Manifestation of eosinophilic granulomatosis with polyangiitis in head and neck*

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Abstract

Introduction: Besides an obvious clinical involvement of the ear, nose and throat (ENT)-region in Eosinophilic Granulomatosis with Polyangiitis (EGPA), systematic data is sparse. Only a few case series and case reports are available that particularly describe rhinological, otological or other manifestations of EGPA in the ENT-region. Therefore, the objective of this study is to systematically describe data on ENT-region involvement in a large series of EGPA patients.

Method: EGPA patients examined in the Department of Otorhinolaryngology of the Christian-Albrechts-University of Kiel between 1990 and 2010 were included in the study. Criteria for ENT-manifestation were assigned to five subgroups (history, ENT examination, audiological and rhinological diagnostic findings and cranial MRI) and documented cumulatively. EGPA patients were examined in a standardized way based on the validated Ear Nose and Throat Activity Score (ENTAS) or its precursor, including audiological and rhinological diagnostic findings. MRI scans were analysed to further evaluate ENT involvement.

Results: A total of 95 EGPA patients were included in the study. In approximately 80% of them, ENT-involvement was documented and the assumption of a frequent rhinological manifestation in patients with EGPA was confirmed. Moreover, the data reveals remarkable evidence for an otological manifestation. A missing correlation between the rhinological and the otological manifestation indicates an independent autoimmune-inflammatory process for this manifestation.

Conclusion: The data of the largest monocentric study presented here confirms the hypothesis of a frequent ENT involvement in EGPA patients, in whom rhinological and otological manifestations are most common. Therefore, treatment should include long term follow-up and should be managed interdisciplinary.

Key words: EGPA, ENT, eosinophilic granulomatosis with polyangiitis, Churg-Strauss syndrome, head and neck

Introduction

The Antineutrophil Cytoplasmatic Antibody (ANCA)-associated small-vessel vasculitis Eosinophilic Granulomatosis with Polyangiitis (EGPA, Churg-Strauss syndrome) is a rare autoimmune disease of unknown aetiology. EGPA was first described as "allergic angiitis and allergic granulomatosis" in 1951 by Churg and Strauss [1,2]. Besides the appearance of blood and tissue eosinophilia, eosinophil-rich broncho-alveolar infiltrates and asthma, the head and neck region seems to be involved regularly [3-14]. In 1984, Lanham et al. described 3 phases. The 1st phase (prodromal phase) is characterized by asthma, frequently allergic rhinitis and recurring rhinosinusitis with nasal polyps. This phase may persist for many years. In the 2nd phase, peripheral blood eosinophilia and eosinophilic tissue infiltrates occur and may persist for years, until finally the life-threatening 3rd phase (vasculitic phase) affecting extrapulmonary organs is reached [8,15].

The occurrence of vasculitic manifestations in a patient with known allergic rhinitis, chronic rhinosinusitis with polyps and late-onset asthma is pathognomonic [2].

Besides the above mentioned clinical obvious involvement of the ear, nose and throat (ENT)-region, EGPA scoring systems relying on expert consensus emphasizing such involvement. Surprisingly only a few case series and case reports are available, that particularly describe rhinological, otological or other manifestations [6,15-23].

Therefore, the objective of this study is to describe the ENT-region involvement in EGPA.

Patients and methods

Study design and population

EGPA patients seen in the Department of Otorhinolaryngology of the Christian-Albrechts-University of Kiel between 1990 and 2010 were included in the study. The ENT examination is a fundamental part of the clinical work within the interdisciplinary vasculitis referral center as described elsewhere [24].
Vasculitis was diagnosed histologically or by clinical surrogate parameters. In addition 4 of the 6 ACR-classification criteria had to be fulfilled [25].

Development of the data collection table

Criteria for ENT-manifestation were primarily defined using the ENT Activity Score (ENTAS), a validated ENT examination method for vasculitis, results of literature research and criteria of established indices as well as definitions [26]. Finally, ENT-manifestations becoming apparent during chart examination were included. The criteria were assigned to five subgroups (history, ENT examination, audiological diagnostic, rhinological diagnostic and radiology).

