Eur Arch Otorhinolaryngol (2011) 268:733–739
DOI 10.1007/s00405-010-1421-x

MISCELLANEOUS

Long-term damage to the ENT system in Wegener's granulomatosis

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Received: 24 August 2010 / Accepted: 25 October 2010 / Published online: 18 November 2010

Abstract The objectives of the study are to describe long-term ENT damage and assess risk factors in patients with newly diagnosed and treated Wegener's granulomatosis (WG) using the vasculitis damage index (VDI). Data from four randomised controlled trials carried out by the European Vasculitis Study Group was used. Patients newly diagnosed with WG with complete data at 5 years were included. Patients enrolled into the trials without 5-year data were excluded. Total and ENT VDI scores were recorded at 12 months and after at least 5 years. Logistic regression models were constructed to assess risk factors using total ENT and overall VDI score over the follow-up period, the proportion of patients with increased VDI score and the presence or absence of damage as the main outcomes. One hundred and thirty-eight patients were included. Ninety patients (65%) had long-term damage and 81% of these (73/90) developed some damage in the first 12 months. Positive ENT activity score (BVAS) at baseline and relapses were associated with higher ENT VDI scores long-term (OR = 6.90, 95% CI 2.01–23.75; OR = 2.65, 95% CI 1.20–5.82). Increasing BVAS score showed a trend towards lower VDI scores (OR = 0.93, 95% CI 0.88–0.99). Only ENT relapses and number of relapses were associated with an increase in VDI over time (OR = 8.38, 95% CI 3.10–22.68; OR = 1.79, 95% CI 1.24–2.58). In conclusion, most of the ENT damage in these patients was accrued within 12 months of diagnosis. We have shown an association between later ENT damage and the presence of ENT disease at baseline; lower initial BVAS and higher rate of disease relapse.

Keywords Wegener's granulomatosis · ANCA-associated vasculitis · Ear · Nose and throat · Otolaryngology · Damage

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Introduction

Wegener's granulomatosis (WG) is a rare condition that can affect virtually any organ, including the upper respiratory tract. Since the advent of steroids and cyclophosphamide, survival at 5 years has gone from near 0 to 90%

[1]. The increase in survival has meant the disease has become a chronic condition; 75% of these patients relapse at follow-up and approximately 20% have a refractory course [2].

WG is characterized by vasculitis of small and medium sized blood vessels and necrotising granulomata in the connective tissues [3, 4]. Both disease processes cause necrosis and consequently, tissue damage. The ear, nose and throat (ENT) system is particularly prone to damage as it is commonly affected by the disease and patients that have ENT system involvement, often have a relapsing or refractory course [5].

The transformation of WG from a fatal disease to one of chronic morbidity characterized by the accumulation of organ dysfunction has created a need to better understand risk factors for organ damage. Damage accumulation is also increasingly used to measure treatment outcomes [2]. Damage not only reflects the effectiveness of the medication to control disease activity, but also patients' concerns about the effects of the disease [6]. A recent preliminary study showed that patients rate ENT damage higher than dialysis or home oxygen [7]. For the purpose of meaningful comparisons in time and research, scoring systems have been devised: the Vasculitis Damage Index (VDI) [8] and ANCA-associated vasculitis index of damage (AVID) [9]. The use of VDI is recommended by the European league against rheumatic diseases (EULAR) and the European Vasculitis Study Group (EUVAS) [10, 11]. VDI measures 11 organ systems and is a cumulative scoring system; i.e. once an item is scored it remains positively scored for the duration of follow-up. VDI records all damage occurring after the diagnosis of vasculitis, regardless of cause (i.e. whether it has resulted directly from disease activity or therapy or complications or any other events).

This study describes the natural history of damage to the ENT system in patients with newly diagnosed and treated WG using the VDI. We describe the timing of and risk factors for ENT damage.

Methods

Data sources

This study used the European Vasculitis Study Group (EUVAS) database containing four clinical trials conducted between 1995 and 2006 CYCLOPS [12], CYCAZAREM [13], MEPEX [14] and NORAM [15]. These trials included patients with newly diagnosed WG and microscopic polyangiitis representing the full spectrum of severity of these diseases. Three trials compared standard remission induction and maintenance immunosuppression to reduce toxicity regimens in limited and generalized disease and one trial compared adjunctive pulse glucocorticoids to adjunctive plasma exchange in severe disease. All four trials assessed their primary outcomes between 12 and 18 months and then had extended observational follow-up conducted.

