Postgrad Med J (1993) **69**, 856 - 861

Prognostic factors in Wegener's granulomatosis

L. Briedigkeit, R. Kettritz, U. Göbel and R. Natusch

Berlin-Buch Clinical Centre, 1st Medical Clinic, D-13125 Berlin, Germany

Summary: We analysed data from 64 patients with Wegener's granulomatosis to determine predictor variables of outcome. The mean period of observation after the diagnosis had been established was 3.2 (range 0.1 - 11.2) years. At the time of diagnosis, 15 (23%) patients had only local symptoms. The disease was generalized to multiple organs in 49 (77%) patients. Renal biopsies were obtained in 33 patients; 13 (39%) had extracapillary glomerulonephritis, which was the most common renal lesion. All but three patients received immunosuppressive therapy. At time of follow-up, 17 (27%) patients were in complete, and 26 (40%) in partial remission. We employed a Kaplan Meier analysis to identify predictor variables of outcome. Renal involvement, initial creatinine concentration, serum albumin or total protein concentration, leukocyte count and erythrocyturia proved to be predictor variables. These variables may be of value in guiding the intensity of treatment in patients with Wegener's granulomatosis.

Introduction

Wegener's granulomatosis (WG) is a form of necrotizing vasculitis characterized by granuloma formation in small and medium-sized vessels. Primarily involved are the upper and lower airways and the kidneys. Prior to the introduction of immunosuppressive therapy in the 1950s, the disease was regularly fatal in less than 5 months after diagnosis.[1] With the advent of immunosuppressive therapy, particularly the administration of cyclophosphamide and prednisolone, the outlook has improved considerably.[1,2] Nevertheless, immunosuppressive therapy is not benign and side effects from treatment account for some of the mortality observed today in patients with WG.[3] Thus, staged immunosuppressive treatment has been proposed.[4]

An estimate of the prognosis in any given patient with WG would be helpful in planning treatment strategies, particularly in terms of aggressiveness and duration. We performed a retrospective analysis of 64 patients with WG to identify predictor variables of outcome. We were able to identify several variables that may assist in predicting the course of the disease.

Patients and methods

The records of 64 patients (37 men, 27 women, average age 48.5, range 17 - 81 years) who developed Wegener's granulomatosis, from 1971 to 1989, were obtained in this multicentre retrospective survey. The diagnosis was based on clinical, laboratory and histological criteria.[1,5]

The patients were classified on the basis of their organ system manifestation at the time of diagnosis (ELK classification: E - ear, nose, throat; L - lung; K - kidney).[6] The outcome was assessed according to the criteria of remission as proposed by Fauci *et al.*[1]

The Kaplan-Meier technique[7] was used to estimate survival. End point for survival analysis was the occurrence of either end-stage renal disease or death (defined as 'survival free of renal failure'). Survivors of subgroups were compared to one another by the log-rank test.[8] The Bonferroni's correction,[9] multiplication of P value by the number of tests performed, was employed to calculate the 'corrected' P value (significant at $P < 0.05$).

All data used in this study were evaluated at the time of diagnosis.

The following factors ($n = 15$) were examined for their prognostic relevance. Age > 50 years; (male) gender; involvement of the lung; involvement of the kidney; extracapillary glomerulonephritis; laboratory data - erythrocyte sedimentation rate > 40 mm/h, serum protein concentration < 6.5 g/dl, serum albumin concentration < 3.5 g/dl, gammaglobulin ratio > 20%, haemoglobin < 12 g/dl, leukocyte count > 10,000/mm^3, thrombocyte count > 400,000/mm^3, serum creatinine concentration > 310 µmol/l, proteinuria > 2 g/24 hours, erythrocyturia. Anti-neutrophil cytoplasmic antibodies (ANCA) could not be considered in this study, since they were first discovered in 1985. Our investigation was begun in 1971.