Data collection

EGPA-patients were examined in a standardized process based on the validated ENTAS or its precursor [26]. In addition, the available MRI data (indication: suspected CNS-involvement) was analysed with respect to the sinuses and the temporal bone. Frequent conspicuous data were further analysed.

Audiology

The WHO hearing level was determined for the better hearing ear [27,28]. Additionally, the audiological data was compared to the age and sex-specific standardized data of the DIN EN ISO 7029:2000 for otologically normal people [29].
To avoid an overrepresentation of patients with more than one measurement, the average of the air conduction data from both ears was determined. To analyse the influence of a possible conductive hearing loss, the difference between air and bone conduction was calculated and tympanograms were analysed. In each MRI, opacification in the middle ear and mastoid on both sides were evaluated by an experienced investigator (MB).

Rhinology

The olfactory function was tested by the "Sniffin´Sticks Screening 12" test [30]. The objective ability to breathe through the nose was evaluated by active anterior rhinomanometry before and after decongestion. A flow of < 300 ml/s (cm^3/s) at 150 Pa was defined as a severe obstruction and a flow ≥ 300 ml/s (cm^3/s) at 150 Pa was classified as a mild or no obstruction [device specific standard values and validated grading [31]].
Since patients had multiple measurements with fluctuating results, patients were subdivided into different levels of obstruction (Level A: patients with exclusively <300 ml/s results, Level C: patients with thresholds ≥300ml/s results and Level B for those patients with variable results).
A modified (omitting the ostiomeatal complex because of low reproducibility in MRI) Lund-Mackay-score was used for the evaluation of MRI scans of the sinuses [32-37].
In addition, the existence or absence of a fluid level in the maxillary sinus was evaluated and the thickness of the mucosa of all sinuses was measured to distinguish acute and chronic inflammation [38,39].

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences, Version 20) and MS Excel (Microsoft Office XP, Version 2003 + 2007).
The existence of any association between signs of an inflammatory process [defined as rhinosinusitis according to the clinical definition of rhinosinusitis by the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 [40]] of the nasal mucosa and a hearing loss based on the WHO classification (hypothesis I) was analysed. Furthermore, an opacification in the MRI of the mastoid and/ or the middle ear (hypothesis II) was analysed with respect to said inflammatory process of the nasal mucosa. To avoid the influence of multiple examinations, only data of the first examination was used.

Results

Patient characteristics

In this study, 95 patients were included (46 women [48%] and 49 men [52%]). There were a total of 295 consultations with each patient having anywhere from 1 to 26 consultations. The average age at diagnosis was 51 years (range: 16-75) and the age at first manifestation was on average 46 years (range: 15-72).

The average Birmingham Vasculitis Activity Score (BVASV3) was 5 (range: 0 - 25; SD = 5.95). The average Vasculitis Damage Index (VDI) was 2 (range: 0 - 11; SD = 2.36).

In 33% (n = 31) of the patients, ANCA were detected (4%, n = 4, C-ANCA and 28%, n = 27 P-ANCA) with 1% (n = 1) anti-PR3 and

