‘Benign’ hypertensive nephrosclerosis

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Summary

Background: Whether benign hypertensive nephrosclerosis (BHN) causes end-stage renal failure (ESRF) is controversial. One reason for this is the lack of biopsy evidence confirming the clinical diagnosis in most cases.

Aim: To investigate whether biopsy-proven BHN leads to ESRF.

Design: Retrospective analysis.

Methods: We analysed all cases of biopsy-proven BHN from a single centre over a period of 20 years (n = 60), followed-up for a mean ± SD 6.7 ± 5.5 years.

Results: Patients were divided into those with stable renal function (n = 17) and those with declining function (n = 43). Mean eGFR at the time of biopsy was lower in the declining function group (29 ± 3 vs. 44 ± 4 ml/min/1.73 m², serum creatinine 280 ± 165 vs. 161 ± 89 μmol/l, p < 0.001), of whom 72% progressed to ESRF. Median renal survival for the whole group was 6.8 years, with 5- and 10-year survivals of 56% and 35%, respectively. Renal survival was significantly affected by initial serum creatinine, and mean systolic and diastolic blood pressures during follow-up period. Mean protein excretion was higher in the declining group, but not significantly so. On multivariate analysis, only diastolic blood pressure during follow-up predicted renal survival (p = 0.017). Median patient survival for the whole group was 9.95 years post renal biopsy, with 5- and 10-year survivals of 70% and 49% respectively. Survival was affected by initial serum creatinine, initial serum albumin and mean systolic blood pressure during follow-up. On multivariate analysis, only initial serum creatinine was significantly correlated with survival (p = 0.017).

Discussion: Biopsy-proven BHN led to ESRF in a high percentage of our patients, and was associated with significant mortality.

Introduction

Hypertensive nephrosclerosis is a common cause of end-stage renal disease (ESRD), accounting for 24% cases of treated ESRD in the US, and 17% in Europe, according to registry data. However, it remains controversial as to whether benign essential hypertension can cause ESRD. Half a century ago, Perera followed up 500 patients with hypertension until their death, and found that 18% of them developed renal impairment. Since then, various longitudinal studies in patients with mild to moderate essential hypertension have suggested that benign hypertension may lead to ESRD. Similar observations have been made from post-hoc analysis of intervention trials.

On the other hand, results of a number of other studies argue against this. Some researchers believe that benign essential hypertension rarely causes renal damage in Caucasian patients. Their belief is based on a number of observations: (i) most epidemiological evidence for the relationship comes from studies conducted in America, and include a substantial proportion of patients of African-American ethnicity, who are known to be more susceptible to hypertension-related kidney damage; (ii) there are no data to exclude the possibility that...
the patients who developed ESRD in these studies had another underlying renal disease; (iii) analysis of data from major hypertension trials do not show an increased incidence of renal failure in the placebo group compared to the treatment group; and (iv) studies conducted in predominantly Caucasian patients with benign essential hypertension with normal protein excretion and seruminin do not show any significant change in renal function. One of the main reasons for this controversy is the lack of biopsy evidence confirming the clinical diagnosis of hypertensive nephrosclerosis in most cases, as only a limited number of studies have included renal biopsy histology. Moreover, very little is known about the natural history of this condition. We present the clinical features and outcome of all cases with biopsy-proven benign hypertensive nephrosclerosis (BHN) seen at our hospital over a period of 20 years.

Methods

From the pathology database of Nottingham City Hospital, we selected all patients that had benign hypertensive nephrosclerosis diagnosed on renal biopsy over a 20-year period between 1977 and 1997. At the time of the study, we had a catchment population of nearly 1 million. All patients with inadequate biopsies (<6 glomeruli in a sample) or doubtful histology were excluded. The case records of all 60 patients with confirmed benign hypertensive nephrosclerosis (BHN) were then reviewed. In most cases, the indication for biopsy was unexplained proteinuria (>1 g/24 h), with or without raised serum creatinine, in the presence of non-malignant/non-accelerated hypertension. In all patients, the presence of two kidneys of normal size and shape was established by intravenous urogram or ultrasonography before any renal biopsy was taken. Patients with clinical, immunological or histological evidence of any other renal disease or systemic disorder were excluded from the study.

Blood pressure (before renal biopsy and during follow-up), serum albumin at the time of biopsy, urinary protein concentration, the date of starting renal replacement therapy and the date of death of patients who died during follow-up were obtained from the case notes and computer records where available. The mean of all blood pressure readings taken at out-patient visits over the follow-up period was calculated for each patient. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation.

