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LARYNGOLOGY

Dilatation tracheoscopy for laryngeal and tracheal stenosis in patients with Wegener's granulomatosis

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Abstract Wegener's granulomatosis (WG) frequently involves the subglottis and trachea and may compromise the upper airway. The objective of this study is to evaluate retrospectively the effect of treatment of subglottic stenosis (SGS) and tracheal stenosis (TS) by dilatation tracheoscopy (DT) in patients with WG. We performed a cohort study on all patients who underwent DT between February 2001 and September 2005 in our institution. From this cohort we identified a total of nine WG patients. In all patients, clinical, serological and histopathological data had been prospectively collected by a standardized protocol from the time point of diagnosis. In the nine patients that were identified with SGS or TS due to WG (eight women and one man), a total of 22 DT's were performed. Two patients needed a tracheostoma (one temporarily). The mean follow-up after the first DT was 25.4 ± 14.1 months. Two patients did not experience a recurrence of SGS or TS. Six patients required a second DT without recurrence of local disease. The remaining patient underwent 8 DT's in a 4-year period. DT can offer a simple and repeatable solution to SGS and TS due to WG. Seven of the nine patients required more than one dilatation and some patients experience a functional restriction. One patient has a definitive tracheostoma.

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Introduction

Wegener's granulomatosis (WG), first described by Friedrich Wegener in Stuttgart in 1936, is multi-system disease characterized by a necrotizing granulomatous arteritis of the upper and lower respiratory tract and a necrotizing crescentic glomerulonephritis [1]. Vasculitis may also affect other organs such as the eyes, skin, joints, heart and the nervous system [1]. Upper respiratory tract manifestations—particularly sinusitis, ulcerations of the nasal mucosa and epistaxis—are common and debilitating presentations. Subglottic stenosis (SGS) and tracheal stenosis (TS), however, are potentially life threatening presentations of WG. SGS has been found to occur in approximately 16–23% in patients carrying a diagnosis of WG [2, 3]. This narrowing of the upper airway at the level of cricoid cartilage and/or upper tracheal rings presents a management dilemma. Dilatation tracheoscopy (DT) is one of the possible options for treatment of SGS and TS. The long-term effects of DT in patients with WG have never been reported.

DT is a minimally invasive self-standing procedure. It can be used for elective and emergency intervention in patients with subglottic and tracheal stenosis. This has been described elsewhere (G.B. Halmos, F.G. Dikkers, Dilatation tracheoscopy in treatment of subglottic and tracheal stenosis, submitted for publication). Patients suffering from WG present differences (age, sex, response to treatment) compared to other aetiologies, which justifies separate publication. The objective of this study is therefore to evaluate

the effect of the treatment of SGS and TS by DT in patients with WG.

Methods

We retrospectively identified all patients from our institution that underwent a DT between February 2001 and September 2005. The total cohort of benign, grade II (Myer-Cotton) subglottic or tracheal stenosis consisted of patients with a history of posttraumatic tracheal stenosis, thermal tracheal stenosis, posttracheotomy cicatricial stenosis, tracheal rupture, postintubation stenosis, and WG, amongst others. As stated before, the cohort is described elsewhere.

From the cohort we identified a total of nine WG patients. These nine patients had been diagnosed with WG between May 1990 and August 2003. During this period a total of 195 patients in our institution were diagnosed as having WG (including the nine patients who underwent DT). From this cohort, one additional patient underwent a DT for SGS in 1992. Three other patients were diagnosed with relatively mild SGS or TS that did not necessitate DT. The reference group for the comparison of demographic and serological data consisted of the total cohort, minus the patients who underwent DT and minus the three patients with mild tracheal stenosis who did not undergo DT. Differences in age between the DT group and the reference group were tested with the Mann Whitney U test; differences in the male/female ratio and antineutrophil cytoplasmatic autoantibodies (ANCA) specificity were tested with chi-square test. Although this was a retrospective study, the clinical, serological and histopathological data of both the DT group and the control group had been prospectively collected by a standardised protocol starting at the time of the diagnosis of Wegener's granulomatosis. Extrarenal organ involvement was categorized as described previously [4]. ANCA was assayed with indirect immunofluorescence. Sera from all patients were assayed for the presence of antibodies against proteinase 3 (PR3–ANCA), myeloperoxidase (MPO–ANCA) and elastase as described previously [5].

