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ANCA-associated glomerulonephritis : insights into etiology, pathogenesis, and prognosis

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Supposing is good, finding out is better.
Mark Twain





Chapter 5

ENT involvement is related to
better renal function in patients
with ANCA-associated
glomerulonephritis

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Abstract

Objective To determine whether ear, nose, and throat (ENT) involvement was associated with less severe histological renal injury and better renal function in patients with anti-neutrophil cytoplasm autoantibody (ANCA)-associated vasculitis (AAV) than in AAV patients without ENT involvement.

Design Cross-sectional observational study.

Setting 29 hospitals in 11 European countries.

Participants 174 patients newly diagnosed with AAV from two international, prospective, multicenter trials. Depending on the trial, patients had mild to moderate renal disease or severe renal disease.

Main outcome measures ENT involvement and glomerular filtration rate (GFR) at diagnosis were the main outcome parameters. 21 histological and nine clinical parameters in the diagnostic renal biopsy were analysed.

Results 48 patients had ENT involvement at diagnosis, 126 patients did not. Multivariate analysis revealed that the percentage of glomerulosclerosis ($r = -0.20$, $p = 0.01$) and the presence of large-vessel sclerosis ($r = -0.25$, $p = 0.02$) were negatively associated with ENT involvement. In combination with ENT involvement ($r = 0.30$, $p = 0.003$), PR3-ANCA pattern ($r = 0.28$, $p = 0.005$), age ($r = -0.34$, $p < 0.001$), the percentage of normal glomeruli ($r = 0.67$, $p < 0.001$), and the extent of tubular necrosis ($r = -0.43$, $p < 0.001$) were associated with GFR at diagnosis.

Conclusions ENT involvement in AAV with renal disease is associated with better renal function and less severe histological renal injury, probably due to diagnosis before the development of irreversible chronic lesions. ENT is a determinant of GFR independent of the ANCA pattern.

Trial registration Trial contract nos. BMH4-CT97-2328 and IC20-CT97-0019.



Introduction

Renal involvement is a common and usually severe feature of anti-neutrophil cytoplasm autoantibody (ANCA)-associated vasculitis (AAV) that can lead to end-stage renal failure or death ¹. Microscopic polyangiitis and Wegener's granulomatosis are the most frequent diagnoses within the spectrum of AAV, while renal-limited vasculitis, a forme-fruste of the systemic syndromes, occurs less frequently ².

Patients with AAV present with renal dysfunction of varied severity, which, to a large extent, defines their initial therapeutic regimen ^{3,4}. For certain patients whose condition indicates dialysis dependence at presentation, it is assumed that subclinical smouldering disease has been present for some time ⁵. Other patients may have rapidly progressing glomerulonephritis without previous renal lesions. Previously, we found that patients with anti-myeloperoxidase ANCA (MPO-ANCA) had more chronic lesions than did patients with anti-proteinase 3 ANCA (PR3-ANCA). It has been suggested that because the majority of patients with PR3-ANCA have Wegener's granulomatosis, they are likely to have ear, nose, and throat (ENT) involvement, which carries the advantage of earlier recognition of their systemic vasculitis ⁵. Alternatively, differences in histological findings between patients with MPO-ANCA and PR3-ANCA might represent different routes in the pathogenesis of vasculitic disease in these subsets of patients.

In this study, we focused on ENT involvement in patients with AAV relative to renal histology and function at the time of biopsy. We hypothesised that ENT involvement in AAV was associated with better renal function and concomitant better renal histopathology than AAV without ENT involvement. We further hypothesised that if patients with systemic vasculitis and ENT involvement were diagnosed earlier, regardless of their diagnosis and ANCA-test results, better glomerular filtration rates (GFR) and fewer chronic lesions would be present in these patients as compared to patients without ENT involvement.