At baseline, all trials recorded demographic data, serum creatinine, the Birmingham Vasculitis Activity Score (BVAS) for overall disease activity and organ-specific manifestations. Throughout the follow-up period, all trials recorded relapses of vasculitis and details of the organ systems involved. Each of the five ENT items from the VDI (Table 1) as well as the total VDI score was recorded at 6–12 months and at 5 years or more of follow-up.

Patients

Only patients with a diagnosis of WG and follow-up VDI data at 5 years or later were included. The criteria used to diagnose WG were adapted from the classification criteria of the American College of Rheumatology and the definitions from the Chapel Hill Consensus Conference [4, 13, 16].

Data collected

We described the proportions of patients that had ENT damage according to the VDI at 6–12 months and at

Table 1 ENT items in VDI score

ENT Item	Description
Hearing loss	Any hearing loss due to middle ear involvement or to auditory nerve/cochlear damage, preferably confirmed by audiometry.
Nasal blockage/chronic discharge/crusting	Difficulties with breathing through the nose and/or with purulent discharge and/or with crust formation usually requiring nasal lavage
Nasal bridge collapse/septal perforation	Saddle nose deformity and/or perforation of nasal septum
Chronic sinusitis/radiological damage	Chronic purulent nasal discharge with sinus pain and/or radiological evidence of sinusitis with or without bone destruction
Subglottic stenosis with or without surgery	Persistent hoarseness and/or stridor preferably confirmed by endoscopy and/or X-ray

>60 months after diagnosis. We also assessed potential risk factors for ENT damage at >60 months using three outcomes: (1) the proportion of patients with any ENT VDI items scored at >60 months, (2) the proportion of patients with an increased number of ENT VDI items scored at >60 months as compared to ≤1 year, and (3) the absolute ENT VDI score at >60 months.

Statistics

Continuous variables were described as medians and interquartile ranges (IQR) and categorical variables were described as counts and percentages. Continuous variables were compared with the Wilcoxon's rank-sum test and categorical variables were compared with the Fisher's exact test. To assess the risk factors for ENT damage at >60 months, we constructed multivariable logistic regression models for the outcomes of (1) the proportion of patients with any ENT VDI damage at >60 months, and (2) the proportion of patients with an increase in ENT VDI damage between 6 to 12 and 60 months. To assess the outcome of the absolute VDI score at >60 months, we constructed an ordered logistic regression model because of the non-interval nature of the VDI scale. Each model was adjusted for trial, and was constructed by entering all candidate variables (forced entry) with no pre-specified interaction terms. The pre-specified candidate variables include age, sex, baseline creatinine, baseline BVAS, baseline ENT activity, number of relapses, occurrence of ENT relapses, positive PR3-ANCA and trial. Because of partial colinearity between the number of relapses and ENT relapses, two models were created for each analysis, one for each variable. To assess the possible impact of lower intensity treatment with methotrexate, the subgroup of NORAM patients was also analyzed with the addition of treatment in the model. Multiple imputation was performed for variables with missing data to allow all cases to be used for analysis. All variables had <4% missing data. All tests were two-sided, and $p < 0.05$ was considered significant. All analyses were conducted with Stat version 11MP (College Station, TX, USA).

Results

Patients

Of the 213 patients with WG in the included trials, 138 had complete data at 5 years or more. Among those excluded, 13 patients died before 5 years of follow-up and 62 were lost to follow-up or had not completed 5 years of follow-up. There were no differences in prevalence of ANCA or ANCA subtype in the selected or in the excluded groups of patients. Table 2 illustrates the demographic characteristics of the patients included for analysis.

Fifty patients were from the NORAM and 55 from the CYCAZAREM, 15 from the CYCLOPS and 18 from the MEPEX studies. Cyclophosphamide was used as an

