Manifestation of granulomatosis with polyangiitis in head and neck

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ABSTRACT

Objective. *Granulomatosis with polyangiitis is a rare autoimmune disease of the group of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides. Involvement of the ear, nose and throat (ENT)-region is only described in a few case series and case reports. The objective of this study is to systematically characterise the ENT-involvement in a large series of GPA patients.*

Methods. *GPA patients examined in the Department of Otorhinolayngology of the Christian-Albrechts-University of Kiel between 1990 and 2012 were included. Diagnosis was based on histological, serological and clinical parameters. GPA patients were examined in a standardised way based on the Ear Nose and Throat Activity Score (ENTAS) or its precursor. Medical history, ENT examination, diagnostic findings (ear, nose) and cranial radiology were documented cumulatively.*

Results. *A total of 230 GPA patients were included in this study. Over 95% of them showed ENT-involvement. 59% of the patients showed nasal obstructions, 57% a loss of smell. A hearing loss was diagnosed in 23% of the patients, 50% involvement in MR or CT scans and 15% showed laryngeal involvement.*

Conclusion. *The data of the largest monocentric study presented here demonstrate a frequent ENT-involvement in GPA patients. Rhinological and otological manifestations are most common.*

Introduction

Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) is a rare antineutrophil cytoplasmic antibody (ANCA)-associated systemic autoimmune disease of unknown aetiology.

GPA is characterised by the Chapel Hill Consensus Conference (CHCC) as a vasculitis, affecting mainly small to medium sized blood vessels, and necrotising granulomatous inflammation with regular involvement of the head and neck region throughout the course of the disease (1, 2). The ear, nose and throat (ENT) region is often the primary site of manifestation (3). Since GPA is a systemic, chronic disease, a regular follow up is essential for early detection of a recurrence (4).

Although Friedrich Wegener described the head and neck region as the site of first manifestation in 1937 (5), the best information achievable for manifestation of GPA in ENT are review articles summarising information of small case series or even case reports (6). The objective for this study is to give a reliable description of the ENT-involvement in GPA in a significant amount of patients and their follow-up. A GPA scoring system (ENTAS) (7) relying on expert assessment was used in the follow-up.

Materials and methods

Study design and population

The GPA patients included in this study were monitored by an interdisciplinary, tertiary vasculitis referral centre. All patients, regardless of suspected involvement, were seen in the Department of Otorhinolaryngology of the Christian-Albrechts-University of Kiel between 1990 and 2012 as a fundamental part of the clinical activity assessment. GPA was diagnosed histologically, by using antibody-testing and clinical surrogate parameters (*e.g.,* nasal or oral inflammation, abnormal chest radiograph, urinary sediment) as defined by the American College of Rheumatology (ACR) (8). The cohort is selected to be very uniform and highly reliable for the diagnosis GPA (preferably supported by biopsy and/or serology).

Development of the data collection table

The ENT-involvement criteria were defined by established indices primarily the ENT Activity Score [ENTAS/

ENTAS2 (7, 9)], results of literature research and expert opinion as well as chart examination. The ENTAS consists of collected data from subjective complaints (symptoms), physical and other findings as well as diagnostic tests leading to an activity grading as well as signs for damage considered to be caused by vasculitis. Items were attributed to be caused by vasculitis if no other (better) explanation for the finding could be defined. Criteria used to group data in this study were: history, examination, clinical diagnostics (ear, nose) and results of diagnostic radiology.

Data collection
GPA-patients were examined using a standardised protocol (ENTAS) or its precursor. The radiologic data was analysed regarding ENT-involvement.

Examination
All patient examinations were performed using anterior rhinoscopy using angled optical systems, otoscopy by microscope and laryngoscopy using rigid or flexible optical systems.