DT was performed when patients complained of progressive dyspnoea in combination with decrease of peak flows. DT is an endoscopically performed intervention. An intubation laryngoscope, a Groningen optical dilatation tracheoscope (Karl Storz 1033R) (Fig. 1), telescope and suction tubes are required for this procedure. The tracheoscope has a length of 30 cm. The proximal end of the tracheoscope is designed in such a way that customary ventilation tubes and a 30 cm Hopkins® straight forward telescope (Karl Storz 27005AA) can be connected. The distal end of the instrument contains numerous lateral tiny openings, which enable air to come through in the centre of the stenosis. The dilatation tracheoscope is available with a diameter of 8 and 12 mm. The appropriate size of the instrument is determined by the size of the patient's larynx and the healthy portion of the trachea.

The intervention is carried out under general anaesthesia. Following the administration of the anaesthesia, with ventilation taking place via an anaesthesia mask, the dilatation tracheoscope is introduced under endoscopic control. The stenosis is then visible through the vocal cords (Fig. 2). The bevelled design of the tip, which can be advanced forward through the stenosis, ensures that the ventilation is maintained during the process. The conical construction of the tip enables the instrument to be advanced up to the wider section of the tracheoscope (Fig. 3), after which the tracheoscope remains in place for 5 to 10 min.

The constellation of the tracheoscope is suitable for most grade II (Myer-Cotton) subglottic or tracheal stenosis. The intervention can be repeated after any time interval.

Fig. 1 Groningen dilatation tracheoscope

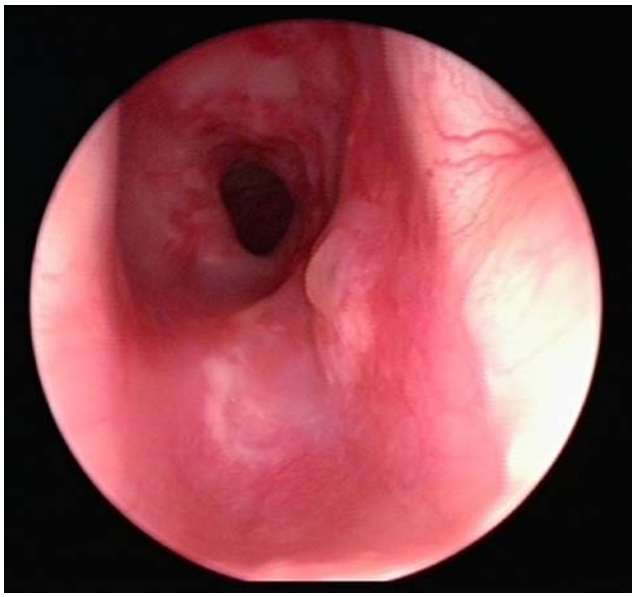

Fig. 2 Patient nr 9 pre dilatation. During laryngotracheoscopy a subglottic stenosis is clearly visible. The vocal cords can be seen bilaterally

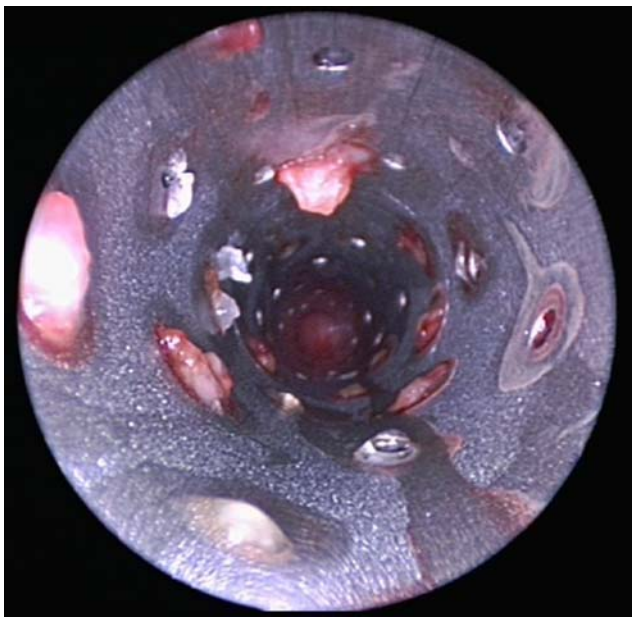

Fig. 3 Patient nr 9 during DT. The dilatation tracheoscope is introduced through the stenosis. Parts of the tissue protrude through the tiny distal openings of the tracheoscope

Typically, no antibiotics or corticosteroids are used. The use of mitomycin-C was considered in each case, but it was never used, because mitomycin-C should be used in fresh wounds. Patients are dismissed the day after DT. Peakflows were measured three times (Respironics Healthscan Inc., Cedar Groove, NJ, USA) in an upright position. The mean of the three measurements was taken.

