Systemic vasculitis in the 1980s — Is there an increasing incidence of Wegener's granulomatosis and microscopic polyarteritis?

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ABSTRACT – Thirty-six cases of Wegener's granulomatosis (WG) and microscopic polyarteritis (MPA) presenting to the nephrology service in Leicester between 1980 and 1989 were reviewed. Apart from the diagnostic respiratory tract lesions seen in WG, cases of MPA and WG could not be distinguished by age and sex, range and severity of organ involvement, response to treatment (oral prednisolone and cyclophosphamide), mortality or renal outcome. The combined incidence of WG and MPA in 1980–86 was 1.5/million/year. Following the introduction in January 1987 of an assay for anti-neutrophil cytoplasmic antibody (ANCA), the incidence of WG and MPA increased in 1987–89 to 6.1/million/year ($p<0.0001$). Cases seen during these two periods did not differ by any clinical parameter except that later cases had less severe renal disease at referral and improved renal outcome. Median serum creatinine was significantly lower at presentation in 1987–89 ($p<0.02$). Of those surviving 3 months from presentation only 1/20 in 1987–89 had end stage renal failure compared with 4/10 in 1980–86 ($p<0.02$). These findings may reflect increasing diagnostic awareness of WG and MPA among physicians since the introduction of ANCA.

Wegener's granulomatosis (WG) and the microscopic form of polyarteritis (MPA) are uncommon diseases caused by small vessel vasculitis of uncertain aetiology. The protean clinical manifestations of WG and MPA result from involvement of skin, eyes, joints, muscles and nerves [1, 2]. The majority have pulmonary and upper airway lesions which in the case of WG are often regarded as diagnostic, or present with glomerulonephritis often resulting in acute renal failure.

Since 1985 there has been wide interest in ANCA (anti-neutrophil cytoplasmic antibody) [3–5], a circulating antibody now regarded as the hallmark of active, untreated WG and MPA, although its possible pathogenic role remains uncertain. The debate over ANCA has created fresh awareness of WG and MPA and has emphasised the close similarity between the two diseases. This period of interest has coincided with an apparent fourfold increase in cases of WG and MPA referred to the nephrology service in Leicester.

This report reviews cases of WG and MPA seen since 1980, emphasises the similarity between the two diseases and assesses possible explanations for the perceived change in incidence.

Method

Case notes were reviewed of all patients satisfying diagnostic criteria for WG and MPA who were referred to the Department of Nephrology at Leicester General Hospital between January 1980 and December 1989.

Diagnostic criteria coincided with those previously published [1, 2].

Wegener's granulomatosis

Diagnosis required 1 and 2 plus one out of 3, 4 or 5:
1. Clinical features of vasculitis in more than one organ system
2. Histological evidence of small vessel vasculitis in at least one site
3. Upper respiratory tract lesions
4. Discrete nodular/cavitating pulmonary lesion
5. Histological evidence of granulomata

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Microscopic polyarteritis

Diagnosis required all three features:
1. Clinical features of vasculitis in more than one organ system
2. Histological evidence of small vessel vasculitis in at least one site
3. Absence of specific respiratory or histological features of WG (3–5 above)

To make a diagnosis of WG or MPA, other causes of vasculitis were excluded, particularly rheumatoid disease, systemic lupus, Henoch–Schönlein purpura, scleroderma and malignancy.

Information collated from notes included:

- Sex
- Age at presentation
- Date of presentation
- Organ systems involved
- Type of respiratory tract disease
- Serum creatinine at presentation
- Requirement for acute dialysis
- Subsequent development of end stage renal failure
- Renal histology
- Initial treatment regime
- Early (within 3 months of diagnosis) and late mortality
- ANCA status

ANCA

ANCA (anti-neutrophil cytoplasmic antibody) was tested by indirect immunofluorescence with FITC-conjugated anti-human IgG following incubation of dilutions of test sera with normal human neutrophils. ANCA positivity was defined as fluorescence at a dilution of at least 1 : 16 of test serum. This assay became available in Leicester in January 1987.

Results

Thirty-six patients were identified: 18 satisfied diagnostic criteria for WG, 18 for MPA. These two diagnostic groups were compared. Age and sex distribution did not differ significantly between the two groups (Table 1).