Audiology
The hearing level was determined for the better hearing ear, applying WHO guidelines (10) where the statistical mean for hearing loss was calculated from four frequencies (500, 1000, 2000 and 4000Hz).
To avoid an over-representation of patients with more than one measurement, the average of the air conduction data from both ears was determined. In addition, tympanograms were analysed to determine the influence of a conductive hearing loss.

Rhinology
The olfactory function was assessed using the Sniffin' Sticks "Screening 12 Test" (11). The ability to breathe through the nose was objectified using active anterior rhinomanometry before and after decongestion. A flow of ≥300 ml/s (cm^3/s) at 150Pa was defined as mild or no obstruction and a flow of <300 ml/s at 150 Pa was classified as severe obstruction (device specific standard values and validated grading applied) (12). Patients were subdivided into different levels of obstruction due to multiple measurements and often fluctuating results (Level A: patients with exclusively <300 ml/s, Level B: patients with varying results and Level C: patients with exclusively ≥300ml/s). Patients with septal perforations were excluded from the analysis of rhinomanometry data.

Radiology
Available MRI and CT scans were used for the detection of fluid level, mucosal thickening, bone erosion or destruction, sclerosing osteitis and granulomas in the ENT-region. 99 MRI and 5 CT scans from 46 patients were included in this study and were evaluated by an experienced investigator (MB). Granuloma were defined as low-signal intensity lesions on T1- and T2-weighted spin echo sequences in the paranasal sinuses and orbits (13).

Statistical analysis
For statistical analysis SPSS (Statistical Package for the Social Sciences, v. 20) and MS Excel (Microsoft Office Excel 2007) were used.

Results
Patient characteristics
In total, 230 patients were included in this study (117 women [51%] and 113 men [49%]). All patients meet the ACR and CHCC criteria. A total number of 1946 consultations with a range from 1 to 58 consultations per patient were analysed. While the average age at diagnosis was 53 years (range of 16–82 years), the average age at manifestation was 50 years (range of 5–82 years). In 183 (80%) patients ANCA were detected (176 patients c-ANCA, 7 patients p-ANCA) with anti-PR3 specificity in 75% (n=172). GPA was biopsy proven in 170 patients (74%). For 103 patients positive biopsy was achieved by nasal biopsies. Roughly in one of five patients a positive histology but negative serology was detected. Six patients (3%) were included in this study in whom diagnosis relied solely on clinical evaluation. The mean cumulative ENTAS was 1.2, the mean disease extent index was 8.4.
Patients received immune modulatory medication based on established patterns and the current disease activity status (prednisolone, cyclophosphamide, methotrexate, azathioprine, interferon, leflunomide, mycophenolatmofetil, mycophenolatnatrium, cyclosporin A, rituximab, infliximab, etanercept, adalimumab). The mean cumulative cyclophosphamide-dosage was 33g.

Manifestation ear
Medical history
36% (n=83) of the patients reported subjective hearing loss; 24% of the patients (n=54) complained about tinnitus and 22% about otalgia (n=50). 9% of the patients (n=21) suffered from aural discharge and 12% (n=27) from dizziness (Fig. 1A).

Otoscopy
An inflamed eardrum was documented in 33% of the patients (n=67). In 10% of the patients (n=23) fluid in the middle ear and in 14% (n= 33) ear drum perforation was detected. Additionally, grommets were identified in 16% of the patients (n=36) (Fig.1B).

Audiology
To evaluate the hearing ability, pure tone audiograms were conducted for 215 patients (Fig. 2).
In total 1512 pure tone audiograms were conducted ranging from 1 to 43 audiograms per patient. For each pure tone audiogram available for both sides, the level of hearing loss was evaluated based on the WHO classification (10).
Hearing loss was diagnosed in 23% of the patients (n=50 of 215, multiple entry due to multiple examinations). Slight impairment was documented in 16% of the patients [n=34], moderate impairment in 5% [n=11], severe impairment in 1% of the patients [n=2] and profound hearing loss in 1% of the patients [n=3].
20% of the patients (n=45) showed a combination of dizziness and hearing loss.
When analysing corresponding tympanograms of 115 patients (507 right and 515 left side [range right: 1–18 tympanograms per patient; left: 1–18 tympanograms per patient]), the calculated median compliance on the right side