The rate of deterioration of renal function was assessed by the change in reciprocal serum creatinine concentration with time, a negative slope indicating deteriorating renal function. The minimum period of follow-up was two and a half years. The primary end-point was end-stage renal failure necessitating dialysis treatment or renal transplantation. The secondary end-point was patient death.

All renal biopsies were examined at the time by two experienced histopathologists. All specimens were examined by light microscopy and immunohistochemistry, and some (from the latter half of the study period) were also examined by electron microscopy. Hypertensive nephrosclerosis was diagnosed at the time of renal biopsy, in accordance with WHO criteria. The main diagnostic features were intimal thickening, medial hypertrophy, reduplication of the internal elastic lamina, glomerular sclerosis and tubular atrophy. There were also variable degrees of increase in mesangial matrix and interstitial fibrosis. Patients with histological evidence of glomerulonephritis, interstitial nephritis or malignant hypertension were excluded from the study.

Standard statistical methods were used to calculate medians, means and standard deviations. After establishing whether the data conformed to normal distribution using the Shapiro-Wilkes test for normality in small sample numbers, parametric or non-parametric tests of significance were applied. Patient survival was determined from the date of biopsy; patients who were alive at the point of analysis of the data were censored. For the purpose of renal survival, the end-point was taken as either the date of starting renal replacement therapy (RRT) or death due to uraemia without dialysis. The log-rank test was used to assess the significance of differences in Kaplan-Meier survival curves. Cox proportional hazard regression analysis was applied to kidney survival and patient survival. Values of *p*<0.05 were considered significant. Data were processed using SPSS.

Results

Altogether 60 patients were included in this study: 40 male and 20 female; 58 were Caucasians and two were Afro-Caribbean. Median age at the time of biopsy was 58 years (range 31–75). Mean ± SD systolic and diastolic blood pressures before renal biopsy were 179 ± 25 and 105 ± 15 mmHg, respectively. Mean ± SD serum creatinine before biopsy was 247 ± 157 μmol/l, the estimated GFR 36 ± 3 ml/min/1.73 m² and mean 24-h protein excretion 2.3 ± 2.4 g (Table 1).
declining function group reached ESRF.

Thirty-one patients (72%) in the declining function group was higher than in those with an initial serum creatinine of laboratory reference range) had a 5-year survival of 37% vs. 83% in those with serum creatinine <250 mol/l was 42% vs. 83% in those with serum creatinine <250 mol/l at the time of renal biopsy (log rank p = 0.002). No significant difference in kidney survival was found using other BP cut-offs. Survival analysis did not reveal a relationship between degree of proteinuria and renal survival. Figure 1 a–d shows show the Kaplan-Meier survival curves for renal survival. On multivariate analysis, mean diastolic blood pressure over the follow-up period was the only significant predictor of renal survival (p = 0.017).

Patient mortality was also affected by initial serum creatinine. Five-year survival in patients with initial serum creatinine >250 μmol/l at the time of renal biopsy (log rank p = 0.036). Patients with initial serum albumin <30 g/l (below the lower limit of laboratory reference range) had a 5-year survival of 31% vs. 81% in those with serum albumin >30 g/l (log rank p < 0.001). Mean SBP also affected

### Survival analysis

Median renal survival for the whole cohort was 6.8 years (95%CI 3.6–9.8), with 5- and 10-year survivals at 56% and 35%, respectively. Median patient survival for the whole group was 9.95 years (95%CI 5.1–14.8); 5-year survival was 70% and 10-year survival was 49%. Twenty-four patients (56%) in the declining function group died in the follow-up period, compared to 6 (35%) in the stable function group (p<0.001). Table 3 shows the causes of death.

Renal survival was worse in patients with serum creatinine >250 μmol/l (all patients had eGFR < 30 ml/min/m²) at the time of renal biopsy than in those with an initial serum creatinine <250 μmol/l: 5-year renal survival 47% vs. 65%, log rank p = 0.005. Renal survival was also significantly affected by mean systolic (SBP) and diastolic blood pressures (DBP) during follow-up. Those with mean SBP >150 mmHg before biopsy had a 5-year renal survival of 41% vs. 77% in those with SBP <150 mmHg (log rank p = 0.002).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age (years)</td>
<td>58 (31–75)</td>
</tr>
<tr>
<td>M:F</td>
<td>2:1</td>
</tr>
<tr>
<td>Mean ± SD systolic BP (mmHg)</td>
<td>179 ± 25</td>
</tr>
<tr>
<td>Mean ± SD diastolic BP (mmHg)</td>
<td>105 ± 15</td>
</tr>
<tr>
<td>Mean ± SD urinary protein (g/24 h)</td>
<td>2.3 ± 2.4</td>
</tr>
<tr>
<td>Mean ± SD eGFR (ml/min/1.73 m²)</td>
<td>36 ± 3</td>
</tr>
<tr>
<td>Mean ± SD serum creatinine (μmol/l)</td>
<td>247 ± 157</td>
</tr>
<tr>
<td>Mean ± SD serum albumin (g/l)</td>
<td>36 ± 7</td>
</tr>
</tbody>
</table>

BP, blood pressure; eGFR, estimated glomerular filtration rate.