Organ involvement (Table 1)

Respiratory involvement was common. Upper respiratory (ENT) involvement was restricted by definition to WG. In MPA the chest radiograph showed diffuse or patchy shadowing with no nodules or cavitation; these appearances were often accompanied by haemoptysis and frank pulmonary haemorrhage. In WG pulmonary lesions were characteristically nodular and cavitating, but not universally so, and some patients with WG had diffuse shadowing with pulmonary haemorrhage.

Table 1. Clinical features of Wegener's granulomatosis and microscopic polyarteritis

	WG ($n = 18$)	MPA ($n = 18$)
Age	61 (21–68)	56 (21–75)
Sex	M12 F6	M12 F6
Organ distribution		
Kidneys	94%	100%
Lungs	44%	61%
ENT	83%	—
Joints	61%	44%
Skin	33%	38%
Eyes	16%	11%
GI tract	5%	—
Peripheral NS	5%	11%

The distribution of other organ involvement is shown in Table 1. No major differences are seen between WG and MPA other than in respiratory lesions.

Renal disease

Renal disease was universal, with histological evidence of focal, segmental, necrotising glomerulonephritis in 35/36 cases. The remaining patient, uraemic at presentation, unexpectedly had renal biopsy evidence of end stage kidney disease of undeterminable cause.

The glomerular lesion was taken as evidence of small vessel vasculitis producing glomerular capillaritis. However, the renal biopsy infrequently revealed other diagnostic features: only 2/18 patients with WG had demonstrable renal granulomata; only 1/36 patients with WG or MPA had extraglomerular renal vasculitis. An interstitial inflammatory infiltrate was very common in both WG and MPA, but in only one patient, with a heavy peripheral blood eosinophilia, was the renal infiltrate eosinophilic.

The severity and course of the renal disease did not differ between WG and MPA as judged by median serum creatinine at presentation, the proportion of patients presenting with normal serum creatinine and those requiring acute or chronic dialysis (Table 2).

Treatment

Induction treatment was uniform: 33/36 received oral cyclophosphamide (2–3 mg/kg/day) combined with oral enteric coated prednisolone (60 mg daily, usually reducing to 15 mg daily by 2 months); 3/36 were treated with prednisolone alone, as this adequately controlled extra-renal disease and renal function was deemed to be irreversible.

Four patients received additional treatment: one (treated in 1980) received anticoagulant; three

Table 2. Renal involvement in Wegener's granulomatosis and microscopic polyarteritis

	WG (17)*	MPA (18)
Serum creatinine at presentation (μmol/l)	718 (84–1500)	363 (90–930)
Serum creatinine < 130 μmol/l	29%	22%
Acute dialysis required	23%	33%
ESRF (if survived > 3/12)	12%	21%

*One patient with end stage kidney excluded

received intravenous methylprednisolone and intensive plasma exchange for life-threatening pulmonary haemorrhage despite oral cyclophosphamide and prednisolone.

Mortality

Follow-up data at 3 months were available for all 36 patients.

Early mortality. Six patients (16%) died during the first 3 months of treatment.

WG (2 patients): one died of gastro-intestinal vasculitis with haemorrhage; one died of stroke after disease manifestations had apparently been controlled with therapy (no autopsy information was obtained).

MPA (4 patients): one died of pulmonary haemorrhage within hours of diagnosis; three died of pneumonitis (one cytomegalovirus, one pneumocystis, one cause unknown).

Thus only two of the six deaths were related to uncontrolled vasculitis, while three were a consequence of opportunistic infection following immunosuppression.

Late mortality. Only 12 patients had follow-up of more than 3 years. Five of them have died. Two were early deaths; the remaining three were patients on renal replacement therapy (2 vascular disease, 1 adenocarcinoma). Only one other patient on renal replacement therapy for at least 3 years is still alive.

ANCA

ANCA was tested on acute sera from 29 patients, including all 28 presenting since January 1985.

Of 14 patients with WG, all were ANCA positive
Of 15 patients with MPA, 12 were ANCA positive

Subtypes of ANCA, defined by immunofluorescence pattern, were not analysed.

Disease incidence before and after 1987

The apparent incidence of WG and MPA has increased rapidly since January 1987 when ANCA became available in Leicester for routine clinical use (Fig. 1). Leicester has a sub-regional nephrology service with a catchment population of approximately 1.3 million. For 1980–86 the combined incidence of WG and MPA was 1.5/million/year; for 1987–89 it was 6.1/million/year ($p < 0.0001$).