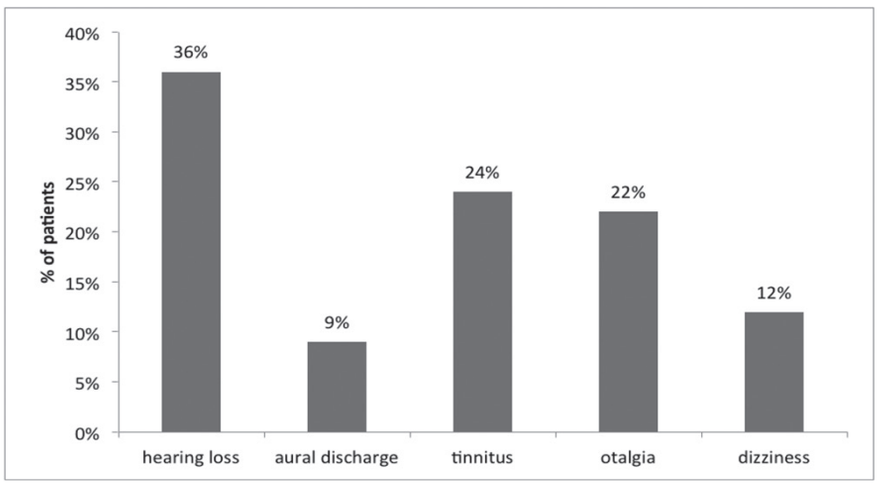

Fig. 1A. Medical history: ear manifestation.

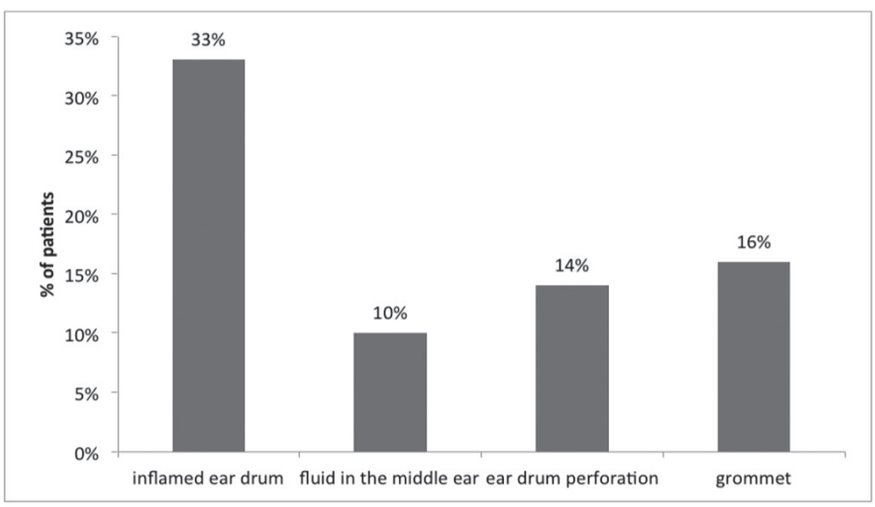

Fig. 1B. Manifestation ear otoscopy.

