ORIGINAL CONTRIBUTION

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Olfactory dysfunction in Wegener's granulomatosis*

Martin Laudien[1], Peter Lamprecht[2], Jürgen Hedderich[3], Julia Holle[2], Petra Ambrosch[1]

[1] University of Kiel, Department of Otorhinolaryngology, Head and Neck Surgery, Kiel, Germany
[2] University of Lübeck, Department of Rheumatology, Vasculitis Center UKSH & Rheumaklinik Bad Bramstedt, Lübeck, Germany
[3] University of Kiel, Department of Medizinische Informatik und Statistik, Kiel, Germany

SUMMARY

Necrotizing granulomatous inflammation of the upper respiratory tract is one of the hallmarks of Wegener's granulomatosis (WG), which may explain the reason for olfactory dysfunction in WG. However, a systematic analysis using modern olfactory testing tools has not been performed and potential causes of dysfunction at different levels of olfactory information processing remain obscure so far. In this study a group of 76 WG-patients was examined with sniffin'sticks screening 12, odour threshold (T) / discrimination (D) / identification (I) TDI-score, active anterior rhinomanometry and a standardized questionnaire for olfactory function. WG-patients were aware of their olfactory dysfunction, as proven by psychophysiological test results. An altered olfactory function was significantly correlated to local administration of mupirocin and to the time interval between first diagnosis and study entry. None of the other variables had a statistical significant effect on the olfactory dysfunction.

Key words: Wegener granulomatosis, olfactory dysfunction, vasculitis, sense of smell, respiratory dysfunction, smell disorder, olfaction

INTRODUCTION

WG is a rare (incidence of $12/10^6$ per year [(1)] autoimmune disorder. WG usually starts as granulomatous disease in the upper and lower respiratory tract, before it converts to systemic autoimmune vasculitis (generalized WG) associated with highly specific antineutrophil cytoplasmic autoantibodies against proteinase 3 (PR3-ANCA) after a variable period of time. WG-relapses are related to the persistence of WG-granulomata in the upper and lower respiratory tract [(2)]. WG-patients are assumed to suffer from a reduced sense of smell although a systematic proof of this assumption is still lacking [(3,4)]. Even though the sense of smell is considered to be a "lower sense" it has an essential impact on social interaction and results in a dramatic decrease in quality of life when lost [(5,6)]. In WG, dysfunction of the olfactory system could be a consequence of: 1) recurrent sinonasal inflammation, granuloma formation, necrosis or crusting, or 2) sensoneurinal olfactory loss, or 3) the use of local (antibiotic ointments) or systemic immunosuppressive drugs. In neurodegenerative diseases like Alzheimer's disease testing of the olfactory system became a helpful tool in diagnosis and monitoring therapy in the course of the disease [(7-9)]. This could potentially also be applicable in WG. In this study, we assessed the so far largest group of WG-patients (n=76) to be analyzed for olfactory dysfunction and the impact of disease activity, disease-associated damage and local/systemic medication on this WG-manifestation.

PATIENTS AND METHODS

Patients

In a prospective study from 10/2006 till 05/2007 76 (44 women, 32 men, age 26-78, median 55 years) consecutive patients with WG were included. They were examined according to the guidelines proposed by Paulsen et al. [(10)]. These guidelines demand a clinical examination of the nose, paranasal sinuses, nasoharynx, oral cavity, oropharynx, hypopharynx, larynx, ears, salivary glands, cranial nerves and cervical lymph nodes. Activity of WG in the head and neck region is rated and therapeutical management is suggested. Endoscopic examination of the nose is the only way to detect low-grade endonasal activity, which is, in combination with the chronological sequence of

List of abbreviations

ANCA: antineutrophil cytoplasmatic antibody; BVAS1: Birmingham Vasculitis Activity Score (new or worse disease activity); BVAS2: Birmingham Vasculitis Activity Score (persistent disease activity); CNS: central nervous system; CRP: C-reactive protein; ELK classification of WG: Ear, Lung, Kidney; ESR: erythrocyte sedimentation rate; VDI: Vasculitis Damage Index; WBC: White blood cell count; WG: Wegener's granulomatosis

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endonasal activity, mandatory for the appropriate therapy [11]. All patients fulfilled the criteria of the Chapel Hill Consensus Conference [12] and the American College of Rheumatology [13] for WG. In this group 50 patients had biopsy-proven WG.

