REVIEW

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Head and neck manifestations of Wegener's granulomatosis*

S. Gottschlich[1], P. Ambrosch[1], D. Kramkowski[1], M. Laudien[1], T. Buchelt[1], W.L. Gross[2], B. Hellmich[2]

[1] Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Schleswig-Holstein, Campus Kiel, Germany
[2] Department of Rheumatology, Rheumaklinik Bad Bramstedt, University Hospital Schleswig-Holstein, Campus Lübeck, Germany

SUMMARY

Wegener's Granulomatosis (WG) is a necrotizing granulomatous angiitis that presents the classic ELK triad of ear, nose, throat (E), lung (L), and kidney (K) involvement. Its potential rapid and fatal outcome makes the early recognition - before irreversible organ involvement occurs - mandatory.

The aetiology is still unknown. Today, immunosuppressive therapy makes WG a treatable disease with a chronically relapsing course. The otorhinolaryngologist plays an important role in early diagnosis of WG, because in up to 95% of the patients initial WG symptoms are observed in the head and neck region. The majority of these patients show nasal or sinunasal involvement. Common manifestations are sinusitis, crusting of the nose, and development of saddle nose deformity. Other head and neck problems are middle and inner ear symptoms and subglottic stenosis. Follow up and activity assessment of the disease are also important roles to play for the otorhinolarygologist.

INTRODUCTION

In 1931 Klinger published a report of a patient with nasal destruction and uraemia who had been found at autopsy to have diffuse granulomata, glomerular lesions and arteritis [(1)]. Friedrich Wegener is credited with the first clinical and histopathologic descriptions of the syndrome as an own entity, which he published in 1939 [(2)]. Wegener`s granulomatosis (WG) is an idiopathic, systemic disease characterized by necrotizising, granulomatous inflammation of the upper and lower respiratory tract in combination with vasculitis of medium and small arteries and focal or proliferative glomerulonephritis [(3)]. Since none or only minimal deposits of immune complexes are typically provable on biopsy, WG also belongs to the group of the "pauci immune" vasculitides [(4)]. WG is the most frequent vasculitis with an ANCA (antineutrophil cytoplasm antibodies) association with an annual incidence of 10 per 1 million inhabitants [(5)]. The prevalence of WG is up to 50 per 1 million inhabitants in Europe. The disease can present at any age, most frequently in adults, with a mean age of onset of 40 years [(6)].

MANIFESTATIONS OF WEGENER`S GRANULOMATOSIS

Head and Neck Region

Otorhinolaryngological involvement may occasionally be the first and only sign of the disease and it is the first symptom of WG in 80-95% of the cases. Therefore the otorhinolaryngologist plays an important role for establishing the first diagnosis. The following section reflects the wide spectrum of manifestations (Table 1). The clinical presentation of WG can show substantial variation. Otorhinolaryngologic symptoms can appear particularly in the early stage frequently without further organ participation or in the context of a generalized vasculitis. Such early forms of WG, which are restricted to the upper and lower respiratory tract, are coined "localised" WG, in contrast to the advanced disease stages with systemic vasculitis ("early systemic", "generalized" or "severe", depending on disease severity).

Nose and paranasal sinuses

The nasal cavity and the paranasal sinuses are affected in 60 to 90% of all cases and thus represent the localisation with the most frequent manifestation of WG in the head and neck region. Over 25% of patients with WG have only nasal symptoms. The clinical manifestation shows a broad spectrum. This can range from a minimal nasal obstruction up to major destruction of the outer nose and the structures of the paranasal sinuses including the involvement of the central nervous system through damage to the skull base. The most common nasal symptoms in these patients are nasal obstruction and discharge. Apart from nasal crusting other symptoms of WG include minor epistaxis, whistling if there is a septal perforation, a reduction in sense of smell and through this taste, and pain in the area of the nose [(7-11)].

The mucosa in WG has a granular quality and stagnant mucus

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Table 1. Organ manifestation of WG in the head and neck region including disease pictures, symptoms and findings.