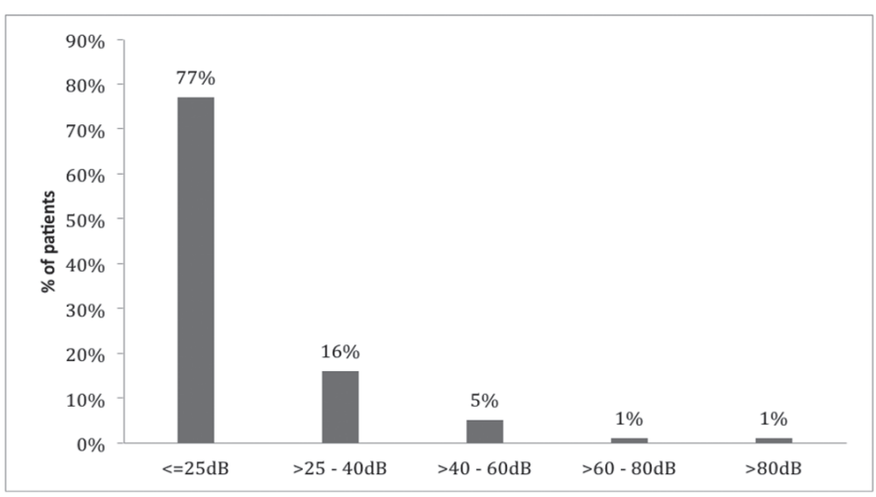

Fig. 2. Level of hearing loss based on the WHO classification for the better hearing ear.

was 0.99 and on the left side 0.98 ml. A median of -27,92 daPa on the right and -10,75 daPa on the left ear was documented for middle ear pressure.

Results of radiologic examination of the temporal bone

In 2 of 46 patients (3 of 104 MRI or CT-scans) an opacification in the middle ear was detected. The mastoid showed an opacification in 21 patients (45 of the scans).

Manifestation nose

Medical history

Overall 70% of the patients (n=161) complained about nasal symptoms. 39% of the patients (n=90) complained about nasal crusts, 38% of the patients (n=88) about epistaxis, and 24% of the patients (n=56) about rhinorrhoea. Dysosmia was reported in 16% of the patients (n=37) and a nasal obstruction in 10% of the patients (n=24). 17% of the patients (n=39) complained about cephalgia or pain above the sinuses, 15% (n=34) about rhinitis, 8% (n=19) about sinusitis and 7% (n=17) about epiphora. 3% of the patients (n=7) reported deformities of the nose. Noticeable was that patients complained about nasal crusts only in 12% (n=243) and about epistaxis in 9% (n=175) of the consultations. 49% of the patients underwent a nasal operation (n=113; surgery of the paranasal sinuses n=97; polypectomy n=18; septum plasty n=10) (Fig. 3A).

Rhinoscopy

In 94% of all patients (n=215) irregularities were detected by rhinoscopy. Nasal crusts were detected in 67% of the patients (n=155) and rhinorrhoea in 35% (n=80). The mucosa was granulated in 27% of the patients (n=63), putrid in 12% (n=27) and bloody submucosal patches were documented in 5% (n=11). Synechia was documented in 26% of the patients (n=60), polyps in 11% of the patients (n=25) and ulceration in 4% of the patients (n=10). 26% of the patients showed evidence of epistaxis (n=59).

18% of the patients had outer deformities of the nose (n=41), 17% a saddle nose (n=39), 28% a hyperplasia of the turbinates (n=65), 20% a perforation of the septum (n=47), 10% showed signs of endonasal mucosal swelling (n=22). 10% of the patients were classified by a physician as having a sinusitis (n=22).

The nasal mucosa showed a redness in 52% of patients (n=117), was coated in 33% (n=76), bloody in 30% (n=70), dry in 27% (n=63), vulnerable in 23%

(n=53) and showed an irregular surface in 20% of patients (n=47). It was noticeable that nasal crusts were seen in 38% (n=733) of the consultations (Fig. 3B).

Olfactory test

The measurement of the olfactory function was analysed using the collected data of 435 Sniffin' Sticks-tests from 125 patients. As a result 18% of the patients (n=23) showed normosmia, 62% hyposmia (n=77) and 20% anosmia (n=25).

Rhinomanometry

A total number of 690 rhinomanometries from 169 patients were evaluated, patients with septal perforations were excluded. A severe obstruction (level A) before decongestion was detected in 18%. 39% of the patients showed no or minor obstructions. After decongestion a severe obstruction was detected in 13% and little to no obstruction in 52% (Table I).