Disease activity was measured using the Birmingham Vasculitis Activity Index (BVAS), organ damage as a consequence of granulomatous inflammation and vasculitis using the Vasculitis Damage Index (VDI) [14] and organ involvement was assessed by ELK-classification [15]. WG-subgroups (localized, early systemic, and generalized WG), relapse and remission were diagnosed and defined according to the European Vasculitis Study Group (EUVAS) definitions and recent European League Against Rheumatism (EULAR) recommendations [16]. To assess WG-activity all patients were subject to a standardized interdisciplinary evaluation as described earlier [17].

Olfactory function

Olfactory function was tested by "sniffin'sticks screening 12" ("sn'st", psychophysical testing of odour identification by a forced multiple choice test) [18]. Four Patients with higher degree of olfactory dysfunction were tested by TDI ("sniffin'sticks", psychophysical testing of odour threshold (T), discrimination (D) and identification (I) by a pen like odour dispensing device) [19].

Questionnaire

A standardized questionnaire for olfactory function was answered by 51 (67%) patients as recommended by Laudien and Maune (http://www.hno.org/2001/2001.htm).

Respiratory function

The respiratory function was tested using active anterior rhinomanometry (Rhinostream, Rhinometrics, Lynge, Denmark).

Statistics

Results were analyzed using SPSS 15.0 for windows and by Kolmogorov-Smirnov test, Chi-quadrate test or Mann-Whitney test. The alpha level was set at 5%.

Ethics

The study protocol was approved by the ethics committee of the University of Kiel.

RESULTS

Patient characteristics

Of all patients 68% had generalized, 8% early systemic and 25% localized disease. The mean time from first manifestation of Wegener's granulomatosis was 7 years before study entry (SD = 6, minimum = 1, maximum = 33) and the mean time from first diagnosis was 6 years (SD = 5, minimum = 0, maximum = 23). Mean time between first manifestation of symptoms and first diagnosis was 1.6 years (SD = 3.4, maximum = 21, minimum = 0). The mean BVAS1 [20] for all patients was 1.13 (SD = 3.010, minimum = 0, maximum = 15) and the mean BVAS2 was 0.89 (SD = 1.181, minimum = 0, maximum = 5). The mean BVAS1 for patients with new or worsened activity at examination was 7 (SD = 3.9, minimum = 4, maximum = 15). New or worsened activity was observed (BVAS1) in kidney, lung or CNS (central nervous system) in 4%, 1% and 1% of the patients and predominantly in ENT patients (53%) with the distribution shown in Figure 1. Of the WG patients with a BVAS 1 score ≥ 1 in the ENT items, 11 were localized, 3 early systemic and 24 generalized. The mean VDI [21] was 0.45 (SD = 0.81, minimum = 0, maximum = 5). Changes were detected in the upper respiratory tract, kidneys, lungs or CNS respectively in 18%, 5%, 1% and 3% of the patients. Of 14 patients with damage to the upper respiratory tract 6 were localized, 1 early systemic and 7 generalized. Patients were examined endoscopically and in patients with severe olfactory dysfunction either no or mild endonasal activity was found. Serologic signs of inflammation were: mean CRP (C-reactive protein) level 1.34 mg/dl (n = 50, SD = 1.51, range 7,5), mean ESR (erythrocyte sedimentation rate) 25.39 mm after the first hour (SD = 22.14), mean WBC (white blood cell count) 7.22/nl (SD = 2.62) and mean c-ANCA (cytoplasmatic ANCA) level 1:469 (n = 53, SD = 629). Systemic medication was heterogeneous and included glucocorticoid, cyclophosphamide, azathioprine, methotrexate, leflunomide, thrimetoprim / sulfamethoxazole, mycophenolate mofetil, infliximab, etanercept, rituximab, adalimumab and desoxyspergualin (NKT-01) in different combinations and dosages.

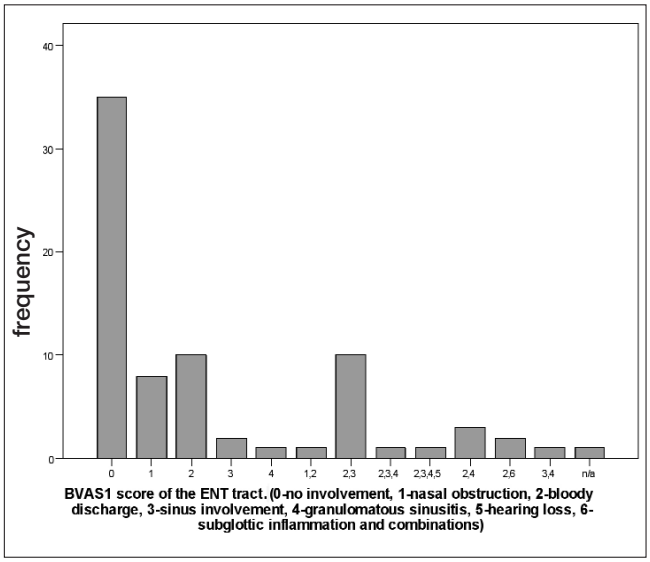

Figure 1. BVAS1 score of the ENT tract.