Nose/ Paranasal Sinuses	**Ear/Mastoid**	**Larynx**	**Oropharynx/ Oral Cavity**	**Salivary Glands**
Disease picture	*Disease picture*	*Disease picture*	*Disease picture*	*Disease picture*
stenosis of lacrimal duct	chronic otitis	subglottic stenosis	gingivitis	sialadenitis
chronic sinusitis	mastoiditis			
meningitis	glue ear			
	meningitis			
	sensorineural hearing loss			
	otitis externa			
Symptoms/signs	*Symptoms/signs*	*Symptoms/signs*	*Symptoms/signs*	*Symptoms/signs*
septal perforation	otorrhoea	dysphonia	ulceration	swelling
saddle nose deformity	erythema	stridor	osteonecrosis	pain
granulomatous inflammation	tinnitus	dyspnoea	ulceration	
hyposmia, anosmia	facial nerve palsy		hypertrophic gingiva	
obstruction of the nose	vertigo			
epistaxis	conductive hearing loss			
rhinorrhoea				
pain				

superinfected with nasal commensals from the nasal vestibule can coat the septum and lateral nasal wall (Figure 1). A septal perforation is a stronger sign, particularly if there is no history of nasal trauma or septal surgery (Figure 2). The involvement and necrosis of the nasal septum can lead to a saddle nose deformity in 5-20% of the patients with nasal manifestations of WG (Figure 3). Sinusitis, presenting with headache, chronic nasal congestion and mucopurulent discharge occur in up to 50% of these patients. Patients also report epiphora as a sign for direct involvement of lacrimal duct or secondary blockage to the same by granulomatous lesions from the nose. The nasal mucosa frequently has a chronic infection with *Staphylococcus aureus* with no or few symptoms. It is suggested, that the chronic existence of *S. aureus* may reactivate disease activity of WG. The mechanism is still unsolved. However it is assumed to be caused by superantigens of *S. aureus* [12].

Ear

Otological involvement [13-16] occurs in 20-70% and may occasionally be the first and only sign of the disease. It may affect the ear in a number of ways, including the external, middle and inner ear.

External ear

Involvement of the external ear is rare, merely edema, erythema and a tens feeling in the area of the auricle are described. Occasionally an otitis externa, mostly caused by a chronic otitis media can be seen. Rarely the external ear can demonstrate necrotizing granulation tissue.

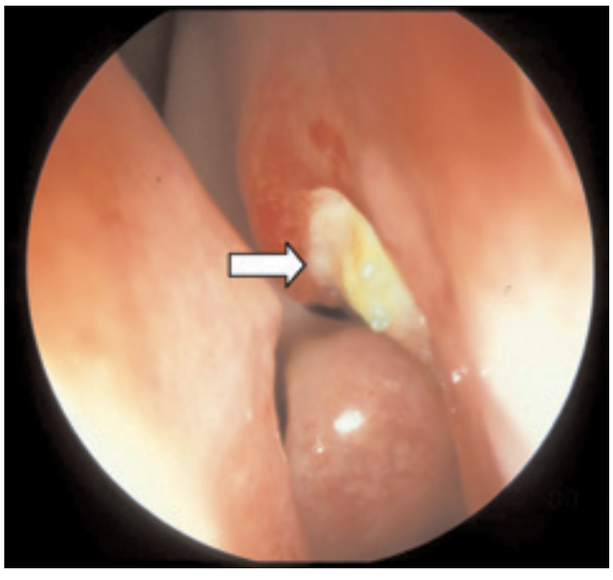

Figure 1. Endonasal affection of a patient with WG (early stage of disease).

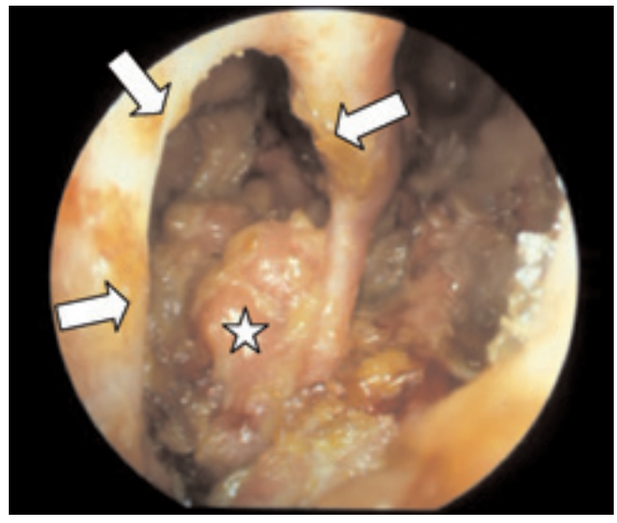

Figure 2. Endonasal view of a patient with WG.
Septal perforation (→); granulomatous inflammation (*).