Correspondence: Lutz Briedigkeit, M.D., I Medizinische Klinik, Klinikum Berlin-Buch, Wiltbergstr. 50, D-13125 Berlin, Germany
Accepted: 23 June 1993

Results

Organ involvement

Grouping of patients according to the ELK classification is shown in Table I. Only five (8%) of 64 patients did not have upper airway involvement. Forty-nine (77%) patients had renal disease, 38 (59%) patients had both pulmonary and renal involvement.

Histology

The diagnosis WG was histologically documented (appearance of granulomata with or without vasculitis) in 59 (92%) patients. In five (8%) patients with strong clinical signs of WG (ELK stage) granulomata were not found in the biopsies.

Renal biopsies were available from 33 patients (67% of all patients with involvement of the kidney). Thirteen (39%) patients had diffuse extracapillary glomerulonephritis (GN); 19 (58%) patients had other proliferative type of GN. One (3%) patient exhibited minimal changes. Table II shows the classification according to the World Health Organisation.

Laboratory data

All laboratory abnormalities in WG, with the exception of ANCA are non-specific; however, their presence and degree may have an impact on the prognosis of the disease. The incidence of pathologically altered laboratory findings is shown in Table III.

Treatment

All but three patients (95%) received immunosuppressive treatment. Forty-five (70%) patients were treated with prednisolone and cyclophosphamide (Fauci scheme), with 17 (27%) receiving methylprednisolone pulses at the beginning of therapy. Plasmapheresis was performed in eight (13%) patients with advanced disease. Azathioprine and prednisolone were the initial medication in 13 (20%) patients and prednisolone was used alone in three (5%) patients. Five patients who were initially treated with azathioprine were then converted to cyclophosphamide because of poor remission.

Outcome

Seventeen (27%) of the 64 patients died; 13 had complications of Wegener's granulomatosis or complications of immunosuppressive therapy, while four patients died of other causes (accident, cardiac disease, etc.). Twelve (19%) patients reached end-stage renal failure and five of them died. The number who sustained either end-stage renal disease or death as a result of WG, was 20 (31%) patients. Overall survival free of renal failure is given in Figure 1.

Table I Grouping of patients ($n = 64$) to ELK classification at the time of diagnosis

Classification	*Number of patients*
E	6
L	1
K	1
EL	8
EK	10
LK	3
ELK	35
Total	64

E = ear, nose, throat; L = lung; K = kidney.

Table II Types of glomerulonephritis (GN) according to WHO classification

Type	*Frequency*
Mesangial proliferative GN	7 (21%)
Diffuse extracapillary (crescentic) GN	13 (40%)
Membranoproliferative GN	–
Membranous GN	–
Diffuse sclerosing GN	2 (6%)
Minimal changes	1 (3%)
Unclassifiable GN	3 (9%)
Focal/segmental changes	7 (21%)
Total	33 (100%)

Risk factors for survival free of renal failure

Involvement of the kidney, serum creatinine, protein and albumin concentrations, leukocyte count and erythrocyturia at the time of diagnosis were significant predictors of survival free of renal failure as shown in Figures 2–7.

Survival curves of proteinuria and male gender showed a trend to poorer survival (Figures 8 and 9).

Discussion

The present, retrospective report underscores the great prognostic significance of renal involvement in patients with WG. Not only involvement of the kidney itself, but also tests of renal function such as creatinine concentration and erythrocyturia proved to be significant indicators of outcome. Total serum protein and albumin concentrations, which were also related to outcome, are indirectly related to renal function. On the other hand, involvement

Table III Laboratory findings

Data	*Range*	*Frequency*
Erythrocyte sedimentation rate	>40 mm/hour	49 (77%)
Serum protein concentration	<65 g/l	20 (32%)
Serum albumin concentration	<35 g/l	30 (47%)
Gamma-globulin rate	>20%	19 (30%)
Haemoglobin	<12 g/dl	35 (55%)
Leukocyte count	>10,000/mm^3	27 (42%)
Thrombocyte count	>400,000/mm^3	16 (25%)
Serum creatinine concentration	>310 µmol/l	43 (67%)
Proteinuria	>2 g/24 hours	19 (30%)
Erythrocyturia		45 (70%)