Table 2 Demographic data of patients

	Overall	At last follow up		*p*
		ENT damage	No ENT damage	
Patients (*n*)	138	90	48	
Median age (range)	58 (20–79)	55 (20–77)	59.5 (23–79)	0.116
Females (%)	65 (47)	47 (52)	19 (40)	0.110
Median relapse number	1 (0–6)	1 (0–6)	0 (0–4)	0.001
Relapse involving ENT system (%)	35/137 (26)	30/90 (33)	5/47 (11)	0.004
Cyclophosphamide 5 years of exposure	12 (0–72)	12 (0–66)	9 (0–72)	0.306
Clinical features at trial entry				
Median BVAS (range)	19 (2–38)	19 (2–38)	24 (9–38)	0.009
ENT disease at trial entry (%)	116/133 (87)	84/89 (94)	32/44 (73)	0.001
Nasal obstruction (% positive)	77/133 (58)	60/89 (67)	17/43 (39)	0.003
Bloody nasal discharge (% positive)	67/133 (50)	53/89 (60)	14/44 (32)	0.003
Nasal crusting (% positive)	66/133 (50)	51/89 (57)	15/44 (34)	0.016
Sinus involvement (% positive)	42/133 (32)	30/89 (34)	12/44 (27)	0.553
Hearing loss (% positive)	49/133 (37)	42/89 (47)	7/44 (16)	0.001
Hoarseness/stridor (% positive)	10/133 (8)	5/89 (6)	5/44 (11)	0.298
ANCA serology				
PR3 (% positive)	114 (83)	74 (82)	40 (83)	0.535
MPO (% positive)	10 (7)	5 (6)	5 (11)	0.237
PR3/MPO negative (% negative)	14 (10)	11 (12)	3 (6)	0.212

p values obtained using χ^2 for categorical variables and Wilcoxon's rank-sum test was used for continuous variables

induction agent in 113/138 (82%) patients, 10 of whom received pulse cyclophosphamide and the remaining 103 received oral treatment. Methotrexate was used for induction in 25/138 (18%) patients with limited disease.

Damage

Ninety patients (65%) suffered ENT damage over the follow-up period; 73 (53%) within 12 months of whom 28 developed further damage after 12 months. Only 17 (12%) began to accrue ENT damage after 12 months of follow-up (Fig. 1). A positive ENT VDI within 12 months was associated with a significant increase in ENT VDI score between 12 and 60 months ($p < 0.0001$; Fig. 2). 44% of patients with one item of ENT damage by 12 months developed further ENT damage long-term and a quarter of those with none, two or three positive items developed further long-term ENT damage. The quantity of ENT damage did not differ between trials, despite the recruitment of WG patients with differing disease severity, at either 12 months or extended follow-up.

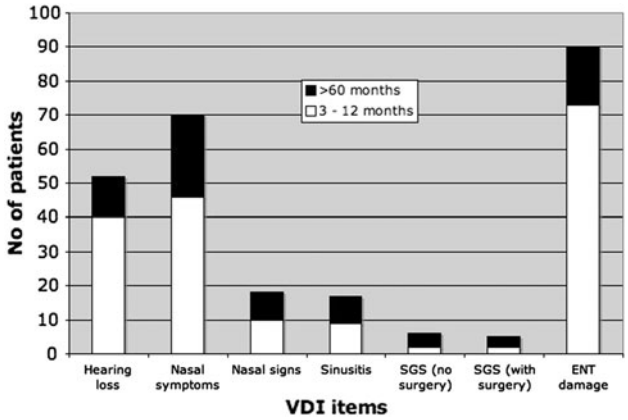

Fig. 1 Distribution of damage and change over time

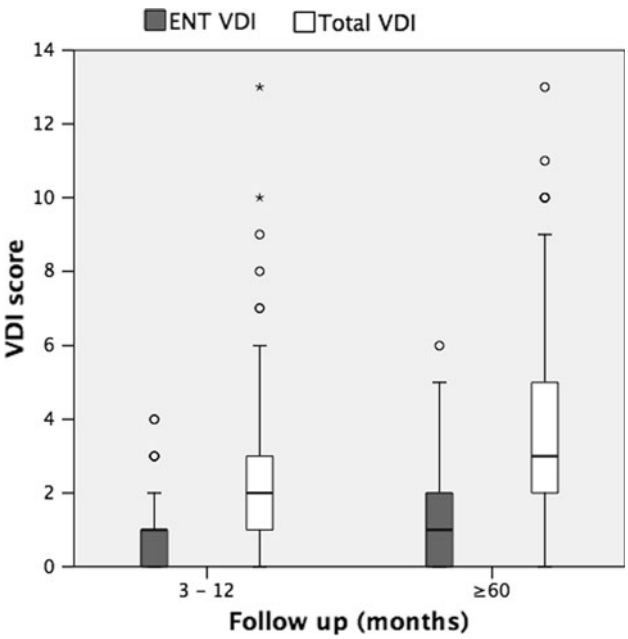

Fig. 2 Change in total and ENT VDI scores over time

The most commonly documented features of ENT damage were nasal symptoms (nasal blockage, chronic discharge and crusting) in 50.7% (70/138) of cases, followed by hearing loss in 37.7% (52/138). The least common ENT items of damage were saddle nose deformity and/or septal perforation (13%, 18/138), and subglottic stenosis (7.9%, 11/138).

The distribution of damage to the different areas of the ENT system is graphically illustrated in Fig. 1. Hearing loss and nasal obstruction were the most common symptoms in this group of patients. The increase in hearing loss over time was the least pronounced at 20% of overall damage. Subglottic stenosis was the least common form of ENT damage, affecting only 3/138 (2%) of patients at onset and 6/138 (4%) at last follow-up.

Prediction of damage

Our models assessing the risk factors for ENT damage are summarized in Table 3. ENT activity at baseline, and number of relapses or the occurrence of ENT relapses were independently associated with any ENT damage at >60 months (OR = 9.44, 95% CI 2.09–42.56; OR = 1.69, 95% CI 1.03–2.78; OR = 4.45, 95% CI 1.20–16.43) and with higher ENT VDI scores at >60 months (OR = 6.90, 95% CI 2.01–23.75; OR = 1.32, 95% CI 1.00–1.75; OR = 2.65, 95% CI 1.20–5.82), while higher BVAS scores at baseline showed a trend towards reduced risk of any ENT damage and lower VDI scores (OR = 0.92, 95% CI 0.85–1; OR = 0.93, 95% CI 0.88–0.99). Only ENT relapses and number of relapses were associated with an increase in the ENT VDI over time (OR = 8.38, 95% CI 3.10–22.68; OR = 1.79, 95% CI 1.24–2.58). There was no effect of ANCA sub-type in any model. The use of methotrexate compared with cyclophosphamide was not associated with increased ENT damage for any of our three outcomes ($p = 0.18$ for any ENT damage; $p = 0.43$ for increase in ENT damage; $p = 0.90$ for absolute ENT VDI score).

Discussion

ENT damage is a cause of significant morbidity for patients with WG. We found that two-thirds of patients suffered from ENT damage at long-term follow-up and most of the ENT damage was accrued in the first 12 months with nasal

Table 3 Multivariable models assessing association between risk factors and three different outcomes of ENT damage after 5 years

Variables	Model 1		Model 2	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Any ENT damage				
Age	0.98 (0.95–1.01)	0.238	0.98 (0.95–1.01)	0.227
Sex	1.67 (0.67–4.21)	0.274	1.88 (0.74–4.78)	0.182
Creatinine	0.86 (0.70–1.06)	0.15	0.84 (0.68–1.04)	0.114
BVAS	0.92 (0.85–1.00)	0.045	0.91 (0.84–0.99)	0.025
ENT activity	9.44 (2.09–42.56)	0.003	8.16 (1.89–35.17)	0.005
No. of relapses			1.69 (1.03–2.78)	0.037
ENT relapse	4.45 (1.20–16.43)	0.025		
PR3-ANCA	0.56 (0.16–1.98)	0.369	0.46 (0.13–1.62)	0.227
Increase in VDI score				
Age	1.02 (0.99–1.05)	0.13	1.02 (0.99–1.05)	0.188
Sex	0.81 (0.33–1.96)	0.635	0.96 (0.42–2.22)	0.931
Creatinine	1.00 (0.81–1.22)	0.99	0.99 (0.81–1.22)	0.956
BVAS	0.96 (0.89–1.04)	0.322	0.95 (0.88–1.03)	0.198
ENT activity	2.77 (0.67–11.50)	0.161	2.13 (0.56–8.10)	0.265
No. of relapses			1.79 (1.24–2.58)	0.002
ENT relapse	8.38 (3.10–22.68)	<0.001		
PR3-ANCA	2.10 (0.62–7.17)	0.236	1.53 (0.47–4.94)	0.477
Total ENT VDI				
Age	0.98 (0.96–1.00)	0.100	0.98 (0.64–1.00)	0.085
Sex	1.40 (0.70–2.82)	0.341	1.45 (0.72–2.93)	0.296
Creatinine	0.91 (0.76–1.08)	0.273	0.90 (0.76–1.07)	0.237
BVAS	0.93 (0.88–0.99)	0.024	0.93 (0.87–0.99)	0.021
ENT activity	6.90 (2.01–23.75)	0.002	6.38 (1.89–21.62)	0.003
No. of relapses			1.32 (1.00–1.75)	0.052
ENT relapse	2.65 (1.20–5.82)	0.015		
PR3-ANCA	0.59 (0.24–1.48)	0.262	0.52 (0.21–1.30)	0.165