Middle Ear

Involvement of the middle ear is found in about 40-70% of the patients [7,13,14,17]. The most common form of presentation in WG is otitis media with effusion, probably occurring secondary to eustachian tube obstruction from luminal granulomata or from nasopharyngeal inflammation and ulceration. The serous effusions can be either unilateral or bilateral. Approximately 20-40% of patients with WG require tympanostomy tube placement at some point of their disease. It is also possible to see a chronic otitis media caused by WG.

The middle ear and the mastoid may also be primarily affected by granulomatous inflammation and destruction, manifesting as chronic suppurative otitis media in 20-30% of the cases. An infection caused by *S. aureus* and *Pseudomona aeruginosa* is frequently found, partially complicated by multi-resistances. The symptoms are comparable with those of a chronic otitis media without WG. Because of the potentially destructive effect of WG on the temporal bone, patients with WG and chronic otitis media can be very susceptible to complications. Cranial nerve palsies, most commonly the facial nerve and meningitis are possible.

Inner ear

Sensorineural hearing loss occurs with a reported frequency of 5-31% in WG [17-19]. The hearing loss may progress fairly rapidly over days or weeks and can be accompanied by tinnitus. The reason for the sensorineural hearing loss in these patients is unclear. Proposed causes include immune-complex deposition in the cochlea, granulomatous compression of the cochlear nerve, and vasculitis of the vasa nervorum or the cochlear vessels. Some authors have reported resolution of the sensorineural hearing loss with immunosuppressive therapy, although others have found little or no response to medical therapy. Vertigo occurs infrequently in WG and is rarely a complaint.

Larynx

Subglottic stenosis occurs in 5 - 20% [7,11,17,18,20] of the cases and is typically associated with the generalized form of the disease. Patients with subglottic stenosis (Figure 4) usually present with hoarseness or stridor. Occasionally patients may present with acute obstruction requiring emergency tracheostomy. Direct laryngoscopy typically reveals a circumferential narrowing of the subglottis with friable, erythematous mucosa and occasional discrete granulomata. Approximately 50% of the patients with a laryngeal participation of the WG required tracheostomy at some time.

Oral cavity

Involvement of the oral cavity is rare, in comparison with other manifestations [7,14,21]. Limited mucosal inflammation, ulcerative stomatitis, granulomata, oroantral fistulae, osteonecrosis of the palate and labial mucosal nodules are described. Gingival involvement is even less common,

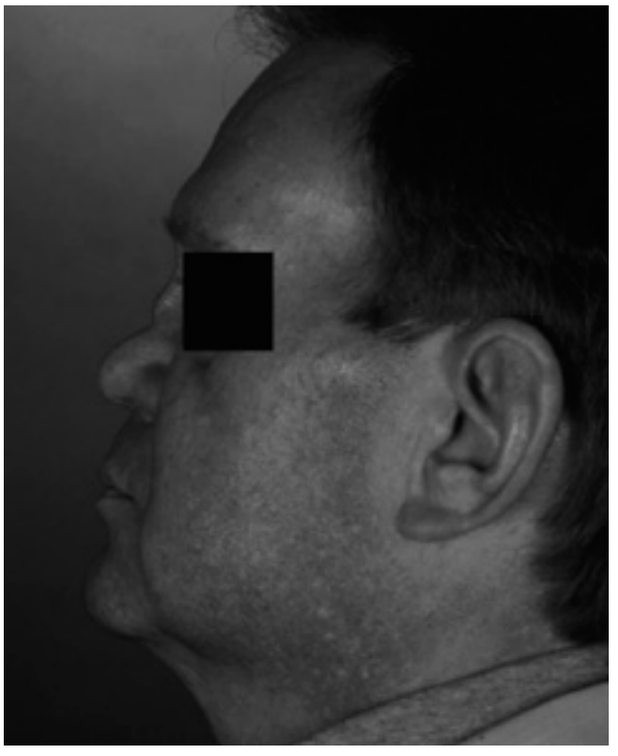

Figure 3. Typical saddle-nose deformity in a patient with WG.