Methods

Patients

Patients were recruited from 29 hospitals located in 11 European countries. One group consisted of patients enrolled in the MEPEX trial, a randomised trial evaluating adjunctive therapy for severe glomerulonephritis (serum creatinine of ≥ 500 $\mu\text{mol/L}$ at entry) in patients with AAV ⁴. The other group consisted of patients enrolled in the CYCAZAREM trial, a randomised trial

evaluating remission maintenance therapy for mild to moderate renal involvement (serum creatinine between 200 and 500 $\mu\text{mol/L}$) in patients with AAV³. All patients had been newly diagnosed and renal biopsies were taken at time of diagnosis. The local research ethics committees approved the studies, and all patients provided written informed consent to participate. Inclusion and exclusion criteria for both trials are described elsewhere^{3,4,6}.

Disease definitions were adopted from the 1992 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis⁷ and a previous European Union Study⁸. The diseases were distinguished based on previously published criteria⁹ and were determined by local physicians. For those patients who were not on dialysis, GFR was determined by the Cockcroft-Gault equation for the estimation of renal function¹⁰. ENT involvement was defined as present if patients scored at least one point on the ENT items from the Birmingham Vasculitis Activity Score¹¹. The items included nasal obstruction, bloody nasal discharge, nasal crusts, sinus involvement, conductive hearing loss, sensorineural hearing loss, hoarseness/stridor, granulomatous sinusitis, and subglottic inflammation¹¹. A local ENT specialist assessed patients with suspected ENT involvement. Other clinical variables included in the analysis were gender, age, and ANCA antigen specificity as determined by enzyme-linked immunosorbent assay.

Assessment of histological lesions

Histological parameters were determined from paraffin sections of diagnostic renal biopsies stained with silver, periodic acid-Schiff, haematoxylin and eosin, and trichrome. Sections were reviewed by two of five participating pathologists (IMB, FF, LHN, RW, or JAB). Both pathologists, blinded to patient data and the other observer's results, scored the biopsies separately and according to a previously standardised protocol^{12,13}. Discrepancies between observers were resolved during central reviews to achieve a consensus for each biopsy.

Statistical Analysis

SPSS 14.0 standard version for Windows (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. Differences between the two patient groups with regard to glomerular lesions were assessed by Student's t-test. Phi-values and Cramér's V tests were used to detect differences between the groups with regard to the dichotomous and categorical tubulo-interstitial and vascular parameters. Correlations with ENT involvement were tested by a Phi-value test if

parameters were dichotomous, by a Cramér's V test if parameters were categorical, and by a Pearson's correlation test if parameters were continuous. Correlation between GFR at time of biopsy and dichotomous or continuous variables was tested using Pearson's correlation test; correlation between GFR and categorical variables was tested using Spearman's rank test. Each parameter that correlated with a P-value ≤ 0.15 for ENT involvement or ≤ 0.10 for GFR was entered in the model as a possible determinant of outcome. The values of exponent β were used to express odds ratios (OR). Correlation coefficients were noted as r , and predictive values as r^2 .

Results

Patients

Of the 151 patients from the MEPEX trial, four declined participation in our study and 10 were excluded because they did not meet the trial inclusion criteria. None of the remaining 137 patients were withdrawn from the study. Renal biopsies from 102 patients were obtained for re-evaluation. Two biopsies were excluded because of the absence of cortical tissue, leaving 100 biopsies available for the final analysis. Data on ENT involvement were missing for 13 of these patients. All required data were available for 87 patients: 22 had ENT involvement, 65 did not. Baseline characteristics are depicted in Table 1.