### Table 1 Patient characteristics at the time of renal biopsy (n = 60)

<table>
<thead>
<tr>
<th>Number reaching ESRF</th>
<th>Stable (n = 17)</th>
<th>Declining (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number reaching ESRF</td>
<td>0</td>
<td>31 (72%)</td>
</tr>
<tr>
<td>M:F</td>
<td>2:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Urine protein (g/24 h)</td>
<td>1.5 ± 1.6</td>
<td>2.5 ± 2.6</td>
</tr>
<tr>
<td>Mean ± SD eGFR (ml/min/1.73 m²)</td>
<td>44 ± 4</td>
<td>29 ± 3*</td>
</tr>
<tr>
<td>Mean ± SD serum creatinine (μmol/l)</td>
<td>161 ± 89</td>
<td>280 ± 165*</td>
</tr>
<tr>
<td>Mean ± SD systolic BP (mmHg)</td>
<td>150 ± 27</td>
<td>157 ± 17</td>
</tr>
<tr>
<td>Mean ± SD diastolic BP (mmHg)</td>
<td>87 ± 10</td>
<td>88 ± 9</td>
</tr>
<tr>
<td>Number reaching ESRF</td>
<td>0</td>
<td>31 (72%)</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>6 (35%)</td>
<td>24 (56%)</td>
</tr>
</tbody>
</table>

BP, blood pressure; eGFR, estimated glomerular filtration rate. *p<0.001.

### Table 2 Clinical features and outcomes for patients with stable vs. declining renal function at the time of renal biopsy

### Table 3 Causes of death

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>All patients</th>
<th>Declining function group</th>
<th>Stable function group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>11</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>9</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>24</td>
<td>6</td>
</tr>
</tbody>
</table>

Similarly, patients with DBP >90 mmHg had a 5-year renal survival of 37% vs. 69% in those with DBP <90 mmHg (log rank p = 0.002). No significant difference in kidney survival was found using other BP cut-offs. Survival analysis did not reveal a relationship between degree of proteinuria and renal survival. Figure 1 a–d shows show the Kaplan-Meier survival curves for renal survival. On multivariate analysis, mean diastolic blood pressure over the follow-up period was the only significant predictor of renal survival (p = 0.017).

Patient mortality was also affected by initial serum creatinine. Five-year survival in patients with initial serum creatinine >250 μmol/l was 42% vs. 83% in those with serum creatinine <250 μmol/l at the time of renal biopsy (log rank p = 0.036). Patients with initial serum albumin <30 g/l (below the lower limit of laboratory reference range) had a 5-year survival of 31% vs. 81% in those with serum albumin >30 g/l (log rank p < 0.001). Mean SBP also affected
mortality: 5-year survival was 56% in those with SBP ≥150 mmHg vs. 90% in those with SBP <150 mmHg (log rank \( p < 0.01 \)). There was no significant association between mean diastolic blood pressure and patient survival. Figure 2 a–d shows the Kaplan-Meier survival curves for patient survival. On multivariate analysis, initial serum creatinine was the only predictor of patient survival (\( p = 0.017 \)).

**Discussion**

This study highlights some important features of the natural history of BHN. It provides further evidence that it is potentially a progressive disorder: >50% of our patients with biopsy-proven BHN progressed to ESRD within 10 years of presentation with a raised serum creatinine or significant proteinuria. BHN was also associated with significant mortality, with a median patient survival of 9.95 years.