Table 2. Manifestation of Wegener`s Granulomatosis [25].

Organ manifestation	Main symptoms	Incidence
lung	dyspnoea, haemoptysis	85%
head and neck region	epistaxis, rhinitis, nasal crusting, sinusitis, loss of hearing, subglottic stenosis	95%
glomerulonephritis	edema, microhaematuria	80%
joints	arthralgia, arthritis, myalgia	70%
eye	episcleritis, conjunctivitis, retrobulbar granuloma	- 60%
general symptoms	fever, weight loss, nocturnal sweating	> 50%
dermal vasculitis	purpura, necrosis, nodules	-50%
polyneuropathia	Peroneal nerve palsy, paraesthecia	20%
central nervous system	epilepsy, psychosis	< 10%
gastrointestinal area	bloody diarrhoea, tenesmus	< 10%

Table 3. Criteria for the classification of Wegener's granulomatosis (ACR 1990) [13].

- Oral ulcers or nasal discharge
- Abnormal findings on chest radiograph (nodules, cavities, or fixed infiltrates)
- Abnormal urinary sediment (red cell casts or greater than 5 red blood cells per high power field)
- Granulomatous inflammation on biopsy

The presence of 2 or more of these 4 criteria is associated with a sensitivity of 88.2% and a specificity of 92.0%.

although some authors consider gingival hyperplasia to be a pathognomonic for WG.

Salivary glands

Manifestation of WG in the large salivary glands is rare, however, can be an initial presentation. The submandibular or parotid glands on one or both sides may become enlarged. Salivary gland involvement typically occurs early in WG and may be seen in limited forms of the disease [22].

Outside the Head and Neck Region

The clinical manifestation of WG varies according to illness activity and affected organs. The early stage is defined as involvement of the upper and lower respiratory tract and is also called localised WG. Beside the manifestation in the upper aerodigestive tract pulmonary granulomas may also occur in the early stage, even if there is no pulmonary vasculitis (capillary arteriitis) or other organ manifestation [23]. In the late stage of the illness there is a complete picture of vasculitis including multiorgan involvement, while some organ systems are more affected than others (Table 2). Often glomerulonephritis, episcleritis, arthritis and fever, weight loss, nocturnal sweats or polyneuropathy can be found. Further symptoms of late stage disease are haemoptysis due to alveolar haemorrhage or rapid progressive polyneuropathy or purpura (Table 2) [24,25].

DIAGNOSIS

Introduction

The diagnosis of a WG is made clinically, based on clinical findings suggestive of vasculitis and granulomatous inflammation. However, if possible, histologic confirmation should always be sought. If it is not possible to verify a diagnosis by a biopsy from the head and neck region, other organs with active disease such as the kidney, lung or skin should be biopsied. For detection and assessment of disease manifestations a systematic examination of different organ systems is required [26]. An interdisciplinary approach has proven most efficient including, rheumatologists, neurologists, radiologists, ophthalmologists and otorhinolaryngologists [24].

Table 3 shows the ACR classification criteria of WG derived from frequent clinical and pathological results [26]. The table is only for further classification of the syndrome, like the definition of the Chapel-Hill consensus-conference (Table 4) [27], when "Vasculitis" has already been diagnosed. Retrospective studies highlight that the ACR classification criteria of WG are not suitable for the primary diagnosis of vasculitis. Above all, other small vessel diseases must be excluded by the clinical presentation, the antibody status and the histological results (Table 5). Other granulomatous illnesses like sarcoidosis or the rare lymphomatoid granulomatosis are negative for anti-PR 3/C-ANCA and are only accompanied by vasculitis in rare cases.

Table 4. Definition of Wegener's granulomatosis (Chapel Hill Consensus Conference, 1992) [27].

