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How to cite

GOKTAS, Onder et al. Chemosensory function in Wegener's granulomatosis: a preliminary report. In: European archives of oto-rhino-laryngology, 2010, vol. 267, n° 7, p. 1089–1093. doi: 10.1007/s00405-009-1184-4

This publication URL: https://archive-ouverte.unige.ch/unige:20969
Publication DOI: 10.1007/s00405-009-1184-4

Eur Arch Otorhinolaryngol (2010) 267:1089–1093
DOI 10.1007/s00405-009-1184-4

RHINOLOGY

Chemosensory function in Wegener's granulomatosis: a preliminary report

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Received: 16 September 2009 / Accepted: 15 December 2009 / Published online: 31 December 2009

Abstract Despite the fact that Wegener's granulomatosis affects the nasal and paranasal cavities and the cranial nerves regularly, chemosensory impairments have not been reported. The objective of this study is to test the three chemosensory systems, olfaction, taste, and intranasal trigeminal function in Wegener disease patients. We tested olfactory, gustatory, and intranasal trigeminal function in nine patients (5 women, 4 men, mean age 57 years) with confirmed Wegener's granulomatosis. Olfaction was tested with the Sniffin'Sticks, gustatory function with the "Taste strips" and intranasal trigeminal function with a lateralization task. One patient had anosmia (11%), four patients had hyposmia (44%) and four patients were normosmic (45%). Gustatory testing function showed pathological taste strip results in five patients (55%) and normal results in three patients (33%). One patient did not undergo taste testing. Intranasal trigeminal function was lowered in five patients (56%) and normal in four patients (44%). Neither previous nasal surgery status nor endoscopic status was associated to a higher frequency in pathological scores for any of the three chemical senses. In conclusion, these preliminary results suggest a consistent affection in chemosensory functions in Wegener's granulomatosis patients.

Keywords Olfaction · Taste · Trigeminal · Retronasal · Wegener's granulomatosis · Lateralization

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Introduction

Wegener's granulomatosis (WG) is a granulomatous inflammation of the upper and lower respiratory tract, which is accompanied by a necrotizing, granulomatous vasculitis of the medium-sized and small vessels [1]. In more than 80% of the cases, WG initially manifests clinically in the head and neck region [2]. Wegener' granulomatosis occurs at all ages, but is most frequently diagnosed from the fourth life decade onwards [3]. In so-called "Head Wegener", the nose and paranasal sinuses account for the main localization with 70–90% [4] with a varying degree of concomitant affection of other organs. Most of these head WG cases are accompanied by rhinitis, sinusitis, nasal ulcers, middle ear effusions, and tracheal manifestations. Besides classical kidney and pulmonary affection [1], WG has repeatedly been associated with peripheral and cranial nerve neuropathies [5]. Among the cranial nerves the facial, optic and abducens nerves are the most concerned, whereas the first cranial nerve (olfaction) seems not to be concerned at all [6]. All chemical senses, olfaction, taste, and intranasal trigeminal perception are mediated by cranial nerves and two chemical senses, olfaction, and intranasal trigeminal function are altered by chronic rhino-sinusitis [7]. As WG potentially affects both, the upper airways and cranial nerves, chemosensory functions might be affected in these patients. We investigate if, and to which extent the chemosensory functions were affected in WG.

Materials and methods

Patients

Nine patients (5 women, 4 men, age median 57 ± 6 years) with confirmed WG underwent chemosensory examination, except one patient who did not undergo taste and retronasal testing. The patient's history was assessed and nasal endoscopy was performed after nasal decongestion. An overview of the patient's details is given on Table 1. All patients were treated with cyclophosphamide and/or steroids and had a stable disease state at the moment of testing. The patients labeled as positive biopsy within Table 1 showed granulomatous inflammation either within the arterial wall or in the perivascular area or granulomatous inflammation involving the respiratory tract, and vasculitis of small and medium sized vessels.

Visual analogical scale ratings

The patients were asked to rate their nasal patency feeling, olfactory and gustatory function, facial pain, or headache as well as rhinorrhea on a visual analogical scale. The scales were labeled from 0 to 10, whereas 0 meant absent olfactory or gustatory function, non-obstructed breathing and absence of rhinorrhea or facial pain/headache. On the other scale end, ten corresponded to completely blocked nose, severe facial pain/headache and rhinorrhea as well as outstanding olfactory and gustatory function.

