Age-related variations in presentation and outcome in Wegener's granulomatosis

ABSTRACT — Wegener's granulomatosis (WG) is increasingly being diagnosed in older people. The object of this study was to see whether age influences the clinical presentation and prognosis. In a retrospective open case-note review of 51 patients with a diagnosis of WG based on internationally accepted criteria, 29 patients (56.9%) below 60 years and 22 (43.1%) aged 60 or above were compared. The incidence of limited (10% vs 9.1%) and classical (89.6% vs 90.9%) disease was similar in the two groups, but some clinical features were commoner in the younger cohort at presentation: ear, nose and throat (100% vs 68.1%; p < 0.01), ophthalmic (48.3% vs 18.2%; p = 0.05) and dermatological (51.7% vs 18.2%; p = 0.05). There were no significant differences in the incidence of renal, pulmonary, rheumatological or neurological involvement or in the presence of antineutrophil cytoplasmic antibody. Outcome was significantly worse for the over 60 group despite a similar treatment regimen (prednisolone, cyclophosphamide, and dialysis if required) (six months' survival: 96.5% vs 59.1%; p < 0.01). Renal function at presentation was a significant determinant of prognosis: mean serum creatinine at presentation was 525 μmol/l vs 291 μmol/l respectively in those who died within six months and in those who survived (p = 0.03). Uncontrolled pulmonary vasculitis was the commonest cause of death.

In conclusion, the classical presentations of WG are similar in older patients. Disease in the latter is more often restricted to the lungs and the kidneys, and this may cause diagnostic uncertainty. The outcome is worse in older patients, with uncontrolled pulmonary vasculitis the commonest cause of death despite immuno-suppressive treatment. Early diagnosis and treatment may improve outcome.

Wegener's granulomatosis (WG) is a small-vessel vasculitis of unknown aetiology, first described as a distinct clinicopathological entity by Friedrich Wegener in 1936. The vasculitis is characterised by granuloma formation in small and medium vessels, and distinguished from other necrotising vasculitides by its predilection for the upper and lower respiratory tracts and the kidneys. Limited forms with no renal involvement are well described. WG frequently follows a two-phase course in which the upper and lower respiratory tracts are affected first and, if untreated, the disease evolves into a life-threatening generalised vasculitic illness with glomerulonephritis.

The diagnosis is based on typical clinical and histological findings. Since the introduction of antineutrophil cytoplasmic antibody (ANCA) into routine clinical practice there has been an increased awareness of the condition, and it is now realised that WG encompasses a wide spectrum of disease with a variable clinical presentation. The prognosis of WG has been transformed by the adoption of treatment regimens using cyclophosphamide and corticosteroids. However, the treatment of WG creates problems because these agents have considerable toxicity and may not be curative.

Over recent years there have been case reports of unusual presentations of WG particularly in patients over the age of 60 years, but there has been no systematic study contrasting clinical features in different age groups. In the study reported here the presentation and outcome were compared in patients above and below the age of 60 years.

Patients and methods

A retrospective open case-note review was performed of all patients in whom a diagnosis of WG was made in Leicestershire between April 1987 and December 1994. Cases were identified through hospital diagnostic coding records held by Leicestershire Health. In addition, independent enquiry was made to the clinical departments of nephrology, rheumatology, ophthalmology and otolaryngology to maximise case ascertainment.

Diagnostic criteria based on clinical and laboratory findings were compatible in all the cases with the diagnosis of WG according to the 1990 American College of Rheumatology (ARC) criteria and the more recent Chapel Hill consensus classification of vasculitis. At least two of the following criteria are necessary for the diagnosis of WG:

- nasal or oral inflammation
- abnormal chest radiograph showing the presence of nodules, fixed infiltrates or cavities
- microscopic haematuria (>5 red blood cells per high power field) or red cell casts in the urinary sediment
- granulomatous inflammation on biopsy.
To make a diagnosis of WG other causes of vasculitis were excluded, particularly rheumatoid disease, systemic lupus, Henoch-Schönlein purpura, scleroderma and malignancy.

Information collected from the notes included:
- age at presentation and gender
- clinical features at presentation: organ systems involved, type of respiratory tract disease, serum creatinine, ANCA
- histology: renal, nasal, other
- initial treatment: immunosuppression, requirement for acute dialysis
- mortality: early (<6 months of diagnosis), late mortality (>6 months)
- morbidity: end-stage renal disease (ESRD).