Small vessel vasculitis	Definition
Wegener's granulomatosis	Granulomatous respiratory tract involvement and necrotic vasculitis of small and medium vessels, for example capillaries, venules, arterioles und arteries, necrotic glomerulonephritis

Biopsy

A histopathological confirmation of the diagnosis of WG should be the gold standard. A biopsy in the ENT area is easily done because of the high rate of involvement in the ENT area and because of the low morbidity associated with taking biopsy. Unfortunately, the histopathological changes are often non-specific and show only signs of acute or chronic inflammation. WG is indicated by three characteristic findings: 1. necrosis, 2. granulomatous inflammation, 3. vasculitis. For the histopathological diagnosis of WG all three characteristics must be found [28]. The combination of all three criteria is found only in 15-25% of the biopsies from the ENT area [29]. In most cases (50-65%) only one criterion of WG is found in the biopsy of the nose. Thus biopsies from the head and neck region frequently fail to establish the diagnosis of WG, but when they may help to support the diagnosis taken together with clinical and serological parameters [30,31].

ANCA

C-ANCA/Anti-PR3 antibodies are positive in 95% of patients in

Table 5. Differential diagnosis of Wegener`s Granulomatosis.

Main Clinical Findings	Additional Findings	Diagnosis	Investigations
pulmonal nodes	episcleritis, purpura	WG	biopsy: granuloma, pauci-immune
haemorrhagic rhinorrhoea			vasculitis
glomerulonephritis			cANCA/Anti-PR3 positive
pulmorenal syndrome	purpura	microscopic polyangiitis	biopsy: no granuloma,
			pANCA/anti-MPO positive
asthma	polyneuropathy	Churg-Strauss-Syndrome	eosinophils: > 10%
nasal polyposis			tissue hypereosinophilia
granulomatous lymphadenopathy	interstitial lung change	Sarcoidosis	ANCA negative
			biopsy: granuloma
polyneuropathy, hepatitis	purpura	Cryoglobulinae/	HCV positive, cryoglobulins
	glomerulonephritis	microscopic Vasculitis	biopsy: immune complex vasculitis

the generalized phase, however only occur in 50% in the localized phase of WG [32-34]. ANCA can also be measured in 80% of patients with microscopic polyangiitis (MPA). The ANCA-titre can correlate with the disease activity so that serial ANCA measurement allows meaningful assesment of the illness. Relapses are accompanied by an increase of ANCA-titre.
The measurement of ANCA uses the direct immune fluorescence technique by using neutrophil granulocytes (fixed in ethanol) and enzymatic immunoassays (ELISA) [32]. Despite international standardization, the results of measuring ANCA are dependent on the undertaken procedure. To achieve a reliable sensitivity and specificity the combination of fluorescence microscopy and ELISA should always be carried out [32].

Other laboratory parameters
As an expression of the acute-phase-reaction occurring during active WG, an elevation of ESR and CRP as well as a leuco- and thrombocytosis is found. The early recognition of renal involvement such as a rapid progressive glomerulonephritis is very important. Urinalysis for sediment should therefore be determined at least once a month. In case of a lately determined erythrocyturia, microscopic examination of the urine should be arranged to look for red blood cell casts and/or dysmorphic erythrocytes. Proteinuria should be quantified by collecting 24h-urine and classified qualitatively by means of differential protein analysis. An isolated albuminuria points to a glomerular source of the proteinuria and together with dysmorphic erythrocyturia is very suspicious for glomerulonephritis.

Imaging

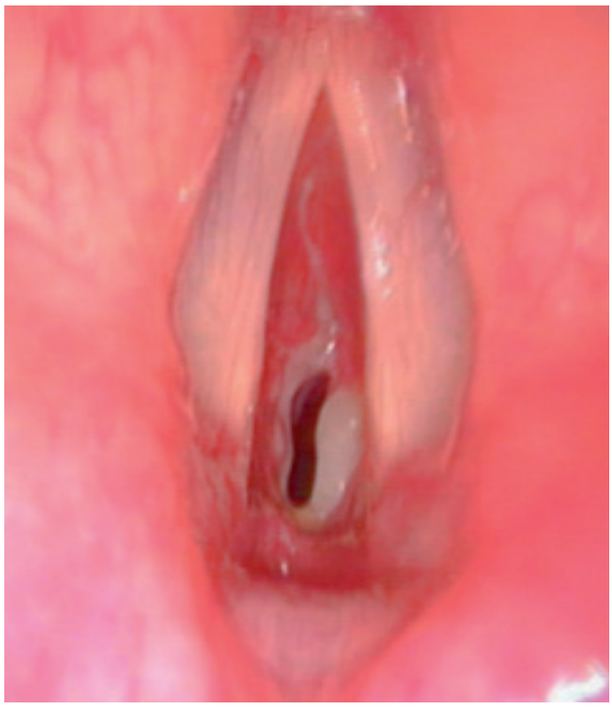

Figure 4. Subglottic stenosis in WG.