Table 1. Baseline characteristics of patients with and without ENT involvement

	ENT+ (n=48)	ENT- (n=126)	P-value
GFR ($\mu\text{mol/L}$; $\pm$ SD)	46.1 $\pm$ 35.6	28.7 $\pm$ 21.4	0.003
Gender (male/female)	25 / 23	66 / 60	NS
Age (years $\pm$ SD)	57.7 $\pm$ 14.8	61.5 $\pm$ 11.6	0.08
Wegener's granulomatosis (n; (%))	39 (81%)	44 (35%)	< 0.001
Microscopic polyangiitis (n; (%))	9 (19%)	69 (55%)	< 0.001
Renal-limited vasculitis (n; (%))	0 (0%)	13 (10%)	< 0.001
PR3-ANCA	33 (80%)	49 (47%)	< 0.001
MPO-ANCA	8 (20%)	55 (53%)	< 0.001
Normal glomeruli (%)	33 $\pm$ 32	26 $\pm$ 27	0.15
Fibrinoid necrosis (%)	27 $\pm$ 26	20 $\pm$ 24	0.12
Total crescents (%)	49 $\pm$ 29	47 $\pm$ 31	NS
Segmental crescents (%)	19 $\pm$ 19	17 $\pm$ 19	NS
Circumferential crescents (%)	30 $\pm$ 27	29 $\pm$ 29	NS
Cellular crescents (%)	46 $\pm$ 30	41 $\pm$ 30	NS
Fibrous crescents (%)	3.3 $\pm$ 7.7	5.2 $\pm$ 9.3	NS
Glomerulosclerosis (%)	15 $\pm$ 21	26 $\pm$ 28	0.01

Numbers represent the number of patients unless otherwise specified. Only P-values below 0.15 are listed. Patients with and without ENT involvement are referred to as ENT+ and ENT-. NS = not significant.

Within the patient group from the CYCAZAREM trial, renal biopsies had been performed for 132 of 152 patients. Of these, 109 were obtained for re-evaluation. From this group, seven patients were excluded at entry (five because cortical tissue was absent in the biopsy specimens and two did not meet the trial inclusion criteria), leaving 102 biopsy specimens available for analysis. Data on ENT involvement were missing for 15 patients. All required data were available for 87 patients: 26 had ENT involvement, 61 did not. The incidences of different ENT lesions in patients with ENT involvement are listed in Table 2. For this study, we analysed patients from both trials as a single group.

Table 2. Overview of different symptoms in patients with ENT involvement and their incidence at diagnosis

ENT symptom	% of ENT involved patients with symptom
Nasal obstruction	46%
Bloody nasal discharge	40%
Nasal crusting	30%
Sinus involvement	24%
Hearing loss	22%
Hoarseness/stridor	3%
Otorhinolaryngologist's opinion	51%
No active vasculitis	16%
Granulomatous sinusitis	16%
Conductive hearing loss	14%
Sensorineural hearing loss	0%
Significant subglottic inflammation	6%

ENT represents ear, nose and throat involvement. All items below 'otorhinolaryngologist's opinion' were only scored by the otorhinolaryngologist.

ENT involvement related to clinical and histological markers

The mean GFR at diagnosis of patients with ENT involvement was 46.1 $\mu\text{mol/L}$; the mean GFR at diagnosis of patients without ENT involvement was 28.7 $\mu\text{mol/L}$. This difference was statistically significantly ($p = 0.003$; Fig 1).

Baseline characteristics of patients with and without ENT involvement (Table 1) revealed that patients with ENT involvement typically had Wegener's granulomatosis and/or PR3-ANCA. Nevertheless, a substantial proportion of patients with ENT involvement (19%) did not have Wegener's granulomatosis. Twenty percent of patients with ENT involvement had MPO-ANCA. Of patients without ENT involvement, about one-half had PR3-ANCA and one-half had MPO-ANCA. 35% of patients with Wegener's granulomatosis did not have ENT involvement.