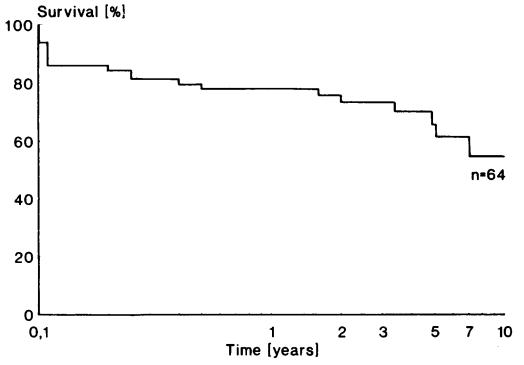

Figure 1 Overall survival free of renal failure in 64 patients with WG.

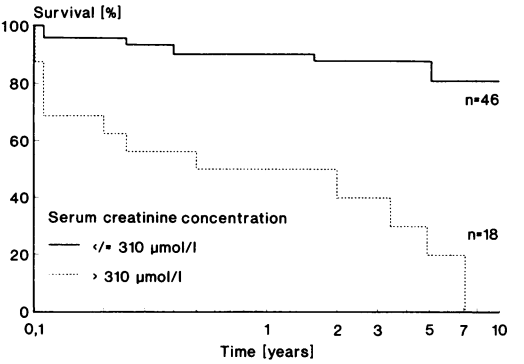

Figure 3 Prognostic relevance of initial serum creatinine concentration to survival free of renal failure ($P = 0.0015$).

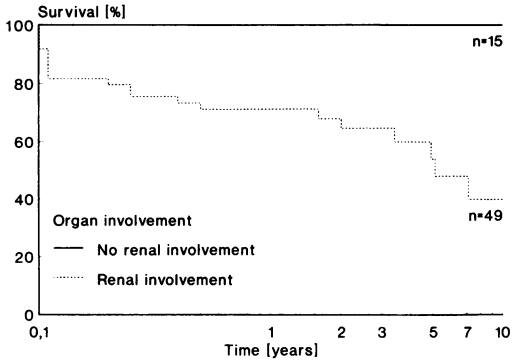

Figure 2 Prognostic relevance of renal involvement to survival free of renal failure ($P = 0.0495$).

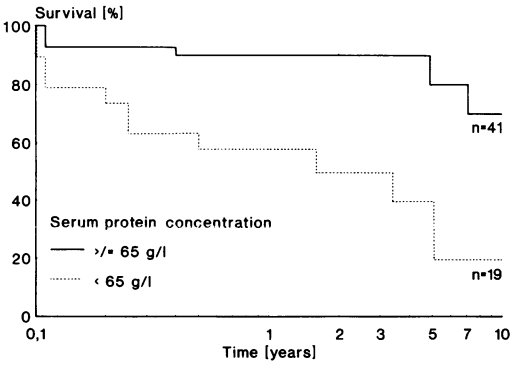

Figure 4 Prognostic relevance of initial serum protein concentration to survival free of renal failure ($P = 0.045$).

of the lung was not related to outcome in our series. This result conflicts with the experience of De-Remee *et al.*[3] who found pulmonary involvement to be related to outcome.