Vasculitis involvement according to ELK classification was: 72 patients (95%) in the upper respiratory tract, in the lower respiratory tract (lung) in 52 patients (69%), in the kidneys in 46 (61%) and in the CNS in 6 patients (8%). Thirty-eight (50%) patients received local medication (mupirocin ointment intranasally). A *Staphylococcus aureus* colonization of the nasal mucosa was detected in 37 (93%, n = 40) patients.

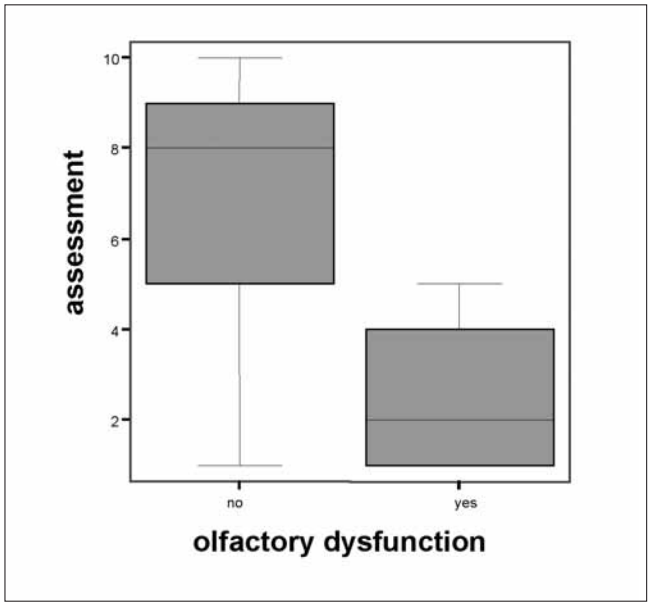

Figure 2. Psychophysical test result (sn'st) and subjective assessment of olfactory performance ($p \leq 0.01$).

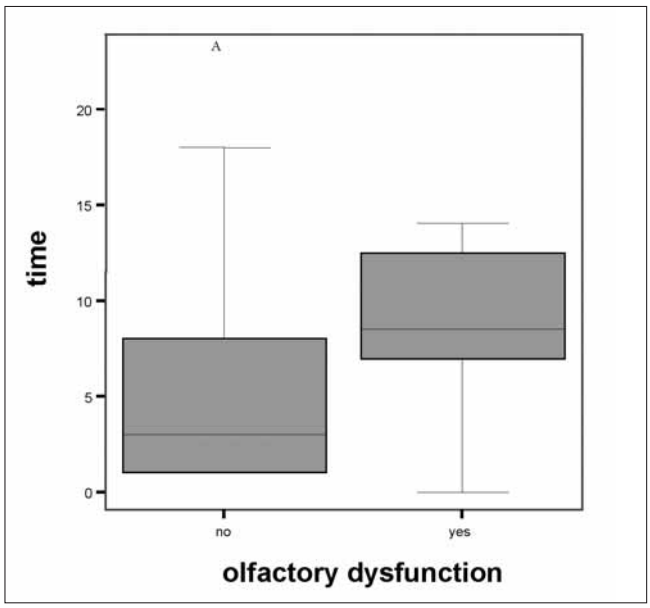

Figure 3. Psychophysical test results and time between first diagnosis and study entry ($p \leq 0.04$).

Analysis of olfactory function

On a visual analogue scale 51 patients estimated their olfactory function (from 1 very poor to 10 excellent) with a mean of 5.69 (SD = 3.089, minimum = 1, maximum = 10).

In 14 (18.4%) WG patients' severe olfactory dysfunction was documented by psychophysically test results (score of 6 or less in the "sn'st") (95% binomial CI, 10%, 29%). Assuming a prevalence of severe olfactory dysfunctions in 5% [22,23] or less of the German population, the olfactory dysfunction in WG is significantly increased (confident: $p = 0.95$). A higher degree of respiratory dysfunction was observed in 6 patients (less than 800 cm^3/s at 150 Pascal birhinal).