Chemosensory testing

Orthonasal olfaction was tested by using the Sniffin'Sticks, a well-validated and widespread European smell test kit. It consists of a threshold, discrimination, and identification test, summed up to a composite TDI score (for details see reference [8]). The three subtests do all allow for a maximum of 16 point each and the total score of can be 48 points. Anosmia is consistent with less than 16 points and normosmia starts above 30 points. Results in between are considered to reflect hyposmia.

Retronasal olfaction was assessed using a previously described 10-item test based on food powders without any concomitant basic taste properties (e.g. banana flavor without sweet taste) [9]. Using validated techniques for application [10] (Iphas Pharma, Würstelen, Germany) odors were applied to the oral cavity in the form of odorized but tasteless food powders (Givaudan SA, Dübendorf, Switzerland). While blocking the nose by gently pressing the wings against the septum, a powder was applied to the tongue. Once the mouth had been closed, participants were allowed to unblock the nose. They were then asked to identify the odor from a list of four items. Following administration of each powder, participants rinsed their oral cavity with tap water.

Gustatory function was examined by using the "taste strips"; a clinical identification test based on impregnated filter papers applied to the anterior two-thirds of the tongue. Normal taste identification is considered when 19 or more of 32 presented taste strips are correctly identified (for details see [11]).

Intranasal trigeminal function was assessed by using the lateralization paradigm, which basically exploits the fact that molecules that stimulate the trigeminal nerve can be localized to the nostril they entered the nose whereas this is not possible for pure odorants. For example, if a subject is presented vanilla (a substance stimulating solely the olfactory nerve) to one nostril and odorless air simultaneously to the opposite nostril, this subject has a 50% chance of localizing the nostril where vanilla was presented. In contrast, if the same is done with menthol (a substance stimulating the olfactory but also considerably

Table 1 Overview of the patients clinical details

Patient	Gender	Age	Previous nasal surgery	Nasal endoscopy	Disease duration (years)	c-ANCA	Positive biopsy	Organs affected
1	F	34	Yes	Normal	5	Negative	Subglottic	Trachea, Lung, Ear, Larynx
2	M	58	Yes	Normal	7	Positive	Renal	Lung, Nose, Kidney
3	F	50	Yes	Crusts	3	Positive	Nasal	Ear, Nose
4	M	68	No	Normal	9	Positive	Nasal	Nose
5	F	77	Yes	Septal perforation	3	Positive	Nasal	Nose, Heart, Spleen Cranial Nerve VI
6	F	37	Yes	Synechia	9	Positive	Nasal	Nose
7	F	67	Yes	Crusts	26	Negative	Nasal	Nose, Trachea
8	M	42	No	Mucosal congestion	1	Positive	Bronchial	Nose, Trachea, Lung, Cranial Nerve XII, Ear
9	M	87	No	Normal	2	Positive	Nasal	Nose, Lung, Kidney

M male, *F* female

the intranasal trigeminal nerve) the subjects chance to localize correctly rise up to 90%. This difference in accuracy of detecting from which side a stimulus comes according to whether the substance has trigeminal properties or not is currently considered the best available psychophysical test to examine intranasal trigeminal function [12]. We used the same clinical procedure previously described by Hummel et al. [13], who presented eucalyptol odor to either one nostril in a high-density polyethylene squeeze bottle (250 ml) filled with 30 ml of eucalyptol (a substance stimulating the olfactory but especially the intranasal trigeminal nerve); at the same time, an identical bottle filled with 30 ml of odorless propylene glycol was presented to the contralateral nostril. A total of 40 stimuli were applied to the blindfolded patients in a pseudo-randomized sequence. After each stimulus, patients were asked to identify the nostril where the odorant had been presented. The sum of correct identifications reflects the intranasal trigeminal function and was used for further statistical analyses.

Statistics

The results are shown as mean value and their standard error of the mean (±SEM). The statistical evaluation was conducted using SPSS 16. For comparison of mean, we used nonparametric statistics Mann–Whitney test and Wilcoxon rank test to compare ortho versus retronasal olfactory function. Correlations were calculated using the Spearman correlation. Analyses of frequencies were calculated using Chi-Square tests. The alpha-level was set at 0.05.

Results

Patient's chemosensory function

Based on TDI scores, one patient had anosmia (11%), four patients had hyposmia (44%) and four patients were normosmic (45%). Retronasal screening testing showed three patients with lowered scores and five patients with normal scores. Gustatory testing function showed pathological taste strip results in five patients (55%) and normal results in three patients (33%). One patient did not undergo retronasal and gustatory testing (Table 2). Intranasal trigeminal function, measured with the lateralization task, was lowered in five patients and normal in four patients. Neither previous nasal surgery status nor endoscopic status were associated to a higher frequency in pathological TDI scores (χ^2 test, $P = 0.3$; χ^2 test, $P = 0.2$), taste strip scores (χ^2 test, $P = 0.1$; χ^2 test, $P = 0.7$) or lateralization scores (χ^2 test, $P = 0.4$; χ^2 test, $P = 0.3$). Ortho versus retronasal olfactory function was not found to be significantly different ($Z = -0.98$, $P = 0.4$).

Table 2 Overview of the patients chemosensory results

Patient	Olfaction (TDI score)	Retronasal olfaction (percent correct)	Trigeminal function (lateralization score out of 40 possible)	Taste (taste strip score)
1	39.5	100	31	27
2	31.25	50	23	23
3	23.25	70	27	12
4	37.75	90	34	18
5	6	70	21	14
6	28.5	80	34	24
7	25.5	90	15	4
8	30.5	100	20	9
9	21.5	Not tested	34	Not tested

Age and disease duration effect

There was no significant effect for age or disease duration on the chemosensory function. Age did not correlate significantly with TDI score ($r_9 = -0.6$; $P = 0.09$); taste strip score ($r_9 = 0.1$; $P = 0.7$) or localization scores representing intranasal trigeminal function ($r_9 = 0.7$; $P = 0.8$). Disease duration did not correlate significantly with TDI score ($r_9 = 0.3$; $P = 0.3$); taste strip score ($r_9 = 0.1$; $P = 0.6$) or localization scores representing intranasal trigeminal function ($r_9 = 0.6$; $P = 0.8$).

Subjective ratings

Ratings of olfactory function correlated significantly with the TDI scores ($r_9 = 0.8$; $P = 0.01$), whereas taste ($r_9 = 0.5$; $P = 0.2$) and intranasal trigeminal function ratings ($r_9 = 0.3$; $P = 0.5$) did not correlate with the respective psychophysical results. Interestingly, ratings of olfactory and taste function correlated ($r_9 = 0.8$; $P = 0.01$). Patients with previous nasal surgery and also those with pathological endoscopic scores rated their nasal obstruction worse than those who did not have prior surgery ($Z = -2$; $P = 0.04$; $Z = -1.9$, $P = 0.05$).

Nasal affection

6 of the 9 patients had received operations on the outside of the nose and/or the paranasal sinuses prior to diagnosis. In 5 out of these 6 cases, a possible WG had not been suspected. Instead, there had been symptoms of chronic rhino-sinusitis which were intended to be remedied by an operation. In these patients, postoperative wound healing problems such as encrusted mucous secretion, synechiae,

large septum perforation, or histological report of the removed tissue suggested the presence of WG. In four cases, endoscopic examination revealed no pathological findings. 2 out of 9 patients had an isolated affection of the nose, and all 9 patients had at least another head and neck manifestation.

Discussion

The present study suggests that patients with WG show lowered overall chemosensory functions. To our knowledge, this is the first study which focussed on chemosensory function in WG patients. Two previous case reports [14, 15] and one large series on cranial nerve involvement in Wegener disease mention anecdotally chemosensory symptoms without having measured and them [16]. Recently, Laudien et al. [17] also screened WG patients for olfactory identification suggesting that up to 18% of them had lowered olfactory identification scores. Unfortunately, these authors did not test the other chemical senses and were able do asses the full Sniffin' Sticks test battery only in 4 out of 76 WG patients. In general, WG affects the nasal and paranasal cavities and cranial nerves and should consequently also lead to chemosensory (olfactory, gustatory or trigeminal) deficits since all of them are mediated by cranial nerves. Astonishingly, cranial nerve affection in Wegener disease has been described for the cranial nerves II–XII whereas optic, abducens, and facial nerve are the most concerned [6]. In contrast, cranial nerve I affection (olfactory) has been mentioned without any further detail in solely one publication [16]. Here, using well-established measurement tools, we have almost half of the patients who have lowered olfactory scores, which seem to corroborate the findings from the above-mentioned screening study [17]. The mechanisms of cranial nerve involvement may be either by continuity, especially from nasal and skull base granulomas, or by vasculitic involvement of small vessels surrounding the cranial nerves, resulting in mononeuritis multiplex [6]. Since nasal affection did not reveal to be a significant factor associated to olfactory function the first mechanism seems rather unlikely. Since no olfactory epithelium or nerve biopsies were available for the present WG patients, it remains speculative to assume mononeuritis multiplex for the first cranial nerve.