Radiological results for the nose and sinuses

Available predominantly MR-scans (99 of 104) primarily focused on central nervous system manifestation and therefore did not cover the neck or larynx. Bony erosion of the nose was described in 41% of the scans (n=43, 37% of the patients; n=17) and granulomas (often in a so called common cavity) in 13% (n=11 / 9% of the patients; n=4) (Table II).

The paranasal sinuses were (partially) blocked in up to 53% of the scans (n=55/59% of the patients; n=27), showed a mucosal thickening in up to 34% (n=35 / 50% of the patients; n=23), bony erosion or destruction in up to 20% (n=21 / 24% of the patients; n=11), an air-fluid-level in up to 13% (n=14 / 23% of the patients; n=12) and granulomas in 19% of the cases (n=20 / 23% of the patients; n=12).

Excluding the ostiomeatal complex, the average of the Lund-Mackay score was 5.2 (range: 0-20, SD: 6.7) in 46 patients .

Manifestation larynx

Medical history

13% of the patients (n=29) complained about hoarseness or dysphonia, 7% about pain in the throat (n=17). 6% of the patients underwent tracheal/laryngeal operations (n=13; bougienage n=6; local glucocorticoid-therapy n=6; tracheostomy n=5) (Fig. 4).

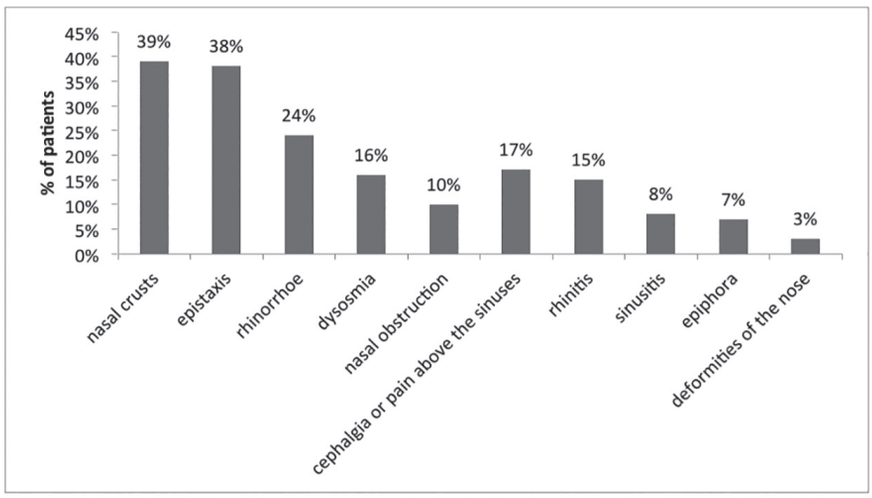

Fig. 3A. Medical history: nose manifestations.

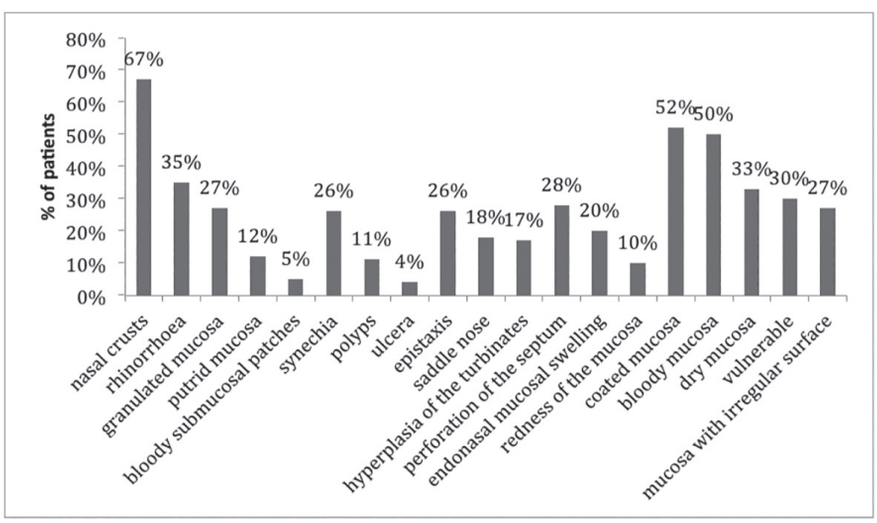

Fig. 3B. Findings by rhinoscopy.