Four of the 14 patients with severe olfactory dysfunction were also tested by TDI and a median overall score of 15 (minimum = 10, maximum = 15) was obtained, which confirmed a functional anosmia according to the definitions of Hummel et al. [19]. The median threshold score was 0 (age adapted all patients scored under the 5th percentile), the median discrimination score was 8 (age adapted one patient each below the 5th percentile, on the 25th and two patients below the 10th percentile) and the median identification score was 5 (age adapted three patients under the 5th percentile and one below the 10th percentile).

Correlation between olfactory dysfunction and disease parameters

There was a significant correlation between psychophysical test results (sn'st) and subjective assessment of olfactory performance (standardized questionnaire) ($p \leq 0.01$, Figure 2), between psychophysical test results and local medication (mupirocin ointment) ($p \leq 0.01$, Table 1) and between psychophysical test results and time between first diagnosis and examination ($p \leq 0.04$, Figure 3).

No correlation was found between sn'st test results and sex, respiratory function, BVAS1/2, organ involvement as assessed by the ELK classification, new or worsened activity (BVAS1) and damage (VDI) of the upper respiratory tract, kidney, lung or CNS, systemic medication before study entry and current systemic medication, state of disease, time between first manifestation and first diagnosis and study entry, *Staphylococcus aureus* colonization, CRP, ESR, c-ANCA, WBC and time between first manifestation of Wegener's granulomatosis and study entry.

Table 1. Psychophysical test results and local medication ($p \leq 0.01$).

		local mupirocin treatment		Total
		yes	no	
olfactory dysfunction	no	25	37	62
	yes	13	1	14
Total		38	38	76

DISCUSSION

We examined olfactory function in WG for the first time in a systematic approach with modern, reliable and validated testing tools of olfactory function.

Activity and damage

Global assessment of activity (BVAS1/2), damage (VDI) and organ manifestation (ELK classification) as well as disease activity of the upper respiratory tract, kidney, lung and CNS observed by BVAS1 and damage assessed by VDI are not sufficient for detecting olfactory dysfunction in our study which may be due to the underrepresentation of otorhinolaryngologic symptoms in these scoring systems or due to our patient population, which showed an overall low disease activity and damage score. It is desirable to develop a more precise scoring system for otorhinolaryngologic activity and changes.

Nasal crusting may influence olfactory function and may be one sign of endonasal activity. For patients with higher olfactory dysfunction no or mild endoscopically proved endonasal activity was documented. All patients use endonasal ointment and douche their nasal cavity regularly. These procedures reduce nasal crusting. Therefore nasal crusting seems not to be the explanation for olfactory dysfunction.

There was no correlation between kidney involvement and olfactory function. Patients with chronic renal failure show olfactory dysfunctions for identification and discrimination [24], as well as thresholds [25]. The reason for this discrepancy may be the less severe renal impairment with none of the included patients on dialysis. Furthermore, in accordance to the literature no correlation of olfactory impairment and lung involvement was found [24,26,27].

Involvement of the CNS may impair the olfactory system, however, there was no correlation between such an involvement (detected by ELK classification, BVAS1 and VDI) and olfactory function. This might be due to the small group of patients (6, one with olfactory dysfunction) with CNS involvement and / or due to the fact that only 4 of the 14 patients with olfactory dysfunction underwent an MRI examination (29/76, 22% of all patients underwent an MRI).

ANCA-titre and marker of systemic inflammation (ESR, WBC and CRP) were not accurate predictors of olfactory dysfunction.

Patients in this study were relatively healthy (BVAS1/2 and VDI scores low) so olfactory disfunction may be different in severely affected patients.

Stage of disease / Staphylococcus aureus colonization

Depite the presence of intranasal disease activity, none of the patients with localized disease had a higher degree of olfactory dysfunction. Statistical analysis was difficult because of the unequal group sizes of patients with localized, early systemic and generalized disease. In our study a local (inflammatory) process was not responsible for olfactory loss. Moreover, there was no correlation between olfactory function and colonization with *Staphylococcus aureus*. There are no studies in humans assessing the effect of *Staphylococcus aureus* colonisation to olfactory function, but *Anopheles gambiae* challenged with heat inactivated microbes showed affected genes of the functional class olfaction [28]. Further studies have to clarify the relation of *Staphylococcus aureus* colonization and olfactory function.

Psychophysical testing / questionnaire

The significant result of severe olfactory disturbance in WG was supported by the patients' self-ratings of olfactory ability (standardized questionnaire).

This seems to be in contrast to the global perception of olfactory disturbances in healthy subjects (self-reported ratings of olfactory function are not correlated with quantitative measures of olfactory function in healthy subjects [29], however, perception of variances of olfactory function is more precise in patients who know about their olfactory dysfunction [30]. It seems that WG patients are aware of their dysfunction.