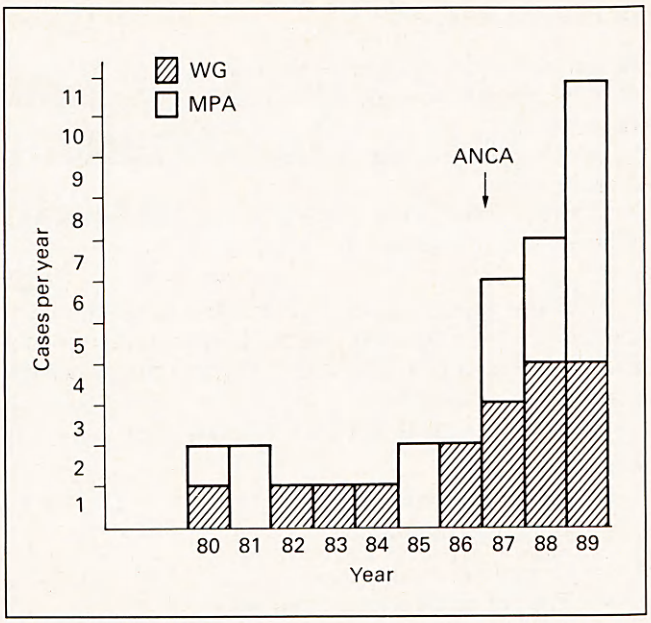


Fig. 1. *Incidence of Wegener's granulomatosis and microscopic polyarteritis; Leicester, 1980–89.* (Arrow indicates date at which ANCA became available for routine clinical use in Leicester)

In view of this fourfold increase, the clinical features were analysed to seek differences between the 12 patients presenting before 1986 and the 24 presenting in 1987–89.

The two groups did not differ in age and sex distribution, range of organ involvement (data not shown) or early mortality (2/12 1980–86; 4/24 1987–89).

The only difference was in the severity of renal disease on referral (Table 3; Fig. 2), with significantly lower median serum creatinine in the 1987–89 group at presentation and fewer requiring acute or chronic dialysis.

Table 3. Severity of renal involvement in Wegener's granulomatosis and microscopic polyarteritis

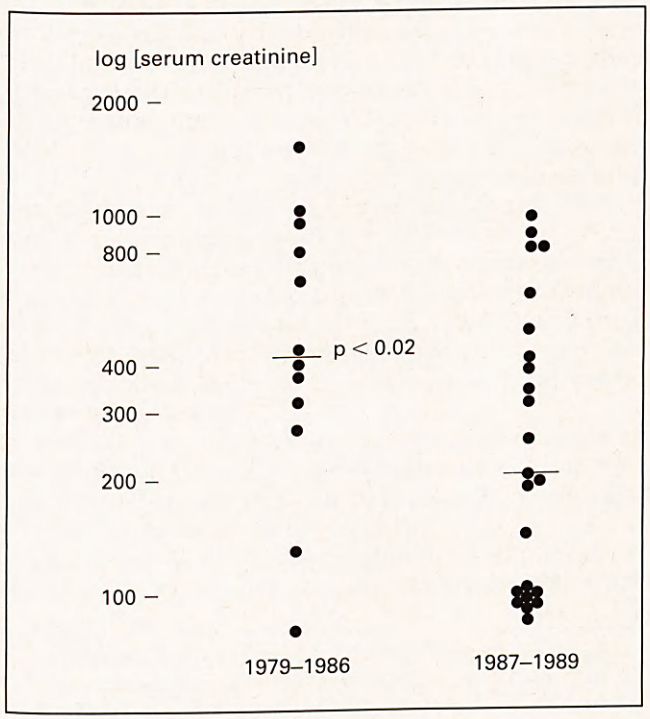
	1980–86 (12)	1987–89 (23)*	
Serum creatinine at presentation (μmol/l)	579 (90–1500)	344 (84–932)	$p < 0.02$
Serum creatinine <130 μmol/l at presentation	1/12	8/23	NS
Acute dialysis required	7/12	3/23	$p < 0.01$
ESRF (if survived > 3/12)	4/10	1/20	$p < 0.02$