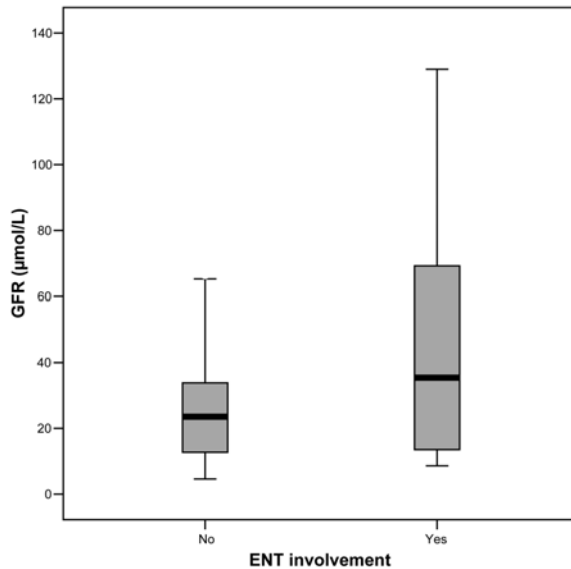


Fig 1. Box plot of ear, nose, and throat (ENT) involvement relative to glomerular filtration rate (GFR). Mean GFR is significantly higher in patients with ENT involvement (46 ± 35.6 $\mu\text{mol/L}$) than in those without (28.7 ± 21.4 $\mu\text{mol/L}$; $p = 0.003$).

Multivariate analysis showed that in addition to ENT involvement, PR3-ANCA pattern, the percentage of normal glomeruli, age, and tubular necrosis determined GFR at diagnosis (data not shown).

Univariate analyses showed a relationship between ENT involvement and diagnosis and between ENT involvement and ANCA-antigen specificity, as shown in Table 3. ENT involvement was negatively correlated with the percentage of glomerulosclerosis ($r = -0.195$; $p = 0.01$) and with the presence of large-vessel sclerosis ($r = -0.253$; $p = 0.02$). No variables from the tubulo-interstitium correlated with ENT involvement.

Multivariate analysis including histological variables that correlated with ENT involvement in univariate analysis ($p < 0.15$) showed that the percentage of glomerulosclerosis ($p = 0.03$) and the presence of large-vessel sclerosis ($p = 0.03$) were independent statistical determinants of ENT involvement. Multivariate analysis including both clinical and histological variables that correlated with ENT involvement in univariate analysis ($p < 0.15$) showed that ENT involvement was statistically determined by the absence of MPO-ANCA and large-vessel sclerosis and by the presence of Wegener's granulomatosis.

Table 3. Correlation of clinical and histologic parameters with ENT involvement and with GFR at diagnosis

	ENT involvement (0/1)		GFR	
	r	P-value	r	P-value
Clinical variables				
ENT (-/+)	-	-	0.295	0.003*
Gender (a)	-0.003	0.97	-0.063	0.52
Age	-0.132	0.08	-0.359	<0.001*
Microscopic polyangiitis (-/+)	-0.324	< 0.001*	-0.230	0.02*
Renal limited vasculitis (-/+)	-	-	-0.153	0.12
Wegener's granulomatosis (-/+)	0.415	< 0.001*	0.296	0.002*
MPO-ANCA (-/+)	-0.273	0.001*	-0.205	0.04*
PR3-ANCA (-/+)	0.279	< 0.001*	0.277	0.005*
Glomerular lesions				
No abnormalities	0.109	0.15	0.667	<0.001*
Fibrinoid necrosis	0.117	0.12	-0.232	0.02*
Crescents	0.033	0.66	-0.382	<0.001*
Segmental crescents	0.038	0.62	-0.155	0.11
Circumferential crescents	0.011	0.89	-0.334	<0.001*
Cellular crescents	0.061	0.42	-0.367	<0.001*
Fibrous crescents	-0.094	0.22	-0.056	0.56
Glomerulosclerosis	-0.195	0.01*	-0.294	0.002*
Interstitial lesions				
Interstitial edema	0.089	0.50	-0.213	0.03*
Interstitial infiltrates	0.191	0.29	-0.423	<0.001*
Neutrophilic infiltrate	0.138	0.57	-0.034	0.74
Monocytic infiltrate	0.151	0.17	-0.072	0.49
Eosinophilic infiltrate	0.172	0.21	-0.166	0.12
Interstitial fibrosis	-0.207	0.11	-0.372	<0.001*
Tubular lesions				
Tubular necrosis	-0.032	0.67	-0.430	<0.001*
Tubular atrophy	-0.182	0.22	-0.368	<0.001*
Intra-epithelial infiltrates	-0.083	0.55	-0.342	<0.001*
Tubular casts	-0.060	0.43	-0.293	0.002*
Granulomas	-0.098	0.80	-0.051	0.48
Vascular lesions				
Arteriosclerosis	-0.140	0.09	-0.278	0.007*
Large-vessel sclerosis	-0.253	0.02*	-0.229	0.07