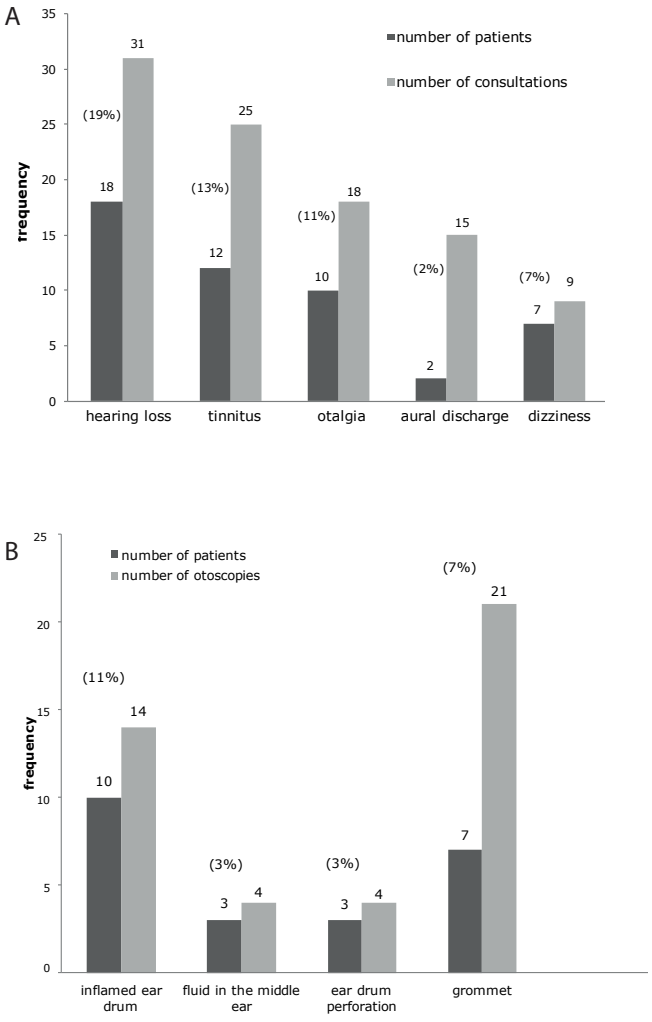

Figure 1. A) Positive history for hearing loss, tinnitus, otalgia, aural discharge and dizziness (95 patients with 295 consultations). B) Positive findings for inflamed ear drum, fluid in the middle ear, ear drum perforation and grommet (95 patients with 295 otoscopies).

25% (n = 24) anti-MPO specificity. The average prednisolone dosage was 11 mg (range 0 - 29, SD 5.57 mg). Further, patients received a variance of different immune modulatory medication (cyclophosphamide, methotrexate, azathioprine, interferon, leflunomide, mycophenolatmofetil, mycophenolatnatrium, cyclosporin A, rituximab, infliximab, etanercept, adalimumab).

Otological manifestation

Medical history

Patients reported subjective hearing loss in 19% (n = 18). Thirteen percent of the patients (n = 12) complained about tinnitus and 11% about otalgia (n = 10). Two percent of the patients (n = 2) suffered from aural discharge and 7% (n = 7) from dizziness (Figure 1a).

Table 1. Level of hearing loss based on the WHO classification for the better hearing ear (209 pure tone audiometries of 89 patients; multiple entries).

Level of hearing loss	ISO-data	number of patients	number of measure-ments	
Level 0	(≤ 25 dB)	80	173	
Level 1	(26 - 40 dB)	15	27	equates 19 patients => 21% of n = 89
Level 2	(41 - 60 dB)	5	5	
Level 3	(61 - 80 dB)	1	4	
Level 4	(≥ 81 dB)	0	0	

Otoscopy

An inflamed eardrum was documented in 11% of the patients (n = 10). In 3% of the patients (n = 3), fluid in the middle ear and ear drum perforation was detected. Additionally in 7% of the patients (n = 7), grommets could be identified (Figure1b).

Audiology

For the evaluation of hearing ability, pure tone audiograms were conducted for 89 patients, 209 for the right ear (1 - 9 audiogramms per patient) and 218 for the left ear (1 - 12 audiogramms per patient). For each pure tone audiogram available for both sides, the level of hearing loss was evaluated based on the WHO classification [27,28] (Table 1).

Hearing loss was diagnosed in 21% of the patients (n = 19 of 89, multiple entry due to multiple examinations: slight impairment in 17% of the patients [n = 15 of 89], moderate impairment in 6% [n = 5 of 89] and severe impairment in 1% of the patients [n = 1 of 89]).

Furthermore, data of sound conduction of both ears between 0.125 - 8 kHz was compared to data of DIN EN ISO 7029:2000 [29] (Figure 2). On the left side, a divergence from the norm with a minimum of 7 dB at 1 kHz and a maximum of 11 dB at 6 kHz was detected. Similarly on the right side, a minimum of 8 dB at 3 kHz and a maximum of 13 dB at 6 kHz was assessed.

Figure 3 shows the difference between sound and bone conduction for both ears between 0.25 - 6 kHz. On the left ear, there is a minimum difference of 5 dB at 2 kHz and a maximum of 10 dB at 6 kHz. Similarly, a minimum difference of 5 dB at 2 kHz and a maximum difference of 10 dB at 0.25 kHz were detected on the right side.