The importance of renal histology has been discussed by numerous authors. Adu *et al.*[10] and Serra *et al.*[11] found that the presence of glomerular crescents indicated a particularly poor prognosis in patients with WG. We could not specifically confirm these findings. Our results are in agreement with the experience that histologically active, rapidly progressive GN in WG patients may respond better

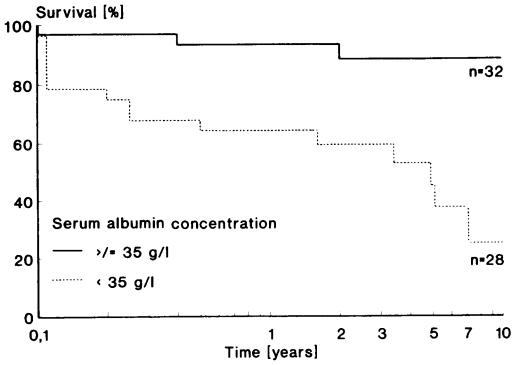

Figure 5 Prognostic relevance of initial serum albumin concentration to survival free of renal failure ($P = 0.0060$).

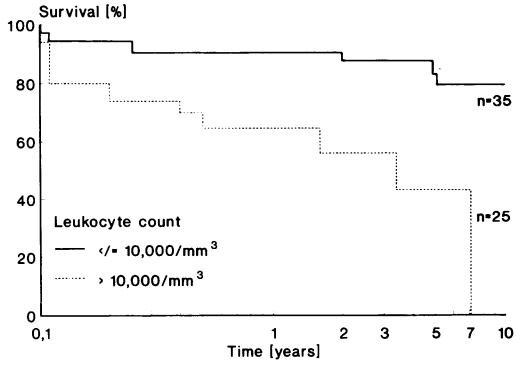

Figure 6 Prognostic relevance of initial leukocyte count to survival free of renal failure ($P = 0.0410$).

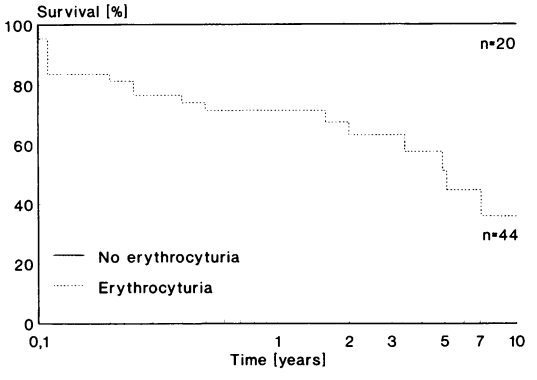

Figure 7 Prognostic relevance of initial erythrocyturia to survival free of renal failure ($P = 0.0135$).

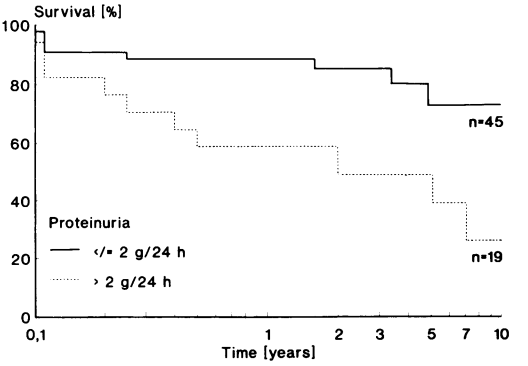

Figure 8 Prognostic relevance of initial proteinuria to survival free of renal failure ($P = 0.0645$, not significant).

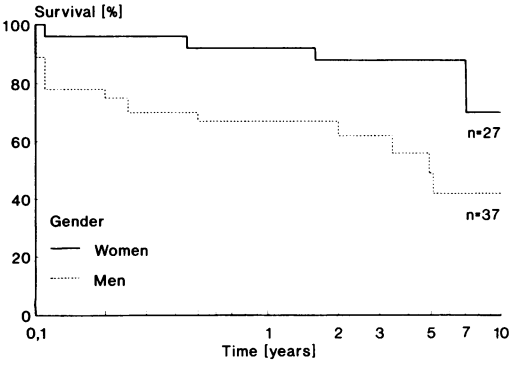

Figure 9 Prognostic relevance of patient gender to survival free of renal failure ($P = 0.1545$, not significant).

to immunosuppressive therapy than chronic idiopathic scarring.[12] For instance, Andrassy *et al.*[13] found that the percentage of obsolescent glomeruli and the degree of tubulointerstitial lesions was more closely correlated to outcome than active glomerular lesions such as crescents and necrotizing granulomata. We did not have sufficient data to investigate this histological issue in detail directly.

