Clinical prognostic factors of renal outcome in anti-neutrophil cytoplasmic autoantibody (ANCA)-associated glomerulonephritis in elderly patients

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Abstract

Background. The purpose of the present study was to determine clinical prognostic factors on renal survival in 37 older patients with antineutrophil cytoplasmic autoantibody-associated pauci-immune necrotizing crescentic glomerulonephritis (ANCA-associated GN) who underwent renal biopsy at our Department between January 1996 and December 2000.

Methods. The date of renal biopsy was used as the start date for entry into the study. Age, gender, 24 h proteinuria, serum creatinine level, blood pressure and ANCA were evaluated. The end-point for renal survival analysis was the start of chronic dialysis.

Results. Twenty-six (70%) patients showed varying degrees of renal insufficiency, nine (24%) patients required dialysis, 13 (35%) were hypertensive (BP ≥140/90 mmHg) and 33 (89%) had proteinuria. During follow-up (31.73 ± 17.39 months), 16% of the patients (6/37) developed end-stage renal disease (ESRD). The actuarial renal survival rate for all patients was 92% at 1 year and 76% at 3 years, for Wegener’s granulomatosis 80% at 1 and 3 years, for microscopic polyangiitis 85% at 1 and 3 years, and for renal limited disease (GN) 75% at 1 and 37% at 3 years. Age (P = 0.024), arterial hypertension (P = 0.018), proteinuria (P = 0.037) and serum creatinine ≥400 μmol/l (P = 0.047) were the most important risk factors for ESRD.

Conclusion. The actuarial renal survival rate in elderly patients with ANCA-associated GN was 92% at 1 year and 76% at 3 years. Older age, arterial hypertension, proteinuria and serum creatinine ≥400 μmol/l related to ESRD.

Keywords: ANCA-associated vasculitis; elderly patients; pauci-immune crescentic necrotizing glomerulonephritis; microscopic polyangiitis; Wegener’s granulomatosis

Introduction

Anti-neutrophil cytoplasmic autoantibody-associated pauci-immune necrotizing crescentic glomerulonephritis (ANCA-associated GN) is the most common condition associated with rapidly progressive glomerulonephritis and acute renal insufficiency in the elderly [1,2]. The diagnosis of ANCA-associated vasculitis is made on the basis of the clinical findings, biopsy of a relevant organ (typically kidney, nasal mucosa or lung) and the presence of ANCA. The prognosis of glomerulonephritis in relation to ANCA-associated vasculitis is a major concern for physicians, because treatment with immunosuppressive drugs is effective in controlling the disease, but is associated with potentially lethal adverse effects, especially in elderly patients. A number of studies on the value of clinical and histological prognostic factors of renal outcome in patients of different age at diagnosis have shown contradictory results [3–5].

The purpose of the present study was to determine clinical prognostic factors on renal survival in 37 consecutive elderly patients who at the time of renal biopsy were at least 60 years old, had ANCA-associated GN with or without signs of systemic vasculitis and who underwent renal biopsy at our department between January 1996 and December 2000.

Patients and methods

Thirty-seven patients (14 men, 23 women; mean age 68.7 ± 5.99, range 60–91 years) from a single centre entered
the study. They were classified according to the Chapell Hill nomenclature: 13 patients had Wegener’s granulomatosis (WG), 16 had microscopic polyangiitis (MPA) and eight had renal limited disease (GN) [6]. Testing for ANCA was performed using both indirect immunofluorescence and antigen-specific enzyme-linked immunosorbent assay [7]; myeloperoxidase (MPO) ANCA positivity was found in 24 patients and proteinase-3 (PR3) ANCA positivity in 13 patients. The date of renal biopsy at diagnosis was used as the start date for entry into the study, and age, gender, clinical presentation, 24 h proteinuria, serum creatinine level and blood pressure were evaluated. The patients were treated according to protocol with a combination of methylprednisolone and pulses of cyclophosphamide in reduced dose according to the age and the degree of renal insufficiency. The patients were followed until January 2002. The endpoint for renal survival analysis was the start of chronic dialysis. Renal survival was estimated by the Kaplan–Meier method. The log-rank test and the univariate Cox proportional hazard model were used to assess the predictive value of selected clinical parameters on renal survival.

Results

At the time of renal biopsy, 26 (70%) patients showed varying degrees of renal insufficiency (serum creatinine level from >110 to 1085 μmol/l), nine (24%) patients required dialysis, 13 patients (35%) were hypertensive (blood pressure ≥140/90 mmHg) and 33 patients (89%) had proteinuria >0.5 g/day. During follow-up (31.73 ± 17.39 months), six (16%) of the patients developed end-stage renal disease (ESRD). The actuarial renal survival rate for all patients was as follows: 92% at 1 year and 76% at 3 years, WG patients 80% at 1 and 3 years, MPA patients 85% at 1 and 3 years, and GN patients 75% at 1 and 37% at 3 years. The predictive value of selected clinical data on renal survival are presented in Table 1.