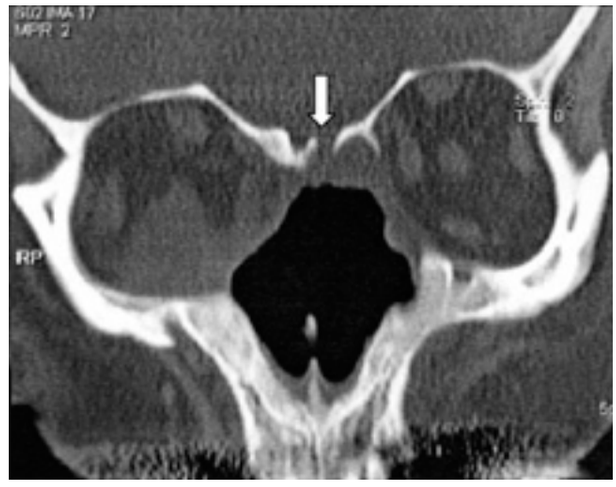

Figure 5. CT of paranasal sinuses with marked destruction of bone structure of the sinuses caused by WG, together with involvement of orbit and skull base (discontinuity of skull base →).

Conventional X-rays, computed tomography (CT) and magnetic resonance imaging (MRI) typically show mucosal swellings in the mastoids and the paranasal sinuses. The surrounding bone structures can show non-specific destruction. Often mucosal swelling in the maxillary sinus can be seen with signs of chronic osteitis [18,28,35]. Marked destruction of the bone of the paranasal sinuses, the orbita and the skull base can be seen in certain cases (Figures 5 and 6).

TREATMENT

Immunosuppressive Therapy
Early cohort studies showed that the course of WG was usually fatal if no immunosuppressive therapy was applied. The introduction of corticosteroid therapy improved outcome, but still resulted in a mortality of 50%. Approximately 25 years ago the addition of oral cyclophosphamide (CYC) to the prednisolone treatment ("Fauci protocol") led to rates of remission for WG of more than 90% [36]. Therefore, the Fauci protocol today still represents as standard therapy of WG [37]. However the morbidity and mortality ascociated with the medical therapy (increased risk of haemorrhagic cystitis, carcinoma of the bladder, lymphoma, myelodysplastic syndrome or heavy infections) are not negligible [24]. Since the long-term toxicity is essentially affected by the cumulative dose of the CYC, the total exposure should be as low as possible. After full or partial remission occurrs the treatment is changed to other, less potent, but better, long-term immunosuppressives such as azathioprine or methotrexate (MTX) for safe maintenance of remission [38]. If involvement of the kidney is absent and the disease is not life- or organ threatening ("early systemic" WG), MTX can be used instead with similar remission rates [39]. Patients with WG in the localised stage with purely granulomatous changes in the head and neck region can be treated with trimethoprim/sulfamethoxazol as an alternative to MTX [40]. In cases of insufficient response to treatment with CYC and

steroids, the therapy can be extended by additional measures. Patients with WG and insufficient response to CYC can be treated with inhibitors of tumor necrosis factor-alpha (TNF-α) like infliximab to induce a remission, whereby vasculitic manifestations seem to react better than granulomatous changes [41,42]. However, in patients with non-refractory disease the addition of etanercept to standard therapy did not increase response rates or reduce relapse rates [43]. Due to the substantial risk of opportunistic infections, each combined immunosuppressive therapy should be limited in time and tightly controlled. For the prophylaxis of an infection with *Pneumocystis carinii*, all patients with potent immunosuppressive therapy (e.g. CYC, high-dose prednisone, TNF inhibitor) should be treated with trimethoprim/sulfamethoxazol.