In addition, we could not confirm an important role for age in determining outcome. Such a result might be expected considering the independent effects of age on renal function. Other authors have reported such an influence.[3,14]

Although gender did not prove to be a significant predictor of outcome in patients with WG, the relationship showed a trend in favour of women. Men had a greater prevalence of renal involvement than women. Further, isolated GN has been more commonly described in men than women.[15]

Le Thi Huong Du *et al.*[14] were the first to seek systematically to identify predictor variables in patients with WG. They found that reduced haemoglobin concentrations were a predictor variable, a finding which we were unable to corroborate. On the other hand, we agree with their conclusion, that reduced renal function is a marker for a poorer outcome.

The occurrence of leukocytosis deserves special mention. Leukocytosis is no longer considered to be a non-specific concomitant phenomenon in vasculitis.[16] Neutrophils may have a primary role in pathogenesis, since antibody-dependent activation of granulocytes has been emphasized in recent studies. In patients with WG, leukocytes have impaired chemotactic response, an increased intravascular lysis, an increased turnover, and altered endothelial cell adhesion.[17] Increased numbers of granulocytes are frequently observed in patients with WG. This finding may be related to enhanced granulocyte differentiation, which in turn may possibly be due to inhibition of myeloblastin (proteinase 3) by anti-neutrophil cytoplasmic antibodies.[18,19] Thus, patients with leukocytosis are more likely to have active, aggressive disease, and therefore an increased risk of renal disease or death. They may be appropriate candidates for more aggressive immunosuppressive treatment, once bacterial infection has been ruled out with iron clad certainty.

Appel *et al.*,[20] as well as Balow,[21] suggested that the degree of proteinuria was of particular prognostic influence in patients with WG. Andrassy *et al.*[13] found that erythrocytes in the urinary sediment were an unfavourable prognostic sign. In an earlier study, we found that proteinuria and erythrocyturia were inversely associated with outcome of GN, irrespective of the cause.[22] Both were associated with a poorer outcome in our WG patients, most likely because they indicated the presence of renal disease. The initial creatinine value at the time of diagnosis was also a significant prognostic indicator of survival free of renal failure, which further emphasizes the importance of renal involvement in terms of prognosis.

On the basis of our findings, we conclude that early diagnosis, consideration of the variables we propose, and prompt therapy will improve prognosis; the improvement in serologic diagnosis of WG will facilitate that end.[20,21] The presence of anti-neutrophil cytoplasmic antibodies and the ability of simple tests has greatly facilitated early diagnosis, as well as providing insight into possible mechanisms of the disease.[19] Most of the WG patients in the present report were diagnosed on clinical grounds years before this test became available.

The prognosis may be estimated according to clinical findings at the time of diagnosis. Balow[21] suggested that the risk of end-stage renal disease would be 10% within 10 years in patients with any evidence of renal involvement. This value increased to 33% in patients with reduced renal function at the time of diagnosis, and to over 50% in patients with rapidly progressive glomerulonephritis. Our results corroborate that view. Involvement of the kidney to any degree is an important prognostic indicator of outcome. Outcome in patients with WG and a guide to subsequent management may be obtained from the serum creatinine concentration and the urinalysis. The presence of proteinuria, and the urinary sediment are pivotal clinical guidelines. Leukocytosis and decreased plasma protein values may also be helpful in determining which patients would be the most likely to warrant immunosuppressive therapy and to what degree.

Acknowledgements

We thank P. Fischer, U. Gläser, S. Hans, L. Lachhein, G. Liebetrau, K. Liebscher, A. Mohnike, U. Oltmanns, E. Schmidt and C. Würzberger for providing patient data. Our thanks also go to P. Kriegel and B. Schicke who performed statistical analyses.