Discussion

The present study analyses the prognostic impact of selected clinical variables in elderly patients with ANCA-associated GN with or without vasculitis.

Table 1. Clinical prognostic parameters of renal survival at the time of renal biopsy assessed by univariate analysis: the univariate Cox proportional hazard model for numeric variables (β) and the log-rank test for dichotomized variables (χ²)

<table>
<thead>
<tr>
<th>Variable</th>
<th>β or χ²</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.246</td>
<td>1.279</td>
<td>0.024*</td>
</tr>
<tr>
<td>Gender</td>
<td>0.16</td>
<td>0.637</td>
<td>0.688</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.003</td>
<td>1.003</td>
<td>0.354</td>
</tr>
<tr>
<td>24-hour proteinuria</td>
<td>0.694</td>
<td>2.001</td>
<td>0.037*</td>
</tr>
<tr>
<td>Arterial hypertension (≥140/90 mmHg)</td>
<td>5.56</td>
<td>6.143</td>
<td>0.018*</td>
</tr>
</tbody>
</table>

HR = hazard ratio per unit change.
*Statistically significant (P < 0.05).

Four clinical factors at renal biopsy were each associated with increased probability of renal death: age, arterial hypertension (blood pressure ≥140/90 mmHg), proteinuria ≥500 mg/day and serum creatinine ≥400 μmol/l. In our study, we were limited to univariate analysis because of the relatively small number of patients and the few renal deaths that occurred. In previous reports including patients of all ages (2–92 years), age emerged as an important prognostic factor [4,5]. This was also confirmed in our group of elderly patients. The presence of hypertension at renal biopsy (at the time of apparent onset of the disease) has been established as the most important clinical predictor of renal survival (risk ratio 6.14, P = 0.018). In elderly people, arterial hypertension may precede the disease by a few months or years and may aggravate the course of the disease, because of already established glomerular hypertension. The hypertensive lesions superimposed on the age-related vascular lesions probably worsen the prognosis of the renal disease. Both types of lesions are difficult to differentiate. In our study, proteinuria was found to be an important prognostic factor of renal death (risk ratio 2.00, P = 0.037), an observation, which was also confirmed in several studies on progression of diabetic and non-diabetic renal disease. Proteinuria together with arterial hypertension is probably one of the major factors contributing to the progression of chronic kidney disease [8].

The current study confirms these previous reports that an elevated serum creatinine prior to treatment identifies patients at increased risk for renal death. In our study, serum creatinine in univariate analysis using a continuous form of entry value did not reach statistical significance. This is most likely to be a consequence of the fact that many patients with renal insufficiency at presentation were treated successfully, with improvement of renal function. When we used the median of the entry serum creatinine value of ≥400 μmol/l as the cut-off point for subgroup analysis, the serum creatinine value became a strong predictor of renal survival (P = 0.04). Hogan et al. found the median of the peak entry creatinine value of 4.5 mg/dl to be an important long-term prognostic marker of renal survival [4]. In the study of the European Vasculitis Study Group (EUVAS), baseline renal function expressed as calculated glomerular filtration rate (GFR) and chronic renal lesions were potent predictors of renal function at 18 months [5]. Physicians must be aware of the worse prognosis in older patients and in those with serum creatinine ≥400 μmol/l, especially when they decide to treat patients with renal limited disease. Histological parameters in the renal biopsy may be used to predict renal outcome after therapy. In the multivariate analysis of Hogan et al., only arterial sclerosis had an impact on renal survival among multiple pathological scores when controlling for serum creatinine [4]. Studies on the value of clinical and histological determinants of renal outcome are difficult to compare due to large differences in study.
design, histological scoring methods and other definitions. In the EUVAS study, the histopathological parameters that most strongly correlated with corrected GFR at 18 months were cellular crescents and fibrinoid necrosis [5].

In our study, the actuarial renal survival at 1 and 3 years was best for patients with WG (80% and 80%) and MPA (85% and 85%) and worst for patients with GN (75% and 37%). The worst survival for GN was also shown in other studies, suggesting that this outcome may be explained by delayed establishment of diagnosis in these patients who have no signs of extrarenal vasculitis compared with patients with WG or MPA. The possibility of different pathways in the pathogenesis of renal diseases in these ANCA subsets should also be considered [3,4,9–12].

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References