Besides the description of our findings, we attempted to analyse our data statistically. Considering the small sample size, we are aware that such an analysis has only limited meaningfulness. Larger prospective studies on WG and chemosensory functions must further confirm our findings. Statistical sub-analysis suggests that the chemosensory affections in WG are not related to the sinunasal affection or prior surgery status. Although statistics do not establish a clear link between chronic nasal involvements and chemosensory functions, we dare to speculate that the possibility of chronic nasal affection as a key factor for chemosensory decrease should not be ruled out. Here, 6 out of 9 patients had nasal surgery before diagnosis was established because of chronic rhinosinusitis symptoms, which reflects the high percentage of nasal involvement in WG. Thus, chronic nasal mucosal inflammation could be a major contributor to chemosensory impairment even though the present results do not underline that. Nasal surgery itself and the prolonged and complicated wound healing observed in some patients could also account for chemosensory affection. In contrast to previous studies [18], and based on the self-ratings, we also found that Wegener disease patients seemed to be aware of their olfactory deficits. Since rating of olfactory function and nasal patency is often confounded [18, 19], this could be further hint that the olfactory lowering found here is sinunasal disease related. Alternatively, cranial nerve affection in WG could be a reason for observed chemosensory changes. However, most patients had no cranial nerve symptoms and we think that it is rather unlikely that silent cranial nerve affection (e.g. such as mononeuritis multiplex of the olfactory nerve) caused the chemosensory impairments. Larger studies must confirm implication of the first cranial nerve in WG and this high preliminary rate of olfactory disorders. Finally, like in other autoimmune diseases [20–22], unknown, maybe systemic factors could contribute to a lowering of the chemosensory function. Since renal insufficiency is known to alter smell and taste function [23], this could account for lowered chemosensory functions in WG patients.

Gustatory function was also found to be affected in more than half of the patients, which is surprising since the patient's ratings did not suggest any taste problem. WG affects preferentially the seventh cranial nerve but also the middle ear cavity. Thus, the chorda tympani function, which was measured here, could be affected due to direct seventh cranial nerve involvement or direct middle ear inflammation, known to affect taste function [24]. In the present study, only three of the five patients with impaired taste results had middle ear disease or cranial nerve affection. Besides these direct disease related reasons, taste is also more susceptible to medication and we cannot completely rule out medication side effects especially from the cyclophosphamide [25], which all patients had received during the disease course. Finally, intranasal trigeminal function was tested here and showed similar rates of impairment as olfactory and gustatory function. Like for olfactory function, statistical analysis did also not reveal any significant link between nasal involvement, prior nasal surgery and endoscopic findings and trigeminal impairment. Similar to olfaction, intranasal trigeminal function

could be altered due to nasal involvement of Wegener disease. Silent trigeminal affection by Wegener disease itself is unlikely since no patient complained about other trigeminal symptoms, such as facial pain or sensory deficits.

Despite the thorough chemosensory workup of these WG patients, our study has several limitations: first, the study sample was small, which is also due to the relative rareness of the investigated disease. Second, the study provides an interesting observation, that of high frequency of overall chemosensory dysfunction in WG patients, without providing or proposing an identifiable cause or mechanism. Finally, the present data, although they largely corroborate very recently made observations of Laudien et al. [17], remain still inconclusive when it comes to characterize the nature of the chemosensory disorder WG patients have.

Conclusion

The present study revealed that chemical senses are consistently and to a comparable extent affected in WG. Based on this transitional study, it is difficult to identify a clear cause for the unexpectedly high rate of chemosensory impairment. Further studies with larger samples must confirm our preliminary data.

Acknowledgments The study was supported by a Grant of the Swiss National Fund for Scientific Research (SSMBS grant no. PASMA-119579/1) to BNL.

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