SURGICAL THERAPY

The primary treatment of WG is medical therapy. Surgical measures are reserved for exceptional cases and complications, whose emergency nature do not permit to wait for a response to medical treatment.

Septalperforation/Rhinoplasty

There are no publications in which the closure of the septal perforation is described or recommended in patients with WG. The use of a septalobturator, as well as intensive topical treatment of the nose produces a reasonable result in the majority of the patients. In contrast to the septal, perforation the obvious saddle nose creates a strong desire for surgery in many patients. A precondition for reconstruction of the nose should be remission of the WG. Because of the frequently complex reconstruction of the nose with rib or ear cartilages and unfavourable conditions for wound healing, unsatisfactory results and complications can occur. Nevertheless, a successful plastic reconstruction can often be achieved in these patients [11,44,45].

Mastoid/tympanic membrane

An indication for the mastoid surgery exists only for complications such as mastoiditis. Only a few authors recommend a mastoidectomy in patients suffering from paralysis of the facial nerve who are not responding to immunosuppressive therapy. The success rate is difficult to judge due to the combination drug and surgical therapy. An indication for closure of a tympanic perforation should be considered very cautiously.

Larynx/Subglottic Stenosis

Many different options have been expressed over the years for the treatment of subglottic stenosis. The goal of all these procedures is the avoidance of a tracheotomy however. Despite diverse therapy modalities tracheotomy rates are reported in up to 50% patients with subglottic stenosis. The dilatation of the stenosis is one of the least invasive procedures, which is frequently combined with a local injection of prednisolone. The long-term success rate of this method is rather low in the published literature [46]. Own experience is that the majority of the cases a tracheotomy can be avoided. Stents, whose success rates are long term also low, because of granulation and dislocation of the stent. Laser-treatment of the subglottic stenosis remains controversial. Some authors describe rates of re-stenosis of up to 100% [46], others see laser treatment of the stenosis as a promising alternative. Extended open laryngotracheoplasty in combination with free flaps can also be regarded as a possible long term solution, even after unsuccessful drug therapy and endoscopic attempts at the treatment of subglottic stenosis. The goal of the treatment of subglottic stenosis should however be to avoid surgical interference by early diagnosis and prompt medical therapy [11,20,47].

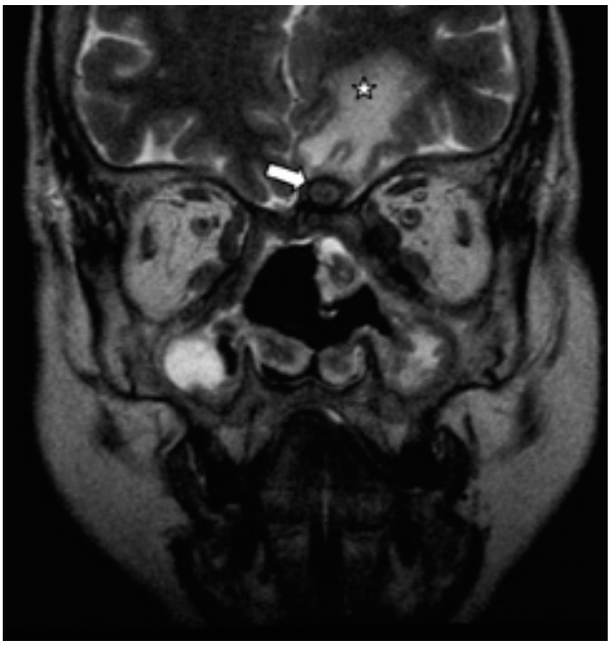

Figure 6. MRI of head, paranasal sinuses and skull base with significant destruction of bony structure of the nose and sinuses, with affection of orbit, skull base (→) and brain (*).

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Stefan Gottschlich, MD
Department of Otorhinolaryngology, Head and Neck Surgery,
University Hospital Schleswig-Holstein, Campus Kiel
Arnold-Heller-Str.14
24105 Kiel
Germany

Tel.: +49-431-597-2240
Fax: +49-431-597-2272
E-mail: gottschlich@hno.uni-kiel.de