*One patient with end stage kidney excluded

Discussion

The two types of small vessel systemic vasculitis described here, WG and MPA, have many similarities and will be part of the differential diagnosis for the nephrologist in patients presenting with acute renal failure in the context of multisystem disease. Wegener believed the granulomatous vasculitis he described to be a variation of polyarteritis [6], but recent attitudes have emphasised the distinctiveness of WG on the basis of its capacity to produce destructive lesions of the upper and lower airways associated with granulomata, even though the latter may be difficult to demonstrate histologically. Development of effective, though empirical, treatment with cyclophosphamide, which has transformed the prognosis in WG and is now the drug of choice, was also thought to emphasise its distinctiveness. However, the present series confirms the great similarity between the two conditions: when WG and MPA were separated by conventional diagnostic criteria, the two groups were not distinguishable by the range of organ involvement (other than the respiratory tract lesions), the renal histology, the severity of renal impairment, the response to treatment or mortality. ANCA positivity also characterised the two groups but the value of this as a unifying observation is uncertain. In the present study ANCA was not analysed by variation in cytoplasmic staining pattern. Recent work suggests that the distinction between diffuse cytoplasmic staining (c-ANCA) and perinuclear staining (p-ANCA) may be important [7, 8], c-ANCA being reactive with a 29 kd protein antigen in neutrophil azurophilic granules and associated with clinical WG and histological evidence of granulomata, whereas p-ANCA, reactive with myeloperoxidase, may be associated with MPA. The proposition that these antibodies are directly pathogenic in the vasculitic process remains unproven. Any possible genetic or environmental factors which might lead to c-ANCA, granulomatous lesions and WG in some patients with small vessel vasculitis also remain unidentified.

Fig. 2. *Log(serum creatinine) at presentation in Wegener's granulomatosis and microscopic polyarteritis.*



The close similarity between WG and MPA is borne out in other recent series which review them alone or combined [2, 9–11]. Although lower respiratory tract lesions may be nodular and cavitating in WG, other patients will have pulmonary haemorrhage not specific for WG or MPA. Furthermore, cases will often be diagnosed as WG in the absence of histological evidence of granulomata which may be difficult to obtain from respiratory tract biopsies and are infrequently found in the kidney. At present precise definition of WG or MPA has no clear management advantage since treatment, mortality and prognosis are not modified by the distinction. The treatment protocol in this series was uniform but was not part of any controlled study. Indeed there are no randomised controlled trials of cyclophosphamide and prednisolone in WG and MPA, although the anecdotal evidence for the benefits of cyclophosphamide is extremely powerful [1, 2]. The present protocol was associated with an early mortality of 16%, and 3 of the 6 deaths were directly attributable to opportunist infection following immunosuppression. This mortality is similar to that reported by others; series with a higher mortality had significant additional immunosuppressive therapy in many patients — either methylprednisolone or plasma exchange [10, 12].

Is there really an increasing incidence of these diseases? To find a sudden, true fourfold change in incidence, as is implied in this report, suggests an environmental factor such as infection. None was identified in this series, nor has one been previously noted, although systemic infection is well described as a trigger of relapse in systemic vasculitis [13]. Furthermore, the original, often unappreciated, description of ANCA was in patients who developed severe glomerulonephritis in association with an acute viral illness [14].

An alternative explanation would be that the debate about ANCA and its diagnostic value in the literature has raised the diagnostic awareness of physicians in this area. Most patients in this series were middle-aged and were referred with undiagnosed multisystem disease and rapidly progressive renal failure. Even if the diagnosis was not appreciated, it seems improbable that such patients would previously not have been referred to a nephrologist for assessment and treatment. However, if the increase in case rate represents a true increase, it should be noted that the median age of the present series is 61, with only two patients older than 70 years at presentation, raising the possibility that these diseases are underdiagnosed in the elderly. Although florid multisystem disease may not present diagnostic difficulty, uncertainty can arise where the disease is mostly limited to the respiratory tract and

the kidneys, since the non-specific chest radiograph signs may be ascribed to common infections, and acute renal failure interpreted as secondary to the toxaemic state which may accompany pneumonia, rather than to glomerular disease.

Whether or not there is an increase in the incidence of WG and MPA, there is an important trend towards earlier referral as judged by degree of renal failure in the more recent cohort of cases. As a result, only one of twenty patients referred since 1987 and who have survived more than 3 months has required long-term renal replacement therapy, whereas four of ten in the earlier group reached end stage renal failure and three of them have died despite renal replacement therapy. The major medical, social and economic advantages of avoiding end stage renal failure make this development in itself a significant step forward.

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