References

1. Fauci, A.S., Haynes, B.F., Katz, P. & Wolff, S.M. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983, **98:** 76–85.
2. Walton, E.W. Giant-cell granuloma of the respiratory trace (Wegener's granulomatosis). *Br Med J* 1958, **2:** 265–270.
3. De Remee, R.A., McDonald, T.J. & Weiland, L.H. Wegener's granulomatosis: observations on treatment with antimicrobial agents. *Mayo Clin Proc* 1985, **60:** 27–32.
4. Steppat, D. & Gross, W.L. Stage-adapted treatment of Wegener's granulomatosis. *Klin Wochenschr* 1989, **67:** 666–671.
5. Godman, G. & Churg, J. Wegener's granulomatosis: pathology and a review of the literature. *Arch Pathol* 1954, **58:** 533–553.
6. De Remee, R.A., McDonald, T.J., Harrison, E.G. & Coles, D.T. Wegener's granulomatosis. Anatomic correlates, a proposed classification. *Mayo Clin Proc* 1976, **51:** 777–781.
7. Kaplan, E.L. & Meier, P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53:** 457–481.
8. Mantel, N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966, **50:** 163–170.
9. Sachs, L. Das zufällig statistisch signifikante Ergebnis. In: *Ange-wandte Statistik*. Springer-Verlag, Berlin, Heidelberg, New York, 1978, pp. 93–94.
10. Adu, D., Howie, A.J., Scott, D.G.I. *et al.* Polyarteritis and the kidney. *Q J Med* 1987, **239:** 221–237.
11. Serra, A., Cameron, J.S., Turner, D.R. *et al.* Vasculitis affecting the kidney: presentation, histopathology and long-term outcome. *Q J Med* 1984, **210:** 181–207.
12. Schneider, W. & Göbel, U. Pathomorphologie der Wegenerschen Granulomatose. *Z Ärztl Fortbild* 1991, **85:** 929–936.
13. Andrassy, K., Erb, A., Koderisch, J., Waldherr, R. & Ritz, E. Wegener's granulomatosis with renal involvement: patient survival and correlations between initial renal function, renal histology, therapy and renal outcome. *Clin Nephrol* 1991, **35:** 137–147.

14. Le Thi Huong Du, Wechsler, S., de Gennes, C. *et al.* Aspects évoluties et prognostiques de la granulomatose de Wegener. *Rev Rhumat* 1989, **56:** 583–588.
15. Heaf, J.G., Jorgensen, F. & Nielsen, L.P. Treatment and prognosis of extracapillary glomerulonephritis. *Nephron* 1983, **35:** 217–224.
16. Wilkowski, M.J., Velosa, J.A., Holley, K.E. *et al.* Risk factors in idiopathic renal vasculitis and glomerulonephritis. *Kidney Int* 1989, **36:** 1133–1141.
17. Gross, W.L. Wegener's granulomatosis. New aspects of the disease course, immunodiagnostic procedures, and stage-adapted treatment. *Sarcoidosis* 1989, **6:** 15–29.
18. Gross, W.L., Czernok, E. & Schmitt, W.H. Antineutrophil cytoplasmic autoantibodies: immunobiological aspects. *Klin Wochenschr* 1991, **69:** 558–566.
19. Jenne, D.E., Schopp, G., Lüdemann, J., Utecht, B. & Gross, W.L. Wegener's autoantigen decoded. *Nature* 1990, **346:** 6284.
20. Appel, G.B., Gee, B., Kashgarian, M. *et al.* Wegener's granulomatosis: clinical-pathological correlations and long-term course. *Am J Kidney Dis* 1981, **1:** 27–37.
21. Balow, J.E. Renal vasculitis. *Kidney Int* 1985, **27:** 954–964.
22. Göbel, U., Natusch, R., Müller, V. *et al.* Langzeitprognose der chronischen Glomerulonephritis. *Z Klin Med* 1988, **44:** 1933–1938.