Hypertensive nephrosclerosis is generally diagnosed clinically after exclusion of other conditions in patients with chronic renal impairment associated with mild to moderate essential hypertension. In some studies, more than half of these patients, when thoroughly investigated, had another underlying cause of their renal impairment. Thus the main strength of this study is that it involves patients with biopsy-proven BHN followed-up for a long period of time (mean 6.7 years). However, the main indication of renal biopsy in most patients was a raised serum creatinine, significant proteinuria or both, suggesting that these patients may have had quite advanced BHN at the time of renal biopsy. This may account for the unfavourable prognosis in the majority of our BHN patients. As the AASK trial demonstrated, cases with less advanced
hypertensive nephrosclerosis have a more favourable outcome.26

Most patients (97%) in this series of biopsy-proven BHN were Caucasian, in whom this condition is reportedly uncommon, Black patients having a relative risk of 6.4 compared with Caucasian patients.27 It is also more common in men,27 and 67% of our patients were male. Their baseline characteristics were similar to those in an earlier study of biopsy-proven BHN using the UK Medical Research Council (MRC) Glomerulonephritis Registry data.16

Our patients were followed-up for a mean of 6.7 years. Most (72%) had progressive chronic renal impairment, and 51% developed ESRD. Reciprocal serum creatinine was used to assess progression of renal disease, in the absence of measured or estimated GFR or creatinine clearance in most patients at the time of the study, and was subsequently corroborated using eGFR. Of the baseline characteristics of the two groups of patients, serum creatinine at the time of renal biopsy was the only predictor of subsequent progression of renal disease. A study of biopsy-proven BHN using the Norwegian Kidney Registry data made a similar observation, and also found baseline urinary protein excretion to be a predictor of progression of renal disease.17 In our study, the baseline urinary protein excretion was higher in the declining function group, but did not reach statistical significance. This may well be due to a smaller sample size. However, another retrospective study of 170 patients with biopsy-proven BHN also found that serum creatinine, but not degree of proteinuria, predicted subsequent deterioration in renal function.21

Mean renal survival, calculated from the time of biopsy to the time of ESRD, was 6.8 years (95%CI 3.6–9.8). Of the factors that we were able to study in this retrospective analysis, initial serum creatinine >250μmol/l, mean systolic BP >150mmHg,
mean diastolic BP $\geq 90\text{mmHg}$ and initial serum albumin $<30\text{g/l}$ significantly affected renal survival. However, on multivariate analysis, only mean diastolic BP over the follow-up period predicted renal survival. These findings are consistent with those of other studies on biopsy-proven BHN. The Norwegian study found serum creatinine $\geq 200\text{mol/l}$, systolic BP $\geq 160\text{mmHg}$ and proteinuria $\geq 1\text{g/24h}$ to be associated with lower renal survival. In the study by Wehrmann and Bohle, serum creatinine $>2\text{mg/dl} (>177\text{mol/l})$ was associated with poor prognosis. In a Japanese study of 590 patients with biopsy-proven BHN, poor BP control was associated with lower renal survival. However, the 5-year renal survival of 56% in our study was better than that reported in the last two studies (35.9% in the first study, and most of the patients with progressive renal impairment in the second study reached ESRF within 5 years of biopsy).

Our patients with BHN had a high mortality; 50% died within the follow-up period of 6.7 years. Patients with declining renal function had a much higher mortality (56%) than those with stable renal function (35%). Moreover, serum creatinine $>250\text{mol/l}$, low serum albumin $<30\text{g/dl}$, and high systolic blood pressure were associated with poorer survival. However, on multivariate analysis, initial serum creatinine was the only factor predicting patient survival. Cardiovascular disease was the commonest cause of death. These findings imply that BHN is associated not only with progressive decline in renal function, ultimately leading to ESRD, but also with increased risk of death. Similar observations have been made by other investigators. However, it is well known that both mild to moderate chronic kidney disease and ESRD are associated with a high risk of mortality, especially from cardiovascular disease. As such, the high mortality found in these patients may be attributable to impaired kidney function rather than to BHN per se. These patients might also have had other associated cardiovascular risk factors, but in this retrospective analysis it was not possible to assess cardiovascular risk factors separately.

Our study has limitations. It is a retrospective study of a relatively small number of patients, although few studies of biopsy-proven BHN have had significantly higher numbers. A prospective design would allow examination of all the factors that are known to affect the course of chronic kidney disease in BHN. As Professor A.E. Raine wrote more than a decade ago, ‘the extent to which ‘benign’ hypertension truly leads to significant renal impairment will only be known if appropriately controlled prospective studies are performed in hypertensive patients initially free of any renal involvement, and in whom histology is obtained if any evidence of renal dysfunction develops’.

In conclusion, biopsy-proven BHN steadily progressed to ESRF in a high percentage of our patients. High serum creatinine and poorly controlled BP significantly reduced renal survival. Mortality was high, and affected by serum creatinine, serum albumin, and poorly controlled SBP. However, on multivariate analysis, poorly controlled diastolic BP and serum creatinine at presentation were the only predictors of renal and patient survival, respectