Intra- and inter-rater reliability of endonasal activity estimation in granulomatosis with polyangiitis (Wegener's)

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ABSTRACT

Objectives. *Granulomatosis with polyangiitis (GPA) frequently starts with an affection of the nasal and paranasal mucosa. Localised GPA of the nasal mucosa or persistent disease activity ("grumbling disease") is often encountered even under immunosuppressive therapy. Necessity for reconstructive surgery is common and careful scheduling to prevent failure and minimise revision rates is crucial. Therefore, reliable estimation of GPA activity in the upper airways using a score is mandatory for diagnosis, follow-up and scheduling reconstructive surgery.*

Patients and methods. *Fifty endoscopic, endonasal images of 45 patients with GPA were used. Twelve (4 German, 8 Mexican) experienced (n=7) and inexperienced (n=5) physicians assessed GPA-activity at two times (T1/T2) in dichotomy and in a grading approach (none, mild, moderate and high activity) using the novel ENT Activity Score (ENTAS). All documents were written in English.*

Results. *Estimation of activity in dichotomy (none vs. mild/moderate/high): Cohen's Kappa (κ) for intra-rater reliability T1/T2 in inexperienced and experienced physicians was κ=0.58 (agreement 85%) and κ=0.72 (agreement 91%). The interrater reliability (Fleiss's κ) T1/T2 for inexperienced and experienced physicians was κ=0.62/κ=0.59 and κ=0.50/κ=0.58 respectively. Estimation of activity in grading approach (none, mild, moderate, high): for inexperienced physicians the intra-rater reliability T1/T2 was κ=0.67 (agreement 56%) and the inter-rater reliability at T1/T2 was κ=0.29 (intraclass correlation coefficient, ICC=0.69) and κ=0.27 (ICC=0.59). For experienced physicians the intra-rater reliability T1/T2 was κ=0.80 (agreement 67%) and the inter-rater reliability at T1 and T2 was κ=0.41 (ICC=0.77) and κ=0.39 (ICC=0.75) respectively.*

Conclusion. *Intra-rater reliability is high in decision in dichotomy and even in grading activity. There is no difference for experienced or inexperienced physicians. Inter-rater reliability is high in dichotomy, but low for activity grading. Thus, the ENTAS provides a reliable instrument for assessing, documenting and following GPA-related disease activity in the upper respiratory tract. The relationship of activity and following damage needs to be investigated in further studies.*

Introduction

Granulomatosis with polyangiitis (GPA) is characterised by granulomatous inflammation predominantly affecting the upper respiratory tract and an autoimmune proteinase 3-specific anti-neutrophil cytoplasmic autoantibody (PR3-ANCA)-associated vasculitis preferentially affecting small renal and pulmonary vessels.

GPA first affects the nose and paranasal sinus, as was described by Klinger and Wegener in the 1930s (1, 2). In over 90% of the patients the upper respiratory tract is involved in the course of the disease and damage to the upper respiratory tract is one of the most common individual items used in vasculitis damage scores (3, 4). Persistent ENT-related disease activity (so-called "grumbling disease") is frequent even under immunosuppressive therapy. In addition, localised GPA (sole manifestation in the ENT-tract) is encountered in about 5% (5) of the cases and recent studies support the hypothesis of a nasal barrier dysfunction (6-10). Moreover, the upper airway can easily be investigated endoscopically and disease activity assessed. Diagnosis of granulomatosis and vasculitis is often

confirmed by nasal biopsy at the beginning of the disease (11).
Therefore, careful investigation of the mentioned region is mandatory for early and correct identification of this rare disease and a prerequisite for prompt therapy onset, which is necessary to prevent the known damage with destruction of bone and cartilage (Fig. 1).
Improvement in the survival of patients was made in the last decades by the introduction of immunosuppressive therapies (12). The individual adjustment of the therapy is based on continuous measurement of clinical disease activity (13) and other serological markers such as CRP. Unfortunately, serological parameters are not very reliable and, therefore, periodical clinical investigation in an interdisciplinary approach has shown to be important in order to detect grumbling disease, localised activity or relapse under therapy as soon as possible (14). Different scoring systems to assess activity in vasculitis had been introduced (Birmingham vasculitis activity score [BVAS], disease extent index [DEI] and vasculitis activity index [VAI] [15-17]), but undervalue activity in ENT (8).
Surgical rehabilitation (functional and aesthetic) is often desirable, especially in the face (Fig. 2) if immunosuppressive therapy was not able to prevent damage. Timing is critical because of higher rates of complications and failure of surgical procedures in active disease (18, 19). Therefore, careful tracking and reliable exclusion of active disease is mandatory before surgery.
A reliable score for the activity of GPA in the ENT-tract is essential to diagnose GPA early, track disease activity in the follow-up (under medication and in remission) and to define the time schedule for surgical rehabilitation. In this study the inter- and intra-rater reliability of a proposed novel endoscopic ENT-activity score (ENTAS, Fig. 3) for GPA was analysed at two separate timepoints (T1, T2) to define the suitability of the score in the mentioned context.

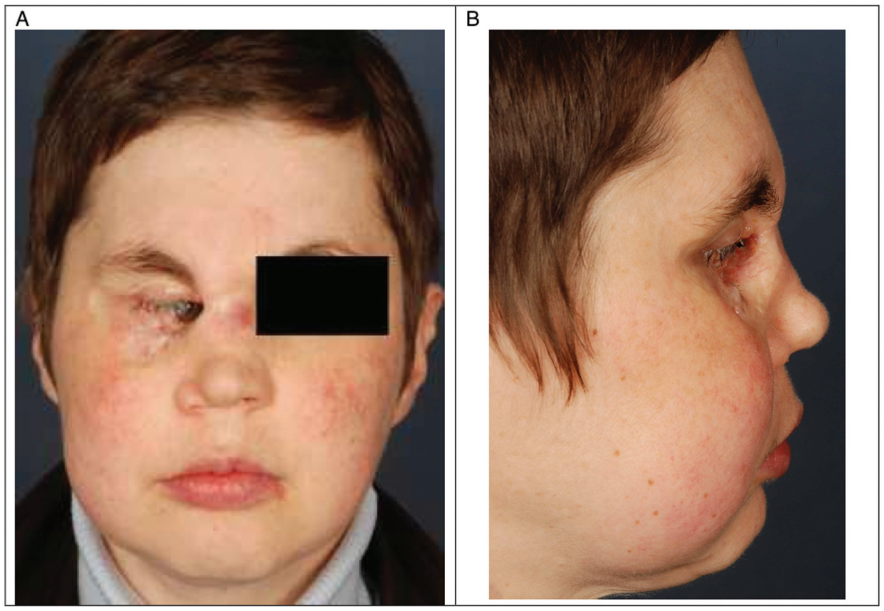


Fig. 1. Destruction of bone and cartilage, transdermal fistula to sinus ethmoidalis.

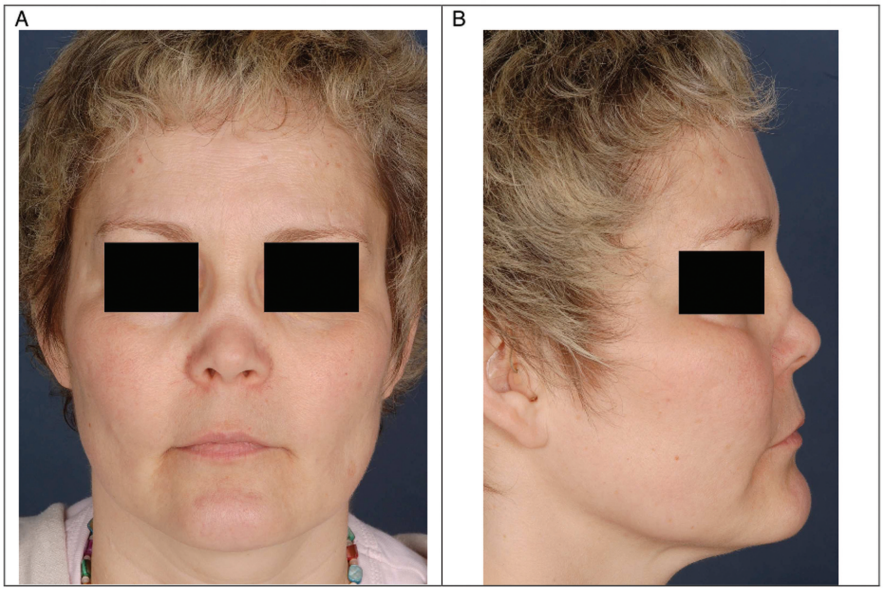


Fig. 2. Saddle nose deformity.

Patients and methods

This prospective study from 8/2009 till 12/2009 concentrates on images of the nasal cavity with varying endonasal activity of GPA defining the inter- and intra-rater reliability of the proposed score for ENT-activity in GPA in an intercontinental approach. Estimation of GPA activity in ENT was assessed by seven experienced (more than 30 GPA-patients examined before participating in the study, 3 German and 4 Mexican physicians) and five inexperienced (less than 30 GPA-patients examined, 1 German and 4 Mexican physicians) otorhinolaryngologists. All documents were written in English (instruction paper, sheets of images, ENTAS). All examiners repeated the evaluation of the images after 4 to 5 weeks (Mexico City, Mexico [T1=8/14/2009, T2= 9/9/2009] and Kiel, Germany [T1=11/12/2009, T2=12/17/2009]). The evaluation was controlled by two of the authors (A.H. and M.L.) and took place in conference rooms and in a private practice office.

Patient population

Fifty endoscopic, endonasal images of 45 patients with GPA (23 women, 22 men, age 21–79 years, mean age 56 years) were used.

ENT ACTIVITY SCORE (ENTAS)

Last Name
First Name
Date of Birth

If any question is answered positive, there is activitiy.

1.0 Activity **Diagnosis:**

1.1 Symptoms

Subjective complaints (new appearance or worsening; not explained by other conditions)

Pain

	yes	no
nose		
paranasal sinus		
headache		
oral cavity		
larynx/throat		
ear		

Functional impairment

	yes	no
nasal obstruction		
olfactory loss		
hypoacusis		
dizziness		
hoarseness		
dyspnea		

Secretion

	yes	no
otorrhea		
epistaxis		
rhinorrhea		

1.2 Physical Findings

Localisation	Clinical Findings
skin	( )absent ( )erythema ( )ulcers
nose	( )absent ( )bloody mucosa ( )oedema ( )ulcers ( )granulation ( )crusts
oral cavity/ oro-, epipharynx	( )absent ( )oedema ( )ulcers ( )granulation ( ) bloody mucosa
hypopharynx, larynx, trachea	( )absent ( )bloody mucosa ( )oedema ( )ulcers ( )granulation ( )stenosis
ear	( )absent ( )bloody mucosa ( )oedema ( )ulcers ( )granulation ( )stenosis ( )secretion ( )tympanic perforation

1.3 Other Findings

(cranial nerve palsy, ocular symptoms, lymph nodes, salivary glands etc)

1.4 Diagnostic Tests

	Diagnostic Findings#
audiometry	( ) normal ( ) CHL >10dB ( ) SHL* 20-40dB ( ) SHL*40-70dB ( ) SHL*>70dB
impedance	( ) normal ( ) effusion ( ) perforation
sniffin' sticks screening	
SDI test	
Rhinomanometry	nasal obstruction: ( ) absent ( ) mild ( ) moderate ( ) severe

 # new or worsened and not explained by other conditions (SHL sensorineural hearing loss; CHL conductive hearing loss), *at 1,2 or 3 kHz

Procedure/Suggestion:

Activity Grading

☐ None ☐ Mild
☐ Moderate ☐ High

2.0 Damage (considered to be caused by Vasculitis)

Septal perforation		Saddle nose		Synechia (endonasal)		Laryngeal/tracheal stenosis		Cranial nerve palsy	
Ocular symptoms		SHL		Cervical lymph nodes		Tympanic perforation		Olfactory distortion	

Date: Examiner: Supervisor:

Fig. 3. ENTAS (ENT-activity score).

Disease definition

All patients fulfilled the criteria of the Chapel Hill Consensus Conference and the American College of Rheumatology, as recommended by the European League Against Rheumatism (16). GPA was biopsy-proven in 30 of 45 patients (67%, 22 of 30 [73%] in nasal biopsies). Disease activity was measured using the BVAS and the DEI. The vasculitis damage index (VDI, [20]) was used to evaluate organ damage as a consequence of granulomatous inflammation and vasculitis. GPA-subgroups (localised, early systemic and generalised GPA), relapse and remission were diagnosed and defined according to the European League Against Rheumatism (EULAR) recommendations (16). As proposed by Paulsen and Rudert (21), all patients were subject to a standardised interdisciplinary evaluation and examined endoscopically by an ENT surgeon (14). Signs for systemic inflammation were assessed by the following parameters: the serum levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and white blood cell count (WBC, Table I). Thirty-eight patients received immunosuppressive medication in different combinations and dosages containing: cyclophosphamide, methotrexate, azathioprine, leflunomide, mycophenolate mofetil, rituximab and cyclosporine A. The mean cumulative cyclophosphamide dosage was 33.5g.

Instruction paper

In the instruction paper, background information on GPA and the general idea of the study were provided. Besides, four images were given to demonstrate the varieties and how to distinguish from no activity up to high activity (Fig. 4).

Questionnaire

Personal data, profession, country, place and date, knowledge of the English language, and level of experience were recorded (Fig. 5).

Fifty endonasal, endoscopic images were given in random order, varying from the first to the second evaluation. In a forced choice mode, examiners were asked to determine activity.

The instruction paper was not allowed to be used while answering the questionnaire.

Statistical analysis

Statistical analysis was performed with SPSS (version 17, SPSS Inc., Chicago, USA) and especially for the evaluation of reliability the package irr (22) within the R environment (23). Data were described as mean values, ± standard deviation (SD), maximum and minimum. Cohen's κ was used to evaluate intra-observer agreement for two evaluations (T1/T2). Fleiss's κ for multiple raters was used to measure inter-observer agreement for each evaluation T1 and T2, and the intraclass correlation coefficient (ICC) was used to measure both inter- and intra-observer agreement for the activity score (none, mild, moderate, high).

Results

Patient characteristics

Mean time from first diagnosis until

Table I. Patient characteristics.

	GPA (n=45)
Mean age in years (range, SD)	56 (21-79, 17)
Sex	23 female, 22 male
Biopsy proof of GPA	30 (67%)
Mean CRP in $mgdl^{-1}$ (range, SD)	1.4 (0–11, 2.2)
Mean ESR in mm after the first hour (range, SD)	36.6 (2–100, 30.1)
Mean WBC in nl^{-1} (range, SD)	8.5 (3.5–18.6, 2.9)

GPA: granulomatosis with polyangiitis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell count; SD: standard deviation.

study entry was 4 years (range 0–18, SD 5) and mean time from first manifestation of GPA until study entry was 6 years (range 0–26, SD 6).

The median C-ANCA level was 1:320 (range 1:40 to 1:5120) and in two patients P-ANCA was detected (1:2560 and 1:80).

According to the EULAR subgroup classification, nine patients were classified as early systemic, 30 generalised, one severe and two as refractory. Furthermore, activity was classified in remission in 12 patients, minor in nine, major in eight, refractory in two, low in seven and as response in four, referring to the EULAR guidelines (16). The median organ damage corresponding to VDI was 1 (range 0–7), the median DEI was 2 (range 0–11). Mean BVAS (new or worse disease activity) was 4.6 (range 0–21, SD 6.1).

Estimation of activity in dichotomy is shown in Table II.

Cohen's Kappa for intra-rater reliability for inexperienced physicians was κ=0.58 (agreement 85%) and for experienced physicians κ=0.72 (agreement 91%).

Fleiss's-Kappa for inter-rater reliability for inexperienced physicians at T1/T2 was κ=0.62/0.59 and for experienced physicians κ=0.50/0.58.

Estimation of activity in grading approach is shown in Table II.

The intra- and inter-rater reliability for inexperienced physicians was Cohen's κ=0.67 (agreement 56%) and Fleiss's κ at T1/T2 κ=0.29/0.27 (intraclass correlation coefficient, ICC=0.69/0.59). For experienced physicians, intra- and inter-rater reliability was Cohen's κ=0.80 (agreement 67%) and Fleiss's κ at T1/T2 κ=0.41/0.39 (ICC=0.77/0.75).

Discussion

With the introduction of modern immunosuppressive therapies, the potentially organ- and life-threatening disease GPA has lost some of its threats. Expectancy of life is in the normal range in GPA patients, even though under aggressive immunosuppressive therapy disease and/or therapy associated cases of death are still observed in up to 11% (range 2.2% to 25%), especially in the first year of diagnosis (24). Chronicity of disease and its adequate treatment remain the challenge in GPA-patients (25). Thus, lifelong follow-up in an interdisciplinary approach is necessary to assess disease activity and diagnose relapses early is important.

On average time between onset of first symptoms and diagnosis is in the range of month to even years, and first symptoms in the head and neck region are common (3). Histological proof of GPA with necrotising granulomatosis and vasculitis is desirable, but often difficult to achieve, even when performing repetitive biopsies (11, 26-28). Therefore, reliable judgement of nasal mucosa alteration and change over time is mandatory for diagnosis.

The disease extent index (DEI) and the vasculitis activity index (VAI) are scores defining disease activity on the basis of physician's assessment (15, 17). The intra- and inter-rater reliability for these scores are very high (29), although there is no literature available about the correlation to histology.

The Birmingham Vasculitis Activity Score (BVAS) is probably the most common score to define activity in vasculitis and the index recommended by the European Vasculitis Study Group (EUVAS) for clinical studies (16). BVAS-questions diverse from general symptoms up to specific abnormali-

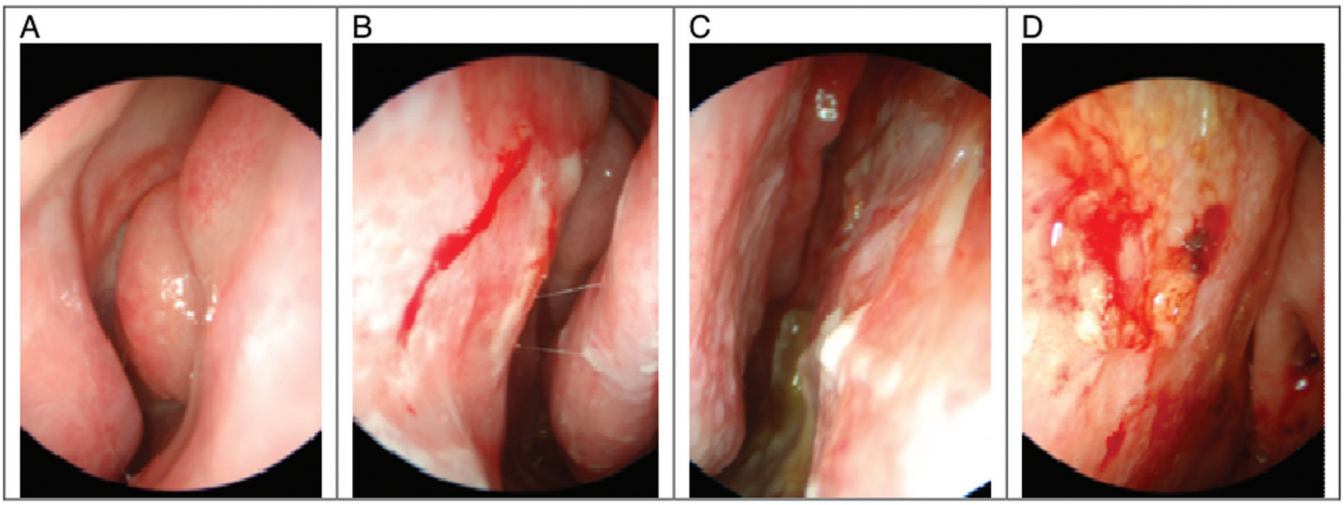
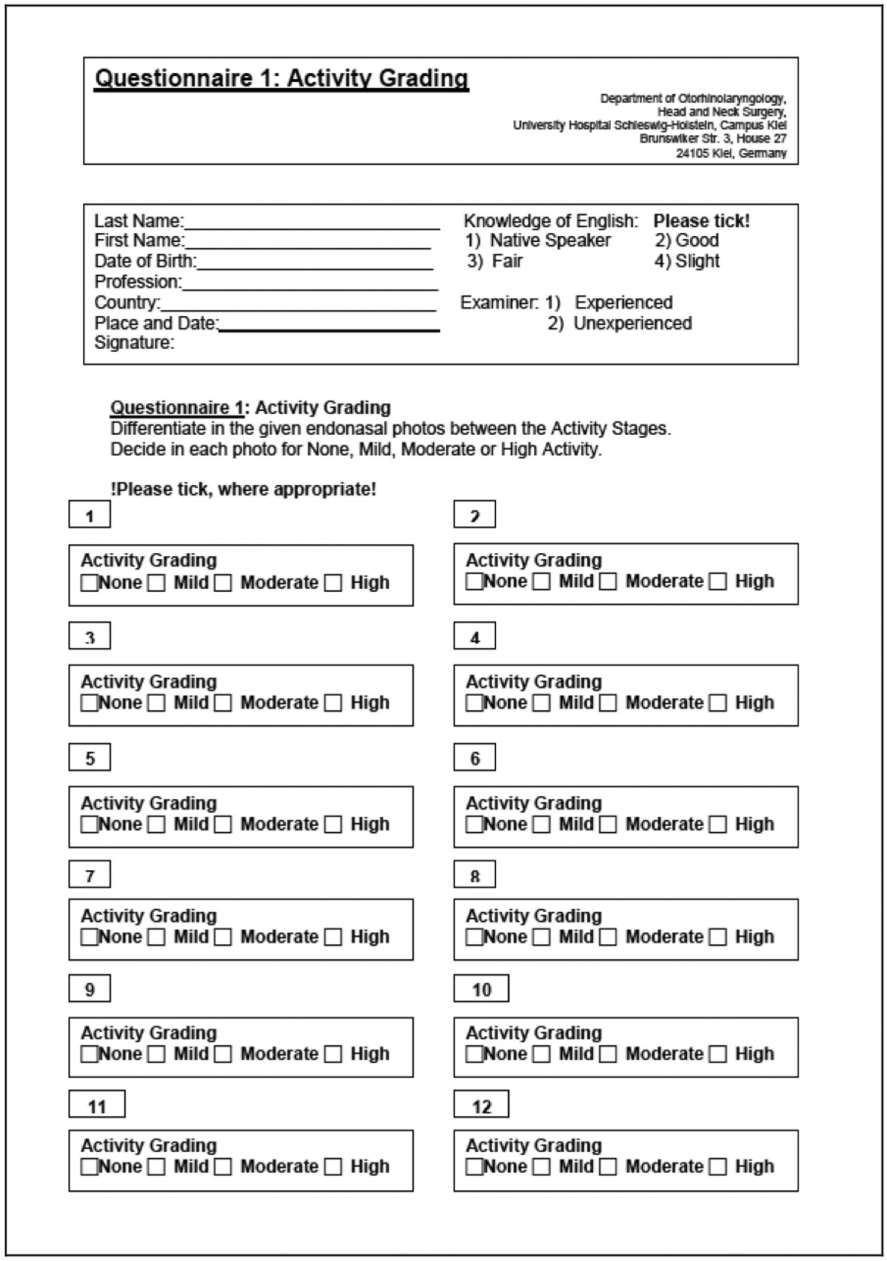