Corresponding tympanograms of 86 patients (205 right and 203 left side [range right: 1-9 tympanograms per patient; left: 1-10 tympanograms per patient]) were analysed. The median

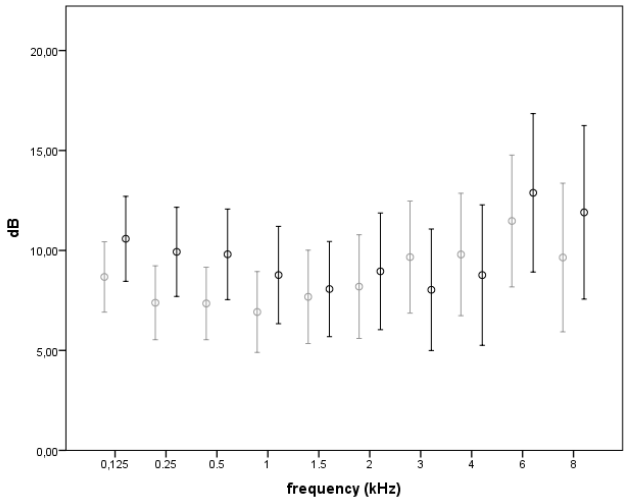

Figure 2. Average and 95% confidence interval of the divergence of the hearing threshold level from the age and sex-specific norm data (DIN EN ISO 7029:2000) for both ears between 0.125-8 kHz. (grey: left ear, 218 audiograms; black: right ear, 209 audiograms).

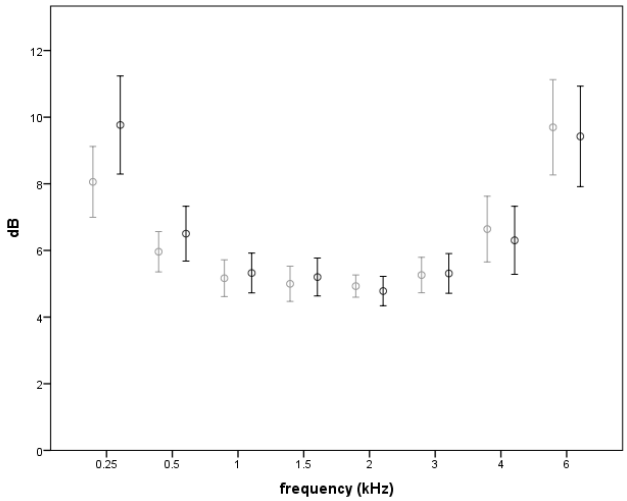

Figure 3. Average and 95% confidence interval of the difference between the sound conduction and the bone conduction for both ears between 0.25-6 kHz (n=89) (grey: left ear, 218 audiograms; black: right ear, 209 audiograms).

compliance on the right side was 0.8 ml (average: 1.0 ml; upper quartile: 1.2 ml; lower quartile: 0.5 ml) and on the left side 0.8 ml (average: 1.0 ml; upper quartile: 1.4 ml; lower quartile: 0.6 ml). A median of 10 daPa (average: 22 daPa; upper quartile: 22 daPa; lower quartile: 5 daPa) on the right and 11 daPa (average: 28 daPa; upper quartile: 26 daPa; lower quartile: 5 daPa) on the left ear was documented for middle ear pressure.

Radiological results of the temporal bone

Thirty nine patients had 56 MRI's of the head including the temporal bone. An opacification in the middle ear was detected in 13% of the patients (n = 5). The assessment of the mastoid has shown an opacification in 49% of the patients (n = 19, Table 2).

Rhinological manifestation

Table 2. Level of opacification of the middle ear and mastoid in the MRI of the temporal bone of both sides.

		no opacification	opacification	
Right middle ear	Number of MRIs	47	9	
	number of patients (multiple entries)	35	5	
	total number of patients with a shadow		**5 (13% of n = 39 patients)**	
Left middle ear	Number of MRIs	51	5	
	number of patients (multiple entries)	37	2	
	total number of patients with a shadow		**2 (5% of n = 39 patients)**	
		no opacification	**partial opacification**	**total opacification**
Right mastoid	number of MRIs	32	19	5
	number of patients (multiple entries)	23	15	5
	total number of patients with a shadow		**18 (46% of n = 39 patients)**	
Left mastoid	number of MRIs	39	11	6
	number of patients (multiple entries)	30	10	3
	total number of patients with a shadow		**13 (33% of n = 39 patients)**	