Results

Patients

The total cohort of patients who underwent DT because of SGS and TS was 25. Nine of them were identified as patients with WG. Eight were female, one was male. The other 16 patients did not have vasculitis as cause of their stenosis. The causes in these 16 patients were posttraumatic [5], postintubation [4], idiopathic [4], post tracheotomy [2] and post thermal [1] injury. The mean age of the patient group at first presentation of WG was 41.6 ± 11.2 years (Table 1). The interval between the presentation of WG and the first symptoms of laryngeal and tracheal stenosis varied between 0 and 122 months (mean 48.9 ± 44.1). The average age at of the time of presentation of the stenosis was 45.6 ± 11.9 years (Table 1).

At diagnosis, all WG patients had additional organ involvement outside the otorhinolaryngologic area. The kidneys, lungs and eyes were affected three times. The joints were affected two times. The skin was affected once (Table 1).

As shown in Table 1, the number of relapses of WG varied between 0 and 12. There was no relation between the number of relapses and the occurrence of TS or SGS. In only one of the DT procedures there was endoscopic and/or histopathological evidence of vasculitis activity. The TS or SGS occurred in 95% in periods where the disease appeared to be less active.

In Table 2 the patient characteristics of the 9 patients who underwent DT for SGS or TS are compared with those patients who were diagnosed with WG in the same time frame but who did not have evidence of SGS or TS. In the DT group, 89% were female whereas 43% of patients in the reference group were female ($P < 0.01$). In the DT group the age at diagnosis of WG was significantly lower in comparison with the reference group ($P < 0.05$).

Follow-up of the DT-group

In the nine patients identified with SGS or TS due to WG, a total of 22 DT's were performed (Table 3). The mean follow-up after treatment was 25.4 ± 14.1 months (Table 3). Two patients (numbers 7 and 8) did not experience a recurrence of significant stenosis. Six patients (numbers 1, 2, 3, 4, 6, 9) required a second DT without recurrence of local disease activity after the second DT. One of these patients (patient number 6) had acute WG in the trachea, proven by biopsy (Fig. 4). She was treated with high dose prednisolone (intravenous methylprednisolone 1000 mg on three consecutive days) and intubation for a week. She could be detubated a week later (Fig. 5). Two patients needed a tracheostoma (patient numbers 2 and 5). One patient (number

Table 1 Patient characteristics of nine patients with Wegener's Granulomatosis (WG) and subglottic stenosis (SGS) or tracheal stenosis (TS). Clinical and laboratory findings. *ANCA* antineutrophil cytoplasmatic autoantibodies, *PR3* proteinase 3, *MPO* myeloperoxidase

Patient No.	Sex	Age at presentation of WG	Organs involved at first presentation of WG	ANCA specificity	Number of relapses of WG	Organs involved at first relapse of WG	Follow-up after diagnosis of WG (years)	Age at first presentation of SGS or TS	Interval between diagnosis of WG and first treatment of TS or SGS (months)
1	M	44	Joints	PR3	12	Joints, skin	17	51	92
2	F	26	Lungs, Trachea	PR3	1	Lungs, kidney	14	26	0
3	F	43	Trachea	MPO	1	Lungs	12	43	0
4	F	57	Joints	PR3	2	Ear, eye, kidney, joints	12	67	122
5	F	26	Trachea	PR3	1	Kidney, eye	11	31	60
6	F	51	Mastoid	PR3	2	Nose (concha inferior), mastoid	10	58	81
7	F	42	Ear drum	Atypical	0	Lung, ear drum	8	45	35
8	F	52	Nose	PR3	1	Nose (septum and concha), joints, eye	7	56	48
9	F	33	Nasal vessels	PR3	0	Vessels	4	33	2

Table 2 Patient characteristics of nine patients with Wegener's granulomatosis who underwent DT for SGS or TS compared with the reference group of 182 patients who were diagnosed with WG in the same period without evidence of SGS or TS

	WG patients who underwent DT ($n = 9$)	WG patients without evidence of SGS or TS ($n = 182$)	*P* value
Male/ female number (%)	1/8 (11%/89%)	104/78 (57%/43%)	<0.01
Age at diagnosis of WG (years, mean ± SD)	41.6 ± 11.2	53.3 ± 17.0	<0.05
ANCA specificity	PR3-ANCA: $n = 8$ (89%) MPO-ANCA: $n = 1$ (11%)	PR3-ANCA: $n = 160$ (88%) MPO-ANCA: $n = 13$ (7.1%) HNE-ANCA: $n = 1$ (0.5%) ANCA-negative: $n = 8$ (4.4%)	Not significant