Fig. 4. Activity stages in the given endonasal images: A: none, B: mild, C: moderate and D: high activity. 0 degree rigid endoscope (KARL STORZ GmbH&Co KG).



Questionnaire 1: Activity Grading

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Last Name:_____
First Name:_____
Date of Birth:_____
Profession:_____
Country:_____
Place and Date:_____
Signature:

Knowledge of English: **Please tick!**
1) Native Speaker 2) Good
3) Fair 4) Slight

Examiner: 1) Experienced
2) Unexperienced

Questionnaire 1: Activity Grading
Differentiate in the given endonasal photos between the Activity Stages.
Decide in each photo for None, Mild, Moderate or High Activity.

!Please tick, where appropriate!

1	2
Activity Grading ☐None ☐ Mild ☐ Moderate ☐ High	Activity Grading ☐None ☐ Mild ☐ Moderate ☐ High
3	4
Activity Grading ☐None ☐ Mild ☐ Moderate ☐ High	Activity Grading ☐None ☐ Mild ☐ Moderate ☐ High
5	6
Activity Grading ☐None ☐ Mild ☐ Moderate ☐ High	Activity Grading ☐None ☐ Mild ☐ Moderate ☐ High
7	8
Activity Grading ☐None ☐ Mild ☐ Moderate ☐ High	Activity Grading ☐None ☐ Mild ☐ Moderate ☐ High
9	10
Activity Grading ☐None ☐ Mild ☐ Moderate ☐ High	Activity Grading ☐None ☐ Mild ☐ Moderate ☐ High
11	12
Activity Grading ☐None ☐ Mild ☐ Moderate ☐ High	Activity Grading ☐None ☐ Mild ☐ Moderate ☐ High

Fig. 5. Questionnaire

ties of the cutis, mucosa and eye, ENT, chest, cardiovascular system, abdomen, kidneys and the nervous system. The investigator should tick the item if it is reported by the patient as a new or worsened symptom which is attributed by the observer to vasculitis and not to other obvious causes. A numeric score weighted by the clinical importance provides quantitative information of activity (30, 31). However, involvement of the upper respiratory tract will always be scored with 2 points regardless whether disease activity is minor or devastating. In the initial publication of the BVAS, the score was compared to serological markers (CRP, erythrocyte sedimentation rate [ESR], haemoglobin and von Willebrand factor) and to physician's global assessment. The interobserver reliability was inside the 95% confidence interval (32). Although BVAS V3.0 suggests a rhinoscopy for evaluation, inter- and intra-rater reliability are still unknown. Using our newly developed ENTAS, we were able to demonstrate a good intra-rater reliability not only in decision in dichotomy (activity / no activity), but also in fine-grading (none, mild, moderate and high) in this study. In primary diagnostics, often only one physician is involved and distinct changes of the nasal mucosa can be detected reliably if the same physician judges activity. It is of special interest that there is no difference between experienced and inexperienced physicians, in particular because GPA is one of the rare diseases.

But not only in the process of diagnosis is reliable rating of signs of activity on the nasal mucosa mandatory in GPA. Persistent ENT-related disease activity ("grumbling disease") often remains a problem in spite of immunosuppressive therapy. To cope with that, immunosuppressive therapy has to be individually adjusted during the course of the disease. Moreover, in about 5% of patients GPA remains localised solely affecting the nasal and paranasal mucosa (5). Since adverse events (severe infections, bone marrow depression) during immunosuppressive therapy are common, reliable estimation of ENT-activity is one prerequisite for adjusting therapy with saving immunosuppressive agents, but preventing relapse. Interdisciplinary approach for best possible care of GPA-patients leads to a variety of involved physicians even of the same specialisation. There has been no information about the inter-rater, or even intra-rater reliability of detected affections of the nasal mucosa so far. For the proposed ENTAS, we were able to demonstrate a good concordance of inter-rater rating of endonasal activity when restricting the estimation to a decision in dichotomy (activity/no activity) in this study. Inter-rater reliability for grading activity was not reliable, even for experienced physicians.

Saddle nose deformity and transdermal fistula to the nose and paranasal sinus are stigma in GPA and incriminate patients and their families. Functional lesions of the nasolacrimal duct lead to recurrent infection and symptomatic epiphora. Destruction of the orbital bone leads to functional and even eye threatening courses of the disease. The relationship of nasal/paranasal activity and/or (localised) granulomatous disease, even without apparent vasculitis, and damage is unknown and subject of current investigation. Reconstruc-

Table II. Results.

		Estimation of endonasal activity in dichotomy	Estimation of endonasal activity in grading approach
Inexperienced physician (n=5)	intra-rater reliability (Cohen's κ)	κ=0.58 agreement 85%	κ=0.67 agreement 56%
	inter-rater reliability T1/T2 (Fleiss's κ)	κ=0.62/0.59	κ=0.29/0.27 ICC 0.69/0.59
Experienced physician (n=7)	intra-rater reliability (Cohen's κ)	κ=0.72 agreement 91%	κ=0.80 agreement 67%
	inter-rater reliability T1/T2 (Fleiss's κ)	κ=0.50/0.58	κ=0.41/0.39 ICC 0.77/0.75

κ: Cohen's and Fleiss's Kappa; ICC: intraclass correlation coefficient; T1: first evaluation; T2: second evaluation.

tion is mandatory but has to be timed carefully, because delicate operational procedures with autogeneous and alloplastic grafting in inflamed regions are often ineffective and/or lead to high revision-rates. Therefore, careful and reliable estimation of the affected anatomic region is essential and long-term follow-up before and after surgical intervention is mandatory. We were able to demonstrate a good intra- and inter-rater reliability for experienced and inexperienced physicians in determining nasal activity or absence of nasal activity (decision in dichotomy) in GPA patients. Therefore, scheduling of reconstructive surgical approaches could be based on endoscopic evaluation without peculiar consideration of the physicians experience.

Conclusion

In the present study, for the first time, inter- and intra-rater reliability for the evaluation of affections of the nasal mucosa in GPA are investigated. Intra-rater reliability is high in decision in dichotomy and even in grading activity and there is no difference for experienced or inexperienced physicians. Inter-rater reliability is high for the decision of activity or absence of activity but low for fine activity grading. Thus, the ENTAS provides a reliable instrument for assessing, documenting, and following GPA-related disease activity in the upper respiratory tract.

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