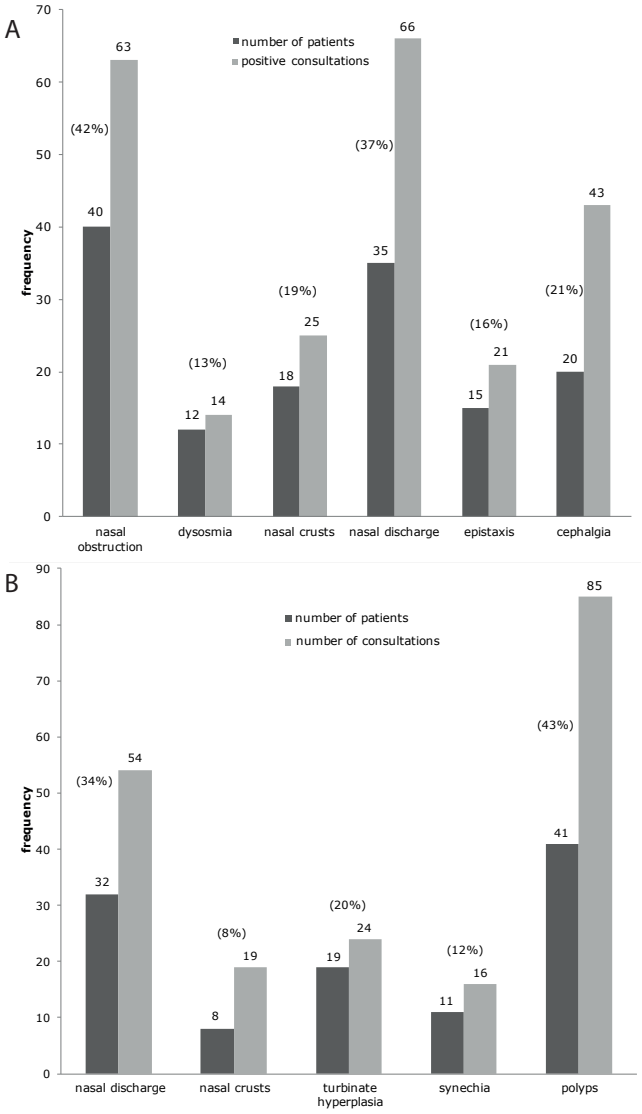

Figure 4. A) Positive history for nasal obstruction, dysosmia, nasal discharge, epistaxis and cephalgia (95 patients with 295 consultations). B) Positive findings for nasal discharge, nasal crusts, turbinate hyperplasia, synechia and polyps (95 patients with 295 rhinoscopies).

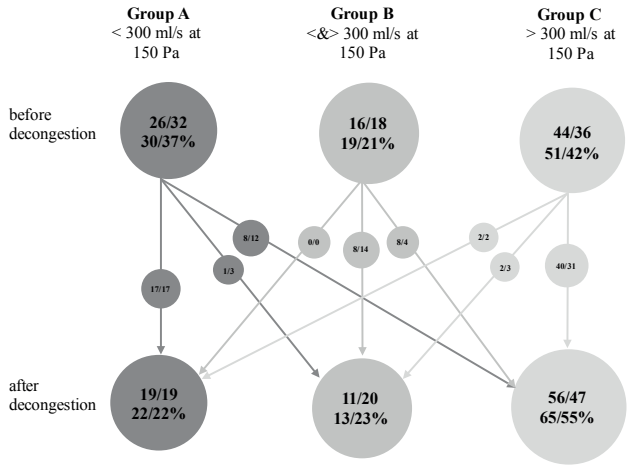

Figure 5. Level of nasal obstruction in the rhinomanometry of the right/left side before and after decongestion by Xylometazolin 0.1% (86 patients with 178 rhinomanometries).

Medical history

Forty two percent of the patients (n = 40) complained about nasal obstruction. A dysosmia was reported in 13% of the patients (n = 12). Nasal crusts were complained about by 19% of the patients (n = 18) and nasal discharge by 37% of the patients (n = 35). Epistaxis was reported by 16% of the patients (n = 15) and 21% (n = 20) complained about cephalgia (Figure 4a). Both history and rhinoscopic information suggested past surgery of the nose in 43% of the patients (n = 41). Thirty seven percent of the patients (n = 35) had sinus surgeries, 8% (n = 8) had polypectomies and a septumplasty was done in 6% of the patients (n = 6).

Rhinoscopy

The appearance of nasal discharge was documented in 34% of the patients (n = 32). Nasal crusts were seen in 8% of the patients (n = 8), a hyperplasia of the turbinates in 20% of the patients (n = 19) and synechia in 12% of the patients (n = 11). Polyps could be demonstrated in 43% of the patients (n = 41, Figure 4b). Forty percent of the patients (n = 38) showed changes of the nasal mucosa like swelling/edema, irritation and vulnerability. A swollen, edematous mucosa was seen in 12% of the patients (n = 11).

Olfactory test

The olfactory system was analysed using the results of 118 Sniffin' sticks-tests (1 - 5 tests per patient) of 65% of the patients (n = 62 of 95). In 79% of the patients (n = 49) a normosmia, in 11% of the patients (n = 7) a hyposmia and in 29% of the patients (n = 18) anosmia was observed. Dysosmia was observed in 40% of the tested patients (n = 25).

Rhinomanometry

One hundred seventy eight rhinomanometries of 86 patients were evaluated. A severe obstruction (group A) before decongestion was detected in about 30% of the patients (right side 30%, n = 26 and left side 37%, n = 32). On the other hand, approximately 50% of the patients (right side 51%, n = 44 and left side 42%, n = 36) had little to no obstruction (group C). In about 20% of the patients (right side 19%, n = 16 and left side 21%, n = 18), varying results were observed over time (group B).
After decongestion of the nasal mucosa, in more than 50% of the patients of group A (right side 65 %, n = 17 of 26 and left side 53%, n = 17 of 32) still a severe obstruction was detected. However, almost all patients of group C (right side 91%, n = 40 of 44 and left side 86%, n = 31 of 36) stayed above 300 ml/s. Twenty to 50% of the patients of group B switched to group C

Table 3. Level of mucosa thickness of the sinuses.

Sinus	no mucosa swelling	≤ 3 mm	>3 mm
maxillaris right	7 (12.5%)	18 (32.1%)	31 (55.4%)
maxillaris left	10 (17.9%)	18 (32.1%)	28 (50%)
ant. ethmoidalis right	1 (1.8%)	25 (44.6%)	30 (53.6%)
ant. ethmoidalis left	3 (5.4%)	24 (42.9%)	29 (51.8%)
post. ethmoidalis right	12 (21.4%)	28 (50%)	16 (28.6%)
post. ethmoidalis left	13 (23.2%)	22 (39.3%)	21 (37.5%)
sphenoidalis right	22 (39.3%)	24 (42.9%)	10 (17.9%)
sphenoidalis left	19 (33.9%)	22 (39.3%)	15 (26.8%)
frontalis right	22 (39.3%)	26 (46.4%)	8 (14.3%)
frontalis left	25 (44.6%)	22 (39.3%)	9 (16.1%)

(right side 50%, n = 8 of 16 and left side 22%, n = 4 of 18) the other showed no shift after decongestion (right side 50%, n = 8 of 16 and left side 78%, n = 14 of 18, Figure 5).

Analyzing both sides together, 15% of the patients (n = 13) showed a severely obstructed nose (group A) in all measurements. After decongestion, 8% of the patients (n = 7) kept a severe both-sided nasal obstruction. However, 31% of the patients (n = 27) showed data above 300 ml/s on both sides before decongestion. After decongestion the remaining patients made up 27% (n = 23).

Radiological results of the sinuses

In total, 56 MRIs of the sinuses of 39 patients (range: 1 - 4) were evaluated. Excluding the ostiomeatal complex, the average of the Lund-Mackay-score was 8.84 (range: 1 - 16, SD: 3.460).