Statistical analysis

The chi-squared test was used, with either Fisher’s exact or Yates’ correction as appropriate. Comparisons of means, where appropriate, were performed using Student’s t-test.

Results

Fifty-one patients satisfying the diagnostic criteria were identified (29 <60 years; 22 ≥60 years) (Table 1). Sex distribution did not differ significantly in the two groups. The occurrence of classical or limited WG was also similar in both age groups, as was the number of organ systems involved at presentation, but there were differences in the pattern of organ involvement and prognosis in the two age groups.

Organ involvement

Ear, nose and throat (Table 2). Ear, nose and throat (ENT) involvement was recorded in 86.3% of patients, but was significantly less common in the over 60 age group (100.0% vs 68.1%; p <0.01). This is such a characteristic feature of WG that the diagnosis was critically reviewed in the seven patients aged 60 years and above without clinical ENT disease. In five, the chest radiograph showed typical nodules/cavitation (post-mortem confirmed no ENT involvement in three of these); in the remaining two, there was a granulomatous vasculitis on renal biopsy.

The recorded manifestations of ENT disease were:
- nasal disease (63.6%)
- hearing loss (50.0%)
- otitis media (18.2%)
- sinusitis (28.4%)
- oral lesions (14.2%)
- laryngeal lesions including subglottic stenosis (4.7%).

A nasal biopsy was performed on 16 patients (31.4%): nine showed granulomas or granulomatous inflammation and the remainder had non-specific inflammatory changes.

Respiratory disease (Table 2). There were no significant differences between the two age groups in either the incidence of respiratory disease or the radiological appearance:
- radiological abnormalities (39; 76.5%):
  - infiltrates (16; 41.0%)
  - nodules (11; 28.2%)
  - infiltrates and nodules (11; 28.2%)
  - pleural effusion (1; 2.6%)
- evidence of cavitation on the chest radiograph (9 out of 30 patients; 22.5%).

The commonest symptom reported with equal frequency in both age groups was haemoptysis (38.5% vs 33.8%; p = not significant (NS)); however, frank pulmonary haemorrhage was more common in the

| Table 2. Clinical features at presentation in Wegener’s granulomatosis (WG) in patients below and above 60 years of age. |
|---------------------------------------------------------------|
| **Clinical feature** | **WG <60 years** | **WG ≥60 years** | **p** |
|---------------------|-----------------|-----------------|------|
| Eye                 | 23              | 17              | 77.2 |
| Kidney              | 26              | 19              | 86.8 |
| Skin                | 14              | 4               | 18.2 |
| Nervous system      | 15              | 5               | 21.7 |
| Constitutional symptoms | 9                | 3.10            | 45.5 |
| Positive ANCA       | 20/22           | 14/16           | 87.8 |

ANCA = antineutrophil cytoplasmic antibody
ENT = ear, nose and throat
NS = not significant
over 60 group (8.7% vs 41%; p = 0.04). All the patients without ENT manifestations had respiratory disease.

Renal disease (Tables 2 and 3). There was no significant difference in the frequency of renal disease between the two groups (89.7% vs 86.3%; p = NS). Glomerular filtration rate was not measured routinely, but the severity of renal disease did not differ in the two age groups as judged by the median serum creatinine at presentation, the proportion of patients presenting with a normal serum creatinine and those requiring acute dialysis. Fewer patients in the older age group survived six months with ESRD: six out of the seven patients who required acute dialysis died before six months.

A renal biopsy was available in 38/46 (82.6%) cases with evidence of renal involvement. No biopsy was performed in eight of these patients (17.4%) because other histological evidence of WG was available. There was evidence of a focal segmental necrotising glomerulonephritis in 34 of the 38 (89.5%), 11 of whom had evidence of an interstitial nephritis, and granulomatous were noted in five. A normal renal biopsy was obtained in two patients, despite the presence of persistent unexplained haematuria. There were no differences in the histological pattern in the two age groups.

Other organ involvement (Table 2). The older age group had less ophthalmic (48.3% vs 18.2%; p = 0.05), rheumatological (58.6% vs 31.8%; p = NS) and dermatological (51.7% vs 18.2%; p < 0.01) involvement than the younger age group. Neurological involvement was uncommon in either group (10.3% vs 21.7%; p = NS).