ENT = ear, nose, and throat; GFR = glomerular filtration rate; PR3-ANCA = anti-proteinase 3 (PR3) anti-neutrophil cytoplasm autoantibodies (ANCA); MPO-ANCA = anti-myeloperoxidase (MPO) anti-neutrophil cytoplasm autoantibodies (ANCA). * correlation with a P-value < 0.05. (a) female was coded '0' and male '1' in this analysis.

Discussion

These data showed that patients with ANCA-associated glomerulonephritis and ENT involvement had significantly better renal function in terms of GFR at diagnosis than did patients without ENT involvement, strongly supporting our hypotheses that ENT involvement can lead to earlier diagnosis of AAV and that renal biopsies are probably taken earlier in the disease course in patients with ENT involvement than in those without. The histological findings further support our hypothesis as patients without ENT involvement had more global glomerulosclerosis, indicating that glomerular disease has been present longer than in patients with ENT involvement. In addition, large-vessel sclerosis was present more often in patients without than in patients with ENT involvement.

There were no differences in the presence of acute glomerular lesions relative to ENT involvement between the two groups. The relationship between chronic and acute glomerular lesions and the number of unaffected glomeruli is complex. One of the few studies including findings from follow-up renal biopsies of patients with AAV reported that during treatment, the percentage of normal glomeruli remained stable, while glomeruli with active lesions progressed to irreversibly damaged glomeruli with glomerulosclerosis or regressed to recovered glomeruli, depending on 'the point of no return' ¹⁴. Taking these findings and those of this report into account, we propose a time course of disease progression in terms of glomerular lesions relative to the point of diagnosis and ENT involvement (Figure 2).

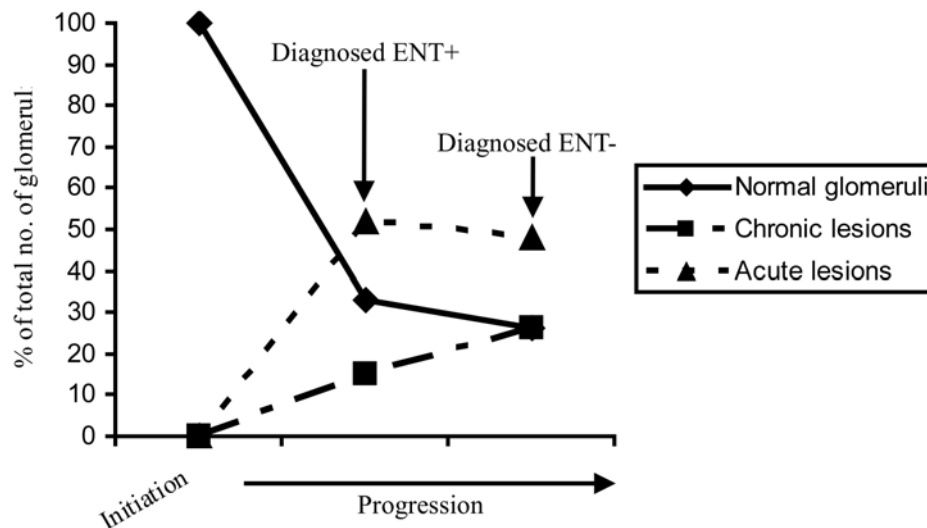


Fig 2. Overview of the process of developing ANCA-associated renal disease. Glomerular injury is visualized, as well as the hypothetical beneficial effect of ear, nose, and throat (ENT) involvement. The x-axis indicates disease progression over time. Diagnosed ENT+ indicates the timepoint at which patients with ENT involvement were biopsied and diagnosed, ENT- indicates this timepoint for patients without ENT involvement.