Table I. Level of nasal obstruction, both nostrils measured, active anterior rhinomanometry, before and after decongestion by xylometazoline 0.1%.

	Inspiration before decongestion	Inspiration after decongestion
Level A	31 (18%)	22 (13%)
Level B	72 (43%)	59 (35%)
Level C	66 (39%)	88 (52%)
n.	169	169

Level A: patients with exclusively <300 ml/s results.
Level B: patients with variable results.
Level C: patients with exclusively ≥300ml/s results.

Assessment by physician

9% of the patients experienced a dysphonia (n=20), 8% dyspnoea (n=19) and 6% stridor (n=13).

Laryngoscopy

15% of the patients (n=35) showed laryngeal involvement (*e.g.* redness and swelling) and in 7% a subglottic stenosis (n=17) was found. Noticeable was that subglottic / tracheal stenosis showed in 8% (n=146) and laryngeal involvement in 5% (n=105) of the consultations.

Statistical analysis

The statistical analysis by Kendall's tau (2-tailed) showed a significant correlation between cumulative ENTAS activity and DEI (p=-0.113; p<0.05). No statistical significant correlation could be detected between ENTAS and ANCA status by Kendalls tau correlation (p=0.061).

Table II. Radiological results of the sinuses in CT/MR scans, total of 104 scans.

	Maxillary sinus	Ethmoidal sinus	Sphenoidal sinus	Frontal sinus
Mucosal thickening	35	24	13	16
Bony erosion / destruction	21	12	7	3
Air-fluid-level	14	6	4	12
Sclerosing osteitis	3	1	1	1
Bony thickening	7	1	3	1
Granulomas	17	20	18	7

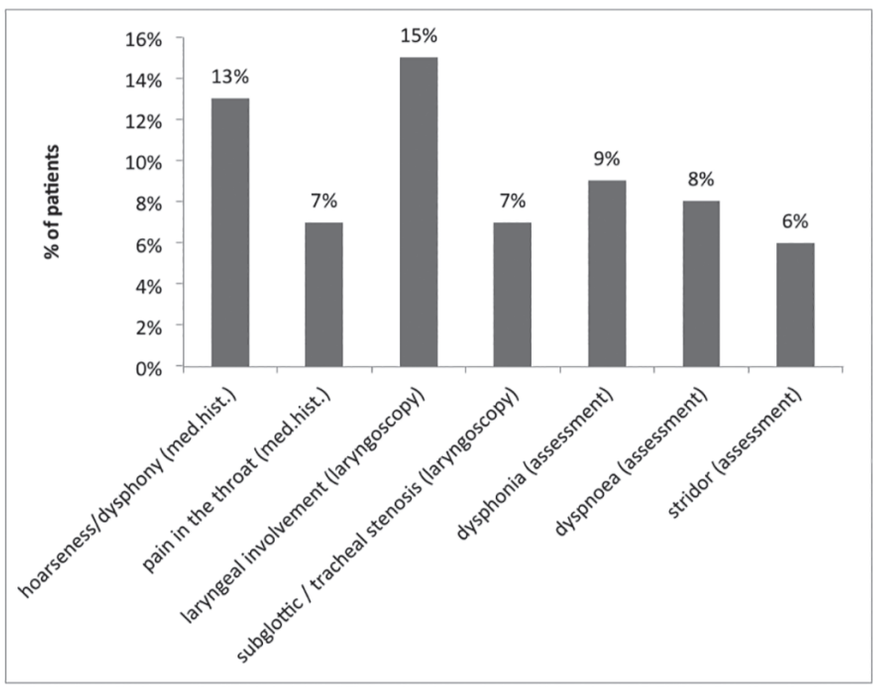

Fig. 4. Manifestation larynx. med. hist.: medical history.