Antineutrophil cytoplasmic antibody (Table 2)

ANCA was positive in a high proportion of patients in both age groups (90.9% vs 87.5%; p = NS). Many of the positive ANCA results available in the early period of the study were given as unspecified positives and did not differentiate between cANCA and pANCA. In the under 60 group 11/22 (50.0%) had a titre of 1:250 or above, 5/22 (22.7%) a titre of less than 1:250, and no titre was available in 6/22 (27.3%). In the over 60 group, 4/16 (25.0%) had a titre of at least 1:250, in 8/16 (50.0%) it was less than 1:250, and no titre was available in 4/16 (25.0%).

Treatment

Induction treatment was uniform in both age groups. On diagnosis, 20/22 patients (90.9%) and 27/29 (93.1%) in the older and younger age groups, respectively, were started on comparable doses of oral prednisolone (0.5–1.0 mg/kg/day) and cyclophosphamide (2–3 mg/kg/day). The most common starting regimen was prednisolone 60 mg and cyclophosphamide 200 mg (minimum doses: prednisolone 50 mg, cyclophosphamide 150 mg). Seventeen patients (33.3%) required acute dialysis. Treatment was tailed down over 2–3 years, provided that there was no evidence of recurrence or clear evidence of drug toxicity, in which case treatment would be tailed down more quickly.

Additional treatment included plasma exchange (6 patients), intravenous immunoglobulin (1), and intravenous methylprednisolone for life-threatening alveolar haemorrhage or disease recurrence despite oral prednisolone and cyclophosphamide (3). Two patients were treated with continuous positive airway pressure and two were ventilated. There were no age-related differences in availability of additional treatment.

Survival and cause of death (Fig 1)

Of the 51 patients (mean follow-up, 43.6 months; range, 1 week–187 months), 18 died and 33 were still alive at the time of analysis. Despite a similar treatment regimen of cyclophosphamide and prednisolone, survival following the diagnosis of WG was considerably less in the older age group (mean survival, 8.9 months; range, 3 days–65 months), 9/22 of whom had died by six months, compared with 1/29 in the under 60 group (mean survival, 73.4 months; range 3–93 months; p = 0.001). Among the early deaths in the 60 and over age group (mean survival, 51.2 days; range, 7–132 days), only one patient had gone into remission and subsequently had a fatal relapse, but there had been no withdrawal of treatment to provoke the relapse.

Early mortality (less than six months)

Autopsy in seven of the 10 early deaths (9 ≥60, 1 <60) in both groups showed the causes of death to be:

| Table 3. Renal involvement in Wegener’s granulomatosis (WG) in patients below and above 60 years of age. |
|---------------------------------------------------------------|
| WG <60 years (n = 29) | WG ≥60 years (n = 22) | p       |
|-----------------------|----------------------|---------|
| Serum creatinine at presentation (µmol/l) (range) | 355 (90–1,020) | 386 (39–1,206) | NS |
| Serum creatinine <130 µmol/l (%) | 10 (34.5) | 7 (31.8) | NS |
| Serum creatinine <130 µmol/l with abnormal urinalysis (%) | 7 (24.1) | 5 (21.7) | NS |
| Acute dialysis (%) | 11 (37.9) | 6 (27.2) | NS |
| ESRD if >6 months’ survival (%) | 4 (28) | 1 (4.5) | NS |
| ESRD = end-stage renal disease |
| NS = not significant |
pulmonary haemorrhage and renal involvement (5)
- pulmonary haemorrhage, renal involvement and an acute pulmonary embolus (1)
- disseminated vasculitis, sparing the kidney but leading to perforation of the sigmoid colon (1).

In the other three early deaths, with no autopsy, the causes of death were disseminated vasculitis with evidence of pulmonary and renal involvement, myocardial infarction and subarachnoid haemorrhage. Thus, eight of 10 early deaths were due to uncontrolled vasculitis, particularly with lung involvement, and two were due to coincidental vascular events. The nine early deaths in the 60 and over age group had more advanced renal disease at presentation (Table 4) and five (55.6%) required acute dialysis. Overall, six patients required acute dialysis, and five of them had evidence of pulmonary haemorrhage, confirmed at autopsy in four patients.