Previously, we found that patients with MPO-ANCA had more chronic glomerular and tubulointerstitial lesions than did patients with PR3-ANCA ⁵. We suggested this could be explained either by earlier disease recognition because of ENT involvement in patients with PR3-ANCA who would be most likely to have Wegener's granulomatosis, or by different pathogenic pathways for MPO-ANCA and PR3-ANCA ⁵. In the present study, the differences in histology between MPO-ANCA and PR3-ANCA could not be accounted for

only by ENT involvement, because multivariate analysis revealed that ENT involvement was a determinant of GFR independent of PR3-ANCA.

Literature on ENT involvement in AAV relative to outcome is scarce (according to an English language PubMed search through June 2008). But it has been reported that ENT involvement predicts better survival in patients with Wegener's granulomatosis^{15,16}. In these papers, this phenomenon was hypothesised to illustrate the difference between two clearly distinguished disease processes within the spectrum of vasculitis: granulomatous and vasculitic disease^{15,16}. ENT involvement is considered a sign of granulomatous disease^{17,18}, whereas a vasculitic component plays a larger role in renal disease¹⁷. It has been suggested that the granulomatous component is a sign of early disease and might provide the necessary proinflammatory environment to breakdown tolerance to PR3. In a later stage, the vasculitic component plays a more prominent role, initiating a self-perpetuating pathological course¹⁹. This hypothesis coincides with the findings from our study: patients with ENT involvement appear to have a larger granulomatous component, which is a marker of early disease.

Because our clinical aim is to diagnose patients with AAV as early as possible in order to prevent severe, irreversible chronic renal disease, we want to understand which clinical symptoms trigger the physician to suspect a diagnosis of systemic vasculitis. Data from this study do not address this issue specifically. However, our study does illustrate that patients without ENT symptoms are at risk for chronic glomerular damage. Therefore, the challenge lies in the early detection of vasculitis in patients without ENT involvement. This issue should be the focus of future research. In our study population, patients without ENT involvement had general symptoms like myalgia, arthralgia/arthritis, body temperature over 38 C, and weight loss ≥ 2 kg (present in 93%), while 51% had chest involvement (e.g. wheezing, nodules, cavities, infiltrates, or haemoptysis) and 18% had cutaneous involvement (e.g. infarcts, purpura, ulcers, gangrene). In order to avoid overlooking a diagnosis of systemic vasculitis, patients should be evaluated for these specific symptoms. Future research should be aimed at methods for the early detection of generalised vasculitis.

In summary, this study shows that patients with ENT involvement in AAV have less severe renal disease and more favourable renal outcomes than do patients without ENT involvement. ENT involvement might facilitate clinical diagnosis at an early stage, before the development of irreversible chronic renal lesions.



What is already known on this topic

ENT involvement predicts better survival in patients with Wegener's granulomatosis, possibly because the disease is recognised earlier because of the more obvious clinical manifestations of ENT involvement.

Patients with Wegener's granulomatosis usually have PR3-ANCA vasculitis. Renal histology shows fewer chronic lesions in patients with PR3-ANCA vasculitis as compared to patients with MPO-ANCA vasculitis.

What this study adds

Patients with ENT involvement in AAV have less severe renal disease and better renal function than do patients without ENT involvement.

The differences in chronic lesions and renal function between patients with MPO-ANCA and PR3-ANCA cannot be accounted for by ENT involvement alone, because ENT involvement is a determinant of GFR independent of PR3-ANCA.

Possible explanations for the observed differences in chronic lesions and renal function are earlier disease recognition in patients with ENT involvement or the existence of different pathogenic pathways.

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