The TDI results had been age adapted very low. The low threshold might be a hint to a distorted peripheral rather than central olfactory disorder as discussed in the olfactory development in the elderly were such threshold changes are common [19], but the highly affected performances in identification and discrimination are rather central olfactory processes [31,32].

The TDI-group is rather small and so statistical analysis is impossible. More detailed examinations of threshold, discrimination and identification need to be performed.

Respiratory dysfunction

Olfactory function did not correlate with respiratory dysfunction, even if high degrees of respiratory dysfunction were present. This finding supports the results of an unaffected olfactory function over a wide range of respiratory dysfunction, which might be due to retronasal olfactory receptor excitation [33-37].

Medication

<u>local</u>

The correlation of olfactory dysfunction and the administration of mupirocin ointment in those patients, who suffered from olfactory dysfunction, might be a local drug effect, although twice as many patients receiving a local ointmenrt had no olfactory dysfunction (Table 1). Additional factors may be required to explain olfactory dysfunction in patients receiving mupirocin.

The natural occurring antibiotic mupirocin inhibits the isoleucyl-tRNA synthetase (an aminoacyl-tRNA synthetase (ARS)) of bacteria by binding reversibly [38]. ARSs are not solely necessary for translation (first activation and specific docking of their substrate amino acid and second transferral for protein synthesis) and exert a wide range of other functions, such as RNA processing, apoptosis and inflammation [39].

There are no studies regarding the effect of mupirocin administration on olfactory function. One study described unspecific symptoms (erythema, swelling, burning or stinging, pruritus and dryness) as side effects of mupirocin [40]. An interaction of ARSs and olfactory function is possible (mucus composition and influence of ARSs on inflammation, olfactory receptor and influence of ARSs on apoptosis and RNA processing).

Further studies have to clarify as to whether local mupirocin administration does interfere with olfactory function in WG, other diseases and healthy controls.

<u>systemic</u>

There was no correlation between olfactory function and previous or current medication.

The wide range of used drugs with different pharmacodynamics could interfere with the olfactory function on every level of olfactory perception.

Damage of chemosensory functions under immunmodulatory drugs has been reported by different groups, but the exact

mechanism of this damage (impairment of fast regenerating tissue (olfactory epithelium) by chemotherapeutic agents?) is just as unclear as the responsible therapeutic agent [41,42].
The diversity of drugs (and doses) administered to the patients made it impossible to group them in a meaningful way for statistical analysis. More standardized treatment and a bigger cohort may clarify the effect of medication on the olfactory disturbance in WG in the future.

Time between first manifestation and diagnosis to study entry
There was neither a correlation of olfactory disturbance and time between first manifestation of WG and study entry nor of olfactory disturbance and time of untreated disease (first diagnosis minus first manifestation). On one hand long-term disease did not induce impairment of olfactory function in this study (even so olfactory dysfunction secondary to atrophic rhinitis could be hypothesised), on the other hand time between diagnosis and study entry correlated significantly with an impaired olfactory system. This finding may be explained by the use of local and systemic therapy interfering with olfactory function. But then the necessity for medical therapy might be an indicator for more serious forms of WG and therefore it is also arguable that olfactory dysfunction in this group may be an expression of damage (e.g. atrophic rhinitis) according to vasculitis itself.

CONCLUSION

WG is associated with olfactory dysfunction. In WG patients with a documented olfactory dysfunction, duration of therapy and local mupirocin treatment correlate significantly with a reduced sense of smell. However, in 25 WG-patients receiving mupirocin, no olfactory dysfunction was induced. Furthermore, these patients are able to perceive their olfactory dysfunction, which is either of peripheral or central origin. Electrophysiological studies on receptor potentials and olfactory event-related responses have to clarify the exact pathophysiology of the olfactory disturbance in WG. Longitudinal studies assessing olfactory function (patients with localized disease progressing to generalized disease) over time may help to elucidate the underlying reasons for olfactory impairment. Studies addressing the impact of medication (systemic immunmodulatory treatment, local mupirocin treatment) will be useful to identify whether medication is involved in olfactory dysfunction in healthy subjects, in WG and other diseases.

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Martin Laudien
Department of Otorhinolaryngology
Head and Neck Surgery
University of Kiel
Arnold-Heller-Straße 14
D-24105 Kiel

Tel: +49 431 597 2324/2241
Fax: +49 431 597 2272
E-mail: laudien@hno.uni-kiel.de