Table 4. Characteristics of Wegener’s granulomatosis (WG) patients over 60 years old with early and late mortality.

|                         | Early (<6 months) mortality (n = 9) | Late (>6 months) mortality (n = 13*) | p        |
|-------------------------|--------------------------------------|--------------------------------------|----------|
| Mean age (years) (range)| 67.4 (62–77)                         | 68.4 (61–83)                         |          |
| Serum creatinine at presentation (μmol/l) (range) | 525 (39–1,206) | 291 (89–864) | 0.03     |
| Prednisolone/ cyclophosphamide (%) | 8 (89)       | 13 (100)   | NS       |
| Acute dialysis (%)      | 5 (55)                              | 1 (7.7)                              | 0.04     |

NS = not significant
* 8 surviving at time of study

Late mortality (more than six months)

Nine patients (5 ≥50, 4 <60) died more than six months after diagnosis, the causes of death being:
- ESRD (4): three died following a renal transplant (one had recurrent glomerulonephritis at death, two died of respiratory infection)
- sepsicaemia complicating neutropenia
- bronchopneumonia (1)
- cancer of the uterus (1).

No information was available for three patients.

Discussion

The clinical features, course of illness and treatment of WG have been well described in some large studies11,12 but, to our knowledge, the clinical features of WG in older patients have not been specifically analysed previously. WG and microscopic polyarteritis (MPA) have overlapping clinical features. Although granulomatous inflammation is a defining feature of WG, histological evidence of granulomata is not mandatory to make a diagnosis because non-invasive evaluations may identify an abnormality that adequately predicts its presence10. The ACR criteria offer a workable standardised approach to classifying patients for clinical studies9. A recent consensus workshop recognised the value of ANCA patterns in helping to distinguish WG from MPA. Unfortunately, this retrospective series includes many early cases in which cANCA and pANCA were not identified separately.

In this series only a small proportion of patients had the limited form of WG. No difference was found in the frequency of limited or classical disease in the two age groups, although in a previous study13 patients with limited disease were generally older at the time of presentation. In the over 60 years old group, WG still presented as a multisystem disorder but with significantly less incidence of ENT, ophthalmic and skin involvement, and also a lower incidence of joint symptoms. The distribution of skin manifestations is consistent with the findings of Barksdale et al8.

There was a significant shortening in the survival of patients over 60 years old (Fig 1) despite similar treatment regimens in both age groups. Of the 10 patients who died within six months of diagnosis, nine were aged over 60 years. One possible explanation for the higher mortality in older patients would be intolerance of the immunosuppressive regimen, with death from infection. This is not, however, supported by the causes of death, which strongly implicate uncontrolled vasculitis in the older patients, particularly lung involvement. Treatment with prednisolone and cyclophosphamide (with appropriate supporting measures, including dialysis) was sufficient to induce remission in the younger age group, but was less successful in the older patients. This may indicate...
more severe disease resistant to conventional therapy, or delay in either diagnosis or treatment.

In this retrospective study, it was not possible to identify with confidence the duration of symptoms prior to presentation as a measure of diagnostic delay before admission. However, in all but two cases the diagnosis was made within three weeks from presentation, and there was no difference in the severity of renal involvement at presentation (Table 3). Nevertheless, developing severity of renal involvement was a prognostic indicator: dialysis was necessary in five of the nine early deaths in the older patients (Table 4). This suggests the possibility of delay in instituting effective treatment after presentation in patients with rapidly progressive disease and deteriorating renal function.

Pulmonary haemorrhage was significantly more common in the elderly group, with pulmonary vasculitis the commonest cause of death. This highlights the emerging importance of lung involvement in determining mortality now that renal failure is actively managed by dialysis.

Conclusions

**Diagnosis:** greater awareness of WG is necessary in older patients since the disease pattern differs. Clinical disease outside the kidney and the lung is less common, including ENT (universal in younger patients), joint, skin and eye involvement.

**Outcome:** the outcome of WG is worse in older patients, not because of the toxicity of immunosuppressive treatment but because of uncontrolled vasculitis (particularly lung disease) despite active treatment.

**Management:** it is not clear whether more intensive treatment, for example the addition of pulsed methyl prednisolone or plasma exchange, would improve the outcome. Earlier diagnosis, allowing prompt treatment before there is irreversible tissue damage, may be more important.

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