Discussion

Granulomatosis with polyangiitis belongs to the ANCA-associated small to medium sized-vessel-vasculitides. It is an autoimmune disease with probably neutrophil granulocytes as the key mediators. By activation the contents of the neutrophil granulocytes damage endothelial cells and lead to the formation of granulomas (14, 15). With an equal gender distribution of roughly 1:1 and an average of 52 years at diagnosis, this study is consistent with the data shown in previous studies (16-18). Collaboration with the vasculitis pathology reference laboratory and examination of multiple biopsies might be the explanation for the high rate of histological proven GPA.

A subjective hearing loss was detected in 36% of the patients. In 23% of the patients a hearing loss could be demonstrated by audiograms. Compared to epidemiological data, based on WHO classification, the prevalence of hearing loss in this study is higher (19). The occurrence of dizziness and hearing loss in about 20% of patients supports the hypothesis of a possibly predominant sensorineural damage.

Furthermore, by history and otoscopy an inflammation of the middle ear was diagnosed in about one third of the examined patients. A median of middle ear pressure of -27,92 daPa represents no relevant alteration. In addition to these findings, just in 4% of the patients (4 of 104 scans) an opacification in the middle ear was detected by CT or MR scan. In contrast, the mastoid showed an opacification in 46% of the patients (in 45 scans). Opacifications of the middle ear were only seen in cases with an opacification of the mastoid. There are only case reports available analysing radiological changes to the ear and the mastoid in GPA patients. MRI-studies of otologically unaffected patients showed a one- or dual-sided opacity in 19–27% (20) which indicates, that the opacity in the mastoid of the GPA study population is high.

Approximately 90% of the patients included in this study showed clinical evidence of a nasal manifestation of GPA demonstrating the relevance of the ENT region and especially the nose for the assessment of this disease. As suggested by the gathered data this affects the structural integrity and the function (ability to breathe as documented by the rhinomanometric data; sense of smell tested by validated olfactory tests; barrier function demonstrated by regular mucosal affection detected via rhinoscopy) of the upper airway tract. While the autoimmune inflammation processes are the root cause of these impairments, the colonisation of the disturbed mucosa with bacteria such as *Staphylococcus aureus* may subsequently lead to further inflammation (21).

Many patients present symptoms overlapping with chronic rhinosinusitis (CRS) (suffering from two or more symptoms longer than 12 weeks: nasal blockage/obstruction/congestion or nasal discharge, facial pain or pressure, reduction or loss of smell) (22). The main difference in treatment of GPA and CRS is the use of antibiotics and steroids in CRS and a complex immunotherapy-scheme in GPA due to the presumably different pathways of inflammation.

GPA and CRS also share basic findings in the radiological diagnostics (mainly (partial) blocking of paranasal sinuses and mucosal swelling). The Lund-Mackay score (23) for CRS (24) was successfully adopted for GPA in this study as well as for EGPA (25). Compared to EGPA the GPA findings were

lower (GPA 3.9 *vs*. EGPA 8.8). However, the full extent of destruction in GPA patients shown in the scans are more diverse in the whole ENT-region. Over 50% of the patients suffered from dysosmia with well known social-economical restrictions (26). Nasal inflammation and obstruction of the airway – as seen in the majority of patients suffering from GPA – are likely to be contributing to dysosmia in ENT patients (26-28).

