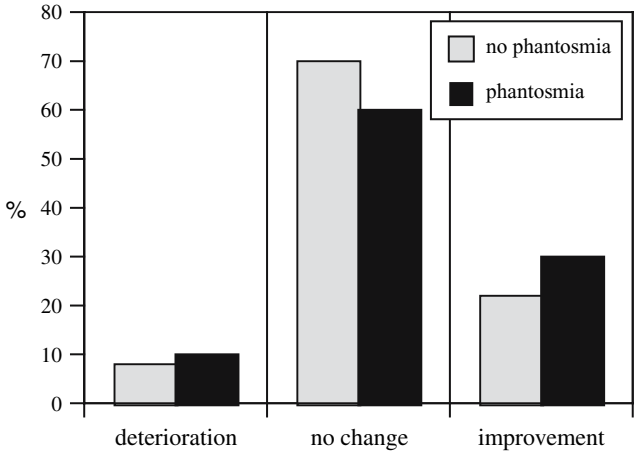

Fig. 5 Change of olfactory function in patients with phantosmia ($n = 47$). *Black bars* indicate the percentage of patients with phantosmia, *gray bars* indicate the percentage of patients without phantosmia. Data are presented separately for subgroups of patients exhibiting improvement, deterioration or no change of olfactory function over an average observation period of 11 months. Improvement rate was not influenced by the presence or absence of phantosmia [$\chi^2(df = 1) = 1.4$; $P = 0.23$]

dysfunctions following upper respiratory tract infection (URTI); (2) likelihood for recovery seems to be unaffected by the occurrence of qualitative disturbances; and (3) phantosmia disappeared in more than half of the patients after approximately 1 year whereas only 29% of parosmic patients lost this symptom during the same period of time.

Up to now, the etiology of distorted olfaction remains unclear. Different mechanisms have been discussed, including central and/or peripheral causes [5]. Centrally, the integration and interpretation of odors could be altered, resulting in a distorted perception. On the other hand—according to the present consensus on the olfactory coding [15]—loss of peripheral receptor neurons reduces particular aspects of the afferent sensory information. Accordingly, the integrity of the olfactory image may change, and the odor is perceived as an incomplete "picture", resulting in parosmia. Interestingly, recent investigations showed that the volume of the olfactory bulb is reduced in patients suffering parosmia after post-URTI or posttraumatic hyp-/anosmia compared to patients without parosmia, indicating a role of the olfactory bulb in the generation of odor distortions [16]. Histological investigations of biopsies from patients with phantosmia revealed an altered organization of the olfactory epithelium, containing fibrosis and decreased density of nerve fascicles, when compared to samples of patients with olfactory disorders without phantosmia [17]. These findings indicate the involvement of the peripheral olfactory system in the generation of phantosmia.

Different pathological situations seem to result in distorted olfactory perception, since olfactory deficits of different etiologies are accompanied by these symptoms. In this set of data, incidence of phantosmia was not different for the different causes of disease. In contrast, parosmia occurred in more than 50% of post-URTI olfactory losses, twice as often as in patients with SND-related olfactory loss. This predominance is in agreement with observations by Seiden, who found 65% of patients with post-URTI olfactory deficit reported parosmias, followed by posttraumatic and SND-related impairment with much lower frequencies of parosmia (36 and 35%, respectively) [18]. It can only be speculated about the reason for this difference. The olfactory pathway provides an entry for potential exogenous substances released by the causative virus [19], which may affect different central regions of olfactory processing, leading to distorted olfaction. Biopsies of the olfactory epithelium of patients with postviral olfactory loss show damage and destruction of the neuroepithelium, as well as scarring and replacement with respiratory epithelium [20]. In addition, recent studies found abnormal disorganized tangles of axon fibers (i.e., neuromas) in the olfactory epithelium of patients with olfactory dysfunction [17]. The morphology of these neuromas differed depending on the etiology of disease. These pathohistological differences may explain—at least in part—the frequent occurrence of parosmia in viral infections of the upper respiratory tract.

It has been hypothesized that parosmias appear during regeneration [10]. As a consequence of this one

would assume not only a change of distorted olfaction, but also recovery of decreased olfactory sensitivity over time; yet, this has never been systematically addressed. Present data does not reveal such a correlation. Neither in parosmic nor in phantosmic patients the degree of change of olfactory function differed significantly of those without distortions. Furthermore, although there was a trend towards this direction, the proportion of recovered patients was not significantly higher in parosmic or phantosmic patients. Even though the onset of parosmia and phantosmia typically occurs simultaneously and is linked to the onset of olfactory impairment, further progression of these symptoms seems to proceed independently from each other. Consequently, the presence of distorted olfaction cannot be taken into account when counseling patients concerning the prognosis of their olfactory impairment, which is also confirmed by previous observations [7]. Reasons for the missing correlation between parosmia/phantosmia and prognosis of olfactory disease may also lie in the problematic categorization of parosmia—currently olfactory distortions are only judged as present or non-present. For example, grading of parosmia/phantosmia according to the frequency of their appearance, their intensity, and possible social consequences resulting weight loss might provide an adequate grading system. While yet to be demonstrated, such a gauge of the significance of olfactory distortion may provide a future means to allow for statements on the prognosis of olfactory loss.

Regarding the development of parosmia and phantosmia itself, recovery rates differ from each other. Twenty-nine percent of patients with parosmia reported disappearance of their distorted perceptions within approximately one year. In contrast, 53% of the patients with phantosmia lost this discomfort within the same period of time. An explanation for this relatively high rate of recovered phantosmias could be that patients adapt to the constant impression of a smell. It is well known that the subjective perception of an odor loses its intensity when presented permanently. This is due to both, adaptation of peripheral receptor cells and to central-nervous habituation. It was reported that desensitization is more pronounced for malodors than for pleasant odors [21]. Characterized as being mostly unpleasant, subjects could habituate to the permanent phantom smell more effectively than to other odors.

Conclusion

In this study we investigated different aspects of qualitative olfactory dysfunctions. The present data revealed that URTI-related olfactory loss is more frequently accompanied by parosmia compared to other etiologies, such as sinunasal disease or head trauma. This knowledge may lead to a better understanding of and a focused research on the pathophysiological processes of both URTI-related olfactory dysfunction and parosmia.

Although it has been suggested that olfactory distortions could be regarded as an indicator of early recovery of decreased olfactory sensitivity, the current data shows that occurrence of parosmia or phantosmia has little prognostic value. Finally, phantosmia disappears at a faster rate than parosmia. These insights into qualitative olfactory dysfunction may be useful when counseling patients with olfactory loss.

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