In the MRIs of two patients (4%, n = 2), air fluid levels were documented in the maxillary sinuses. A thickened mucosa of > 3 mm was detected in the maxillary and anterior ethmoid sinuses in ≥ 50% of MRIs. Moreover, thickened mucosa of >3mm was also detected in about 15% in the frontal sinuses, in 33% in the posterior ethmoid sinuses and in 20% in the sphenoid sinuses (Table 3).

Statistical analysis of hypotheses I and II

The statistical analysis by the chi-square-test demonstrated no association between the attributes of an inflamed nasal mucosa and the existence or the absence of a hearing loss according to the WHO classification (hypothesis I). Additionally, it can be concluded that there is no association between an inflamed nasal mucosa and an opacification in the MRI of the mastoid and/ or middle ear (hypothesis II).

Discussion

Together with Granulomatosis with Polyangiitis (GPA, Wegener´s) and microscopic polyangiitis (MPA), EGPA belongs to the ANCA-associated small-vessel-vasculitides.

Eosinophils are considered as key mediators. They damage tissue by releasing their toxic granule constituents and are involved in the modulation of the immune response. While the pathogenetic role of anti-neutrophil cytoplasmic antibodies (ANCA) is still uncertain, B-cells seem to activate T-cells, which secrete IL5, the main survival factor for eosinophils [3,14,41].

The gender distribution with a ratio of 1:1 and the mean age of 51 years at diagnosis confirm the data of previous studies [3,16].

With the mean BVASV3 of 5 a low activity of vasculitis was documented in the cohort. This is similar to a low damage documented by the mean VDI of 2.

As a major symptom, a subjective hearing loss was detected in 19% of the patients and corresponding results could be demonstrated by audiograms [27-29].

Compared to epidemiological data, based on WHO classification, the results presented are above the reported prevalence of hearing loss[42].

A few case reports have indicated an otological manifestation of EGPA [uni- or bilateral conductive hearing loss, a sensorineural hearing loss or a combination of both [15,17-19,21,22]].

Regarding a conductive hearing loss, both the results of the pure tone audiogram and the results of the tympanograms do not indicate a higher conductive component. Furthermore, there was no statistical association between an inflamed nasal mucosa and a hearing loss with respect to a secondarily induced serous otitis media (hypothesis I) as described for GPA [43,44].

The occurrence of tinnitus and dizziness in about 10% of patients support the hypothesis of a mostly sensorineural damage. The cause of an involvement of the inner ear/central nervous system as a complication of a vasculitis is yet to be sufficiently investigated [43]. However, 6-10% of EGPA patients show a CNS involvement, in which palsies of central nerves are described [3,5,8,45-48]. In addition to a secondary labyrinthitis, a vasculitis of the Aa. labyrinthi or its branches including necrotizing granuloma could also lead to neuronal or local damages causing a sensorineural hearing loss [18].

Ishiyama and Canalis as well as Bacciu et al. described an improvement of the otological symptoms after immunosuppressive therapy supporting the hypothesis of a damage by vasculitis [15,18].

Furthermore, the history and the otoscopic data suggest an inflammation of the middle ear for a small percentage of patients. In relation to this, an increased opacity of the mastoid was pro-