Calculations based on 135 patients with complete data. Odds ratios are based on the following changes for continuous variables: age based on 1 year unit changes, creatinine based on 50 μmol/L unit changes, BVAS based on 1 unit change in score

disease and hearing loss being the most common damage manifestations. The increase in damage over time was statistically significant ($p < 0.0001$). Disease activity affecting the ENT system at baseline and relapses during follow-up were associated with greater risk of ENT damage long term (OR = 6.90, 95% CI 2.01–23.75; OR = 2.65, 95% CI 1.20–5.82, respectively). As previously reported [17], there was a trend for less long-term damage in patients with higher initial BVAS. This is likely to have been due to the contribution of renal disease to BVAS and the reduced frequency of ENT involvement in those with renal disease. Gender, age, positive PR3-ANCA and use of methotrexate at induction were not associated with ENT damage.

Baseline involvement of the ENT system in our study was similar to other cohorts (87% compared with 75–99% [1, 5, 18, 19]). However, ENT damage at the end of follow-up was at the lower end of the spectrum when compared with previously published data (65% compared with 51–99% [1, 17, 18, 20]). Increased awareness, earlier diagnosis and the fact that only newly diagnosed patients were included in the cohort studied may be the cause for this. By comparison to a North American cohort of patients with WG [21], the current cohort had more hearing loss (38 vs. 25%) and nasal symptoms (51 vs. 17%). These results imply that the overall ENT damage may be lower than our cohort (40% had ENT damage at baseline). Geographic factors could play a role in the differences, because the present cohort is European and the comparator is from North America. The availability of resources, such as audiology services could also explain some of the variation. In addition, in North America damage, items were scored positive when they were present for 6 months while in Europe, VDI items were scored when they were present for 3 months. In North America, the items also had to be attributable to vasculitis, but this should not influence the result, as all ENT items were considered attributable to the disease. As in the present cohort, Seo et al. found that increased number of flare ups was associated with increased long-term damage.

The data presented in this paper suggests that early recognition of the disease and prompt treatment reduces later damage. Moreover, as survival has improved with

cyclophosphamide, the focus of patient management has moved to minimize damage and improve quality of life. Consensus reports have emphasized the need for damage assessment in vasculitis studies [6]. Many WG patients pursue a frequently relapsing or refractory disease course, and these subgroups are an important target for newer therapeutics to reduce their ENT damage risk [22–24].

This is one of the most comprehensive prospective assessments of long-term damage to the ENT system in a large cohort of newly diagnosed patients with WG. Other studies have assessed damage in general in WG [1, 18, 19] have focused on different aspects of ENT disease [25, 26] or had a shorter follow-up period [21]. However, this study includes patients from four different trials, and is limited to the items and rules of VDI. The adjustment for trial was felt necessary because the inclusion criteria of each of the trials included different creatinine levels and disease distribution and risked introducing sample bias. The limitations of VDI as a scoring system are that it lacks detail (e.g. specific hearing loss measured by pure tone audiometry or more documentation of detailed intranasal appearances seen with a nasendoscope) does not allow for progression or regression of damage items, and is often not scored by ENT specialists which may be addressed in the future by improved scoring systems [9]. This last point may explain the lower incidence of subglottic stenosis in this study (6.5% compared to 12–17.8% [1, 18, 21]).

Conclusion

Most of the ENT damage in this cohort was accrued within 12 months of diagnosis (53% of patients at 12 months and 65% at last follow-up), although statistically the ENT and total VDI scores significantly increased over time. A positive association was found between later damage and disease activity in the ENT system at baseline (OR 7.03, 95% CI 2.03–24.29) and later damage and the total incidence relapses as well as those affecting the ENT system (OR 1.34, 95% CI 1.01–1.79), while a high initial BVAS score showed a trend towards less later damage (OR 0.94, 95% CI 0.88–1). Methotrexate and creatinine levels at induction, age or gender were not associated with later ENT damage. Finally, we have shown that possible predictors of later ENT damage include baseline ENT disease activity, and relapse, which could be used to target therapy to higher risk patients. However, to be able to use the VDI to record the ENT phenotype of the disease, greater detail is required.

Acknowledgments This study is based on data from the European Community Systemic Vasculitis Trial project (Contract nos. BMH1-CT93-1078 and CIPD-CT94-0307) and the Associated Vasculitis European Randomized Trial project (Contract nos. BMH4-CT97-2328 and IC20-CT97-0019) funded by the European Union.

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