WG Wegener's granulomatosis, *DT* dilatation tracheoscopy, *SGS* subglottic stenosis, *TS* tracheal stenosis, *ANCA* antineutrophil cytoplasmatic autoantibodies, *PR3* proteinase 3, *MPO* myeloperoxidase, *HNE* human neutrophil elastase

5) developed a cricoid stenosis 5 years after the diagnosis of WG. Initially the stenosis was treated with two DT's. During a pregnancy the patient required an emergency tracheotomy because of a threatened airway. After pregnancy she was treated with a CO_2 laser and three DT's. Unfortunately, however, she required a definitive tracheostomy. Currently the process of decannulation is taking place. One patient (number 2) became respiratory insufficient at diagnosis of WG and had a tracheotomy for 3 months. She subsequently developed a cicatricial SGS, but she has enough lumen to live without a tracheostomy (Table 3).

The effect of DT on peakflows was evaluated in five patients. In these patients the mean (±SD) peakflow increased from 164 ± 45.7 l/min before DT to 226 ± 69.6 l/min after dilatation. An example of the effect of DT on the peakflow is shown in Fig. 6. Two months after this patient had been diagnosed with WG she developed complaints of dyspnoea. Tracheoscopy revealed a SGS with signs of active vasculitis. After treatment with high-dose corticosteroids she had a regression of the WG activity. Fourteen and 28 months after first diagnosis of SGS a dilatation tracheoscopy was performed successfully.

Discussion

There are multiple causes of benign laryngeal or tracheal stenosis, the most common being traumatic. However, if there is no prior history of tracheal trauma, the aetiology of the stenosis may be obscure and difficult to determine, necessitating a systematic approach to make the diagnosis. Excluding trauma, the differential diagnosis of TS can be subdivided into four categories: congenital, neoplastic, infectious, and inflammatory.

Table 3 Follow-up after last DT

Patient number	Location of stenosis	Number of DT's	Follow-up after last treatment (months)	Tracheotomy required
1	Subglottic	2	19	No
2	Subglottic	2	21	Yes, temporary
3	Trachea	2	43	No
4	Trachea	2	14	No
5	Cricoid	8	12	Yes
6	Subglottic	2	16	No
7	Subglottic	1	54	No
8	Subglottic	1	26	No
9	Subglottic	2	24	No

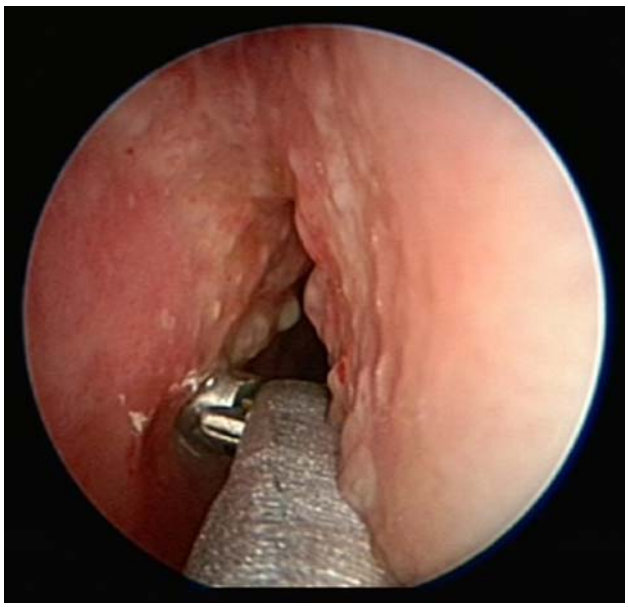

Fig. 4 Patient nr 6 with acute WG during biopsy of a subglottic stenosis

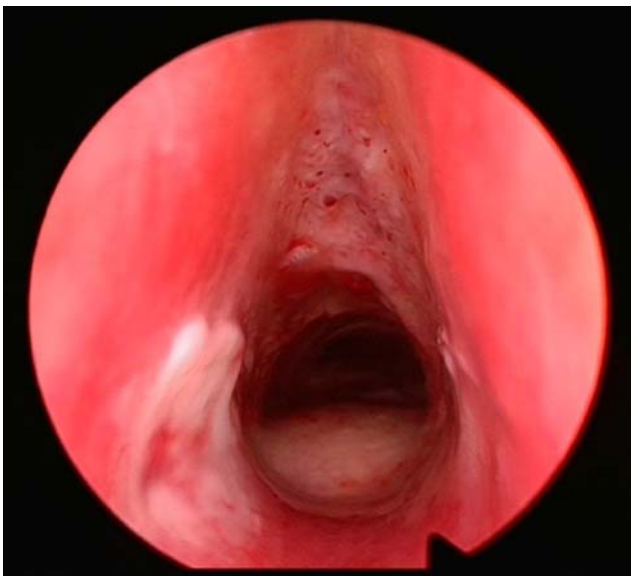

Fig. 5 Patient nr 6 after pulse therapy and intubation. The picture was taken one week after Fig. 4

Congenital TS is really quite rare and is often the result of posterior fusion of the tracheal rings, thereby forming complete rings. Other causes of congenital stenosis include vascular rings and other congenital cardiovascular anomalies such as an anomalous subclavian artery. These patients typically present at young age.

Primary benign tumours of the trachea such as chondromas, fibromas, squamous papillomas, hemangiomas, and granular cell tumours are also unusual causes of stenosis. In addition, extrinsic compression of the trachea can occur by thyroid neoplasms and goiters.

A number of infections of the bronchopulmonary tree can lead to TS. Fungal infections such as histoplasmosis and blastomycosis should always be considered when the aetiology of the stenosis is unclear. Serologic testing and histopathologic examination can be helpful in this regard. Other infectious causes of TS include rhinoscleroma, tuberculosis, syphilis, and diphtheria.

Non-infectious, inflammatory causes of TS include sclerosing mediastinitis, primary amyloidosis, and sarcoidosis. WG and relapsing polychondritis can also cause TS, but they are almost always seen in combination with other, more classic hallmarks of these diseases.

A laryngeal or tracheal stenosis is optimally diagnosed via tracheal visualization, which is generally performed by an otorhinolaryngologist. Indirect and fiberoptic laryngoscopy are non-invasive examination techniques that can be performed in the office, but usually do not show the entire trachea. A subglottic stenosis is not always visible, therefore direct rigid tracheoscopy in general anaesthesia is indicated in cases suspect of WG.

Recurrent SGS is a well recognized but uncommon feature of WG. Patients with WG who develop laryngotracheal disease have usually already been diagnosed as such because of the presence of disease in other organs at the same time or at a previous occasion [6]. Isolated involve-

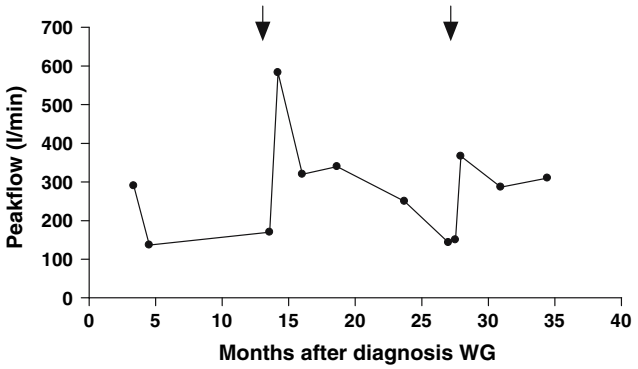

Fig. 6 Peak flow measurements after dilatation of patient number 9. The *arrows* indicate the DT procedures

ment of the subglottic larynx is conspicuously rare—only a few cases have been reported in the literature [2, 7, 8]. In our series, however, three patients had SGS or TS as presenting symptom of their WG. We do not have an explanation for this rare presentation.

Another particular finding is that eight of our nine patients were female. This contrasts significantly with the male/female ratio in the reference group that consisted of WG patients that were diagnosed in the same period as the DT group but who did not have evidence of SGS or TS. It is difficult to speculate on the reason for this female preponderance. Anatomically the female airway is narrower than the male, making it more prone for post-intubation stenosis. However, we even had females presenting with a SGS or TS. More research in larger series has to be performed to explain this phenomenon.

In cases where the diagnosis of WG is suspected, ANCA testing should be part of the routine laboratory evaluation [9]. C-ANCA has been shown to be a specific marker for WG with rare false-positive results; p-ANCA testing is much less specific. Only the particular laboratory findings of c-ANCA reacting with PR3 and p-ANCA reacting with myeloperoxidase (MPO) are specific for the autoimmune vasculitides [9, 10]. Notably, seven of our nine patients that underwent DT were PR3-ANCA positive and one patient was MPO-ANCA positive.

All patients had involvement of additional organs. In three patients the disease presented as a stenosis, and laryngotracheoscopy revealed the size and site of the lesion. Organs involved showed no pattern in which there should be additional suspicion for the development of SGS or TS. There was no relation between the number of relapses and the development of TS or SGS. The TS or SGS occurred more often in periods where the disease appeared to be less active.

Remarkably, TS or SGS predominantly became manifest in periods in which WG appeared to be inactive. Interestingly, seven out of our nine patients who developed TS or SGS had not been diagnosed previously with tracheal involvement of WG, neither at first presentation nor at relapse(s). We speculate that during active disease a subclinical tracheal involvement occurs which may subsequently heal with scar formation. To examine this hypothesis in patients, elective tracheoscopy should be performed in all patients with WG. The time interval between presentation of clinical stenosis in these seven patients (mean 63 months, median 60, range 2–122) favours watchful waiting.

DT with the Groningen dilatation tracheoscope is a safe, minimally invasive procedure for the treatment of Cotton-Myer grade II subglottic or tracheal stenosis of various origin. It is an elegant, self-standing surgical intervention, where no additional interventions are needed. For an overview of the effect of DT the reader is referred elsewhere (G.B. Halmos, F.G. Dikkers, Dilatation tracheoscopy in treatment of subglottic and tracheal stenosis, submitted for publication).

Nowadays, mitomycin-C, an alkylating agent that inhibits cell division, protein synthesis, and fibroblast proliferation [11], is increasingly used as adjuvant treatment in the management of selected cases of laryngeal and tracheal stenosis, for example luminal obstruction in fresh circular sutured wounds. However, the laryngeal and tracheal stenoses of WG patients are almost always of older age and display advanced scarring at the time of diagnosis. Dilating such “mature” stenoses will inevitably lead to damage of tracheal epithelium. However, this damage is considerably different from granulomatous scarification in sutured lumina and, therefore, we do not expect an additional favourable response to mitomycin. Therefore, we have not applied mitomycin-C in our WG patient cohort.

In cases where TS or SGS develops, there is always the question whether or not to intervene, and the question of timing of the intervention. There are two main parameters in these patients: complaints, and physical signs. One might see this as a two-by-two table, with complaints on the *x*-axis, and peakflow values on the *y*-axis. Progressive complaints and progressive decline of peakflow values (+/+) indicate intervention by DT. Absence of progressive complaints and unchanged peakflow values (−/−) indicate watchful waiting. Absence of progressive complaints with decline of peakflow values (−/+) need to be addressed when the values reach a critical level, in which it can be expected that a common cold might lead to severe stenosis of the airways. Finally, progressive complaints with unchanged peakflow values (+/−) indicate that pulmonary function tests should be performed, and, if negative, indicate that the patient has an incorrect perception of his physical potentials. This can then be addressed. Unfortunately, in only five of the nine patients in this retrospective study, we have peak flow measurements. A reason is that two patients have or had a tracheostomy.

We have registered no complications or deaths during or because of DT. We have three reasons to regard dilatation tracheoscopy as a minimally invasive intervention. We have experienced no complications related to dilatation tracheoscopy. It requires short hospitalization (generally 3 days). The intervention is not straining for the patients.

A variety of surgical techniques has been used to treat SGS or TS of other aetiologies [12, 13]. The success of these surgical techniques in upper airway stenosis related to WG has been variable [3, 14]. In our series two out of nine patients were treated once for upper airway stenosis with dilatation without any re-stenosis because of WG.

Unfortunately, two patients required a tracheostomy. One was temporary, but one patient needed a permanent tracheotomy (11%): this was the pregnant woman needing an emergency procedure. This number equals that of Gluth et al. [9].

Conclusion

WG as such is a rare disease, and SGS and TS are rare symptoms in patients with WG. DT can offer a simple and repeatable solution to this very serious symptom. Patient complaints and monitoring of peakflow values offer simple tools for the decision whether or not to intervene. However, a causative solution to WG should be the ultimate goal.

Conflict of interest Dr. F.G. Dikkers has improved the design of the originally used dilatation tracheoscope to the Groningen dilatation tracheoscope. Dr. Dikkers holds an unrestricted educational grant offered by Storz with which a fellow laryngologist is being trained at the University Medical Center Groningen, University of Groningen, The Netherlands.

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