minently observed. MRI-studies show one or dual-sided opacity of the mastoid in 19-27% in otologically unaffected patients [49]. Based on this data, the occurrence of a hyperintens signal in the mastoid of the EGPA study population seems to be high. This could possibly be a sign of an autoimmune inflamed process, especially because there is no significant correlation between the rhinological results and the results of the MRIs (hypothesis II).
According to the definition of rhinosinusitis in the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012 for epidemiological studies [40], a high percentage of EGPA patients of this study are suffering chronic rhinosinusitis with well-known individual and health economic consequences.
The supporting history (cephalgia, nasal crusts, dysosmia and epistaxis, nasal obstruction and nasal discharge) was confirmed by rhinoscopic data (polyps, nasal discharge, turbinate hyperplasia, nasal crusts, synechia and further symptoms) and almost half of the patients (43%) underwent one or more surgical procedures on the nose and/or nasal sinus.
In a small case series 59% of EGPA patients were suffering from polyposis nasi at the time of diagnosis, 24% of them had sinunasal surgery with early recurrence of symptoms [16].
In comparison to this data chronic rhinosinusitis affects about 5-15% of the general population. The prevalence of nasal polyps is less than 5% [40].
History and rhinomanometric data showed a severe nasal obstruction in about one third of all patients and in 40% of the examined patients a dysosmia (general population: up to 20%) was detected [50-52]. Dysosmia as a result of rhinosinusitis with polyps is described as sinunasal dysosmia and caused by a combination of conductive and inflammable reasons [53].
Mediators also detected in EGPA (e.g. IL5) seem to directly influence the olfactory mucosa or possibly the neural system, while detailed knowledge of the pathomechanism is missing [53-55].
The frequent occurrence of structural nasal obstruction seems to support the hypothesis of a conductive olfactory disorder in EGPA. However, it is known that even in the healthy population, only a small portion of inhaled air reaches the olfactory epithelium (approximately 15%). Damm et al. could only show a positive correlation between the results of the rhinomanometry and the olfactory abilities for a severe nasal obstruction [56,57].
Interestingly, there are noticeably fewer patients (13%) with a positive history of dysosmia compared to the results of the olfactory test. However, it is known that especially patients who are suffering from chronic rhinosinusitis do not complain about a dysosmia although it is detected in olfactory tests [58].

Compared to previously reported data, the number of patients with nasal crusting and epistaxis in this study appear to be lower (epistaxis: 16% vs. 60%; nasal crusting: 19% vs. 75%). Patient selection might influence these differing results (consecutive patients of a tertiary referral center versus a highly motivated and skilled patient support group). In addition, nasal crusting and epistaxis was confirmed by endoscopy in less than 10% of patients. The difference from the previous study might be explained by the fact that in the presented study only data from examination days is considered whereas the earlier stated study presents patient history based on patient surveys (point versus cumulative longitudinal examination) [23]. The average of the Lund-Mackay-score of all MRI scans yields 9. However, the total score would most likely be higher if the omitted analysis of the ostiomeatal complex is also considered.
Even for patients without any clinical sign of rhinosinusitis, it is known that the Lund-Mackay-score is not zero [59]. Accordingly, an average Lund-Mackay-score of 4 was found in a group of patients without clinical signs of rhinosinusitis [60]. Hence a score of 9, as shown in this study, is valued as pathological. Furthermore a chronic inflammatory process of the sinus is likely since a thickened mucosa was detected in up to 50% of the examined patients.

The presented data of the largest monocentric study confirms the hypothesis of a high (approximately 80%) percentage of ENT-region involvement in EGPA-patients. In addition the rhinological manifestation is possibly an important factor in the initial phase of the disease [3,8,11-13,15,20].
To prevent complications and permanent damage from EGPA, this frequently occurring manifestation should be identified at an early stage. The long-term follow-ups should be managed interdisciplinary. Since the autoimmune inflammatory process itself seems to be a cause for the otological and rhinological manifestations, adjusting immunomodulating therapy should be the initial focus.
Today, EGPA is considered a chronic relapsing disease and life threatening manifestations can usually be prevented. Therefore therapeutic decisions have to increasingly include aspects of quality of life.
Hence, in addition to an accurate immunotherapy, a symptomatic therapy is of particular importance. Due to the lack of data for EGPA patients, the current symptomatic therapy should be based on the existing national and international guidelines [40]. Surgical interventions are primarily reserved for severe or acute complications [18]. Rehabilitation of functionality should be achieved to minimize the burden of EGPA.
The strength of this study is its uniform, interdisciplinary diagnostic approach. However, there are limitations based on the retrospective character and the small sample size.

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Author contributions

HP: conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of manuscript, final approval; PG: conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of manuscript, final approval; MB: conception and design, analysis and interpretation of data, critical revisal of manuscript, final approval; MH: analysis and interpretation of data, critical revisal of manuscript, final approval; PA: critical revisal of manuscript, final approval; JPB: analysis and interpretation of data, critical revisal of manuscript, final approval; JH: critical revisal of manuscript, final approval; FM: data acquisition, conception and design, analysis and interpretation of data, critical revisal of manuscript, final approval; ML: conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revisal of manuscript, final approval.

Conflict of interest

There is no conflicts of interest.

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