The disease burden of a reduced ability to breathe through the nose is demonstrated by the severely reduced air flow in 18% of the patients, comparable to patients with chronic nasal obstruction (29). Compared to previously reported data, the number of patients with nasal crusting and mucosal granulation in this study appear to be higher (nasal crusting: 67% *vs*. 16-36%; mucosal granulation: 27% *vs*. 10%), while sinusitis were found to be lower (10% *vs*. 63%) (16, 30-32). The most striking difference between this study and other studies is presumably the underlying data. While most studies collected data from single point visits, this analysis is based on multiple longitudinal examinations - defined rather by a standardised visit-protocol than a visit based on an increase of ailment.

The sinuses showed radiologically a more pronounced involvement than in endoscopy as suggested by other studies (31). This difference may be simply due to the inability to view sinuses endoscopically. The Lund-Mackay score was similar to other studies (33). In histopathologically and serologically inconclusive patients the shown radiological changes in the ENT region may support a clinical diagnosis of GPA (34).

Compared to patients in ENT-treatment seen in outpatient centres - based on ICD-10 statistics - epistaxis (6% GPA; 2.2% outpatient centres) and polyps (3% GPA; 1.8% outpatient centres) as well as rhinorrhoea (8% GPA; 7.3% outpatient centres) have been diagnosed in more consultations in GPA patients. In addition, inflammatory processes of the larynx are also diagnosed more often (5% GPA; 2.1% outpatient centres) (35).

GPA has a higher and more diverse manifestation in the ENT-region than MPA and EGPA. In comparison the GPA findings with the highest incidences to similar EGPA findings nasal crusts (67% GPA; EGPA 8%) are more frequent and data for hearing loss (23% GPA; 21 - 50% EGPA) vary in frequency in EGPA depending on the study (25;36-38). The study with the largest cohort (n=95) showed slightly less frequent hearing loss in 21% of the patients. Laryngeal involvement is a unique manifestation in GPA which is not seen in EGPA and MPA. Although the laryngeal manifestation was not particularly prominent in the examined cohort for this study as well as in the literature, the high number of consultations per patient suggest a higher impact of symptoms in these patients (39).

Although data analysis was cumulative the dependency of DEI and cumulative ENTAS demonstrate a possible interaction of systemic and local disease activity. Otherwise it was not possible to detect a statistically significant correlation of cumulative ANCA status and ENTAS. Future detailed analysis of the disease course has to define the role of systemic and local disease activity in GPA.

Although GPA is an ANCA-associated disease, a number of patients do not show an ANCA-positive serology and / or positive histology in biopsy (36). We suggest the optimal clinical workup for diagnosis in patients with suspected GPA is repeated clinical (ENT-)examination preferably in specialised centers, biopsy and serology especially if the tests are negative at first. Multiple biopsies and examination in vasculitis pathology reference laboratories as well as imaging by CT and MRI (34) may facilitate in suspicious cases. A systematic ENT-examination of all indistinct patients may be an essential way to reduce delays in diagnosis experienced by many patients and follow-up examinations may help predict disease courses (40-42).

To prevent complications and minimise long-term damage from GPA, patients suffering from this disease should be seen regularly in an interdisciplinary follow up. Although surgical therapy to restore form and function can be required at some time, the main focus should be adjusting the immunomodulating therapy according to clinical and serologic findings. As a consequence of improved drug therapy, GPA is no longer considered to be a life-threatening disease. A symptomatic therapy should be considered as an addition to the immunotherapy but there is no definite guideline how and when this should be done (43).

The main strength of this study is its uniform, comprehensive and interdisciplinary approach; its main limitation is the retrospective character.

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We would like to acknowledge the work of Julia Holle and Frank Moosig as the main rheumatologists of the presented GPA patients.

Declaration of Helsinki

Our study complies with the Declaration of Helsinki. The locally appointed ethics committee has approved the research protocol and informed consent has been obtained from the subjects (or their legally authorised representative).

Key messages

1. ENT-examination of all indistinct patients may be an essential way to reduce delays in diagnosis.
2. Patients suffering from GPA should be seen regularly in an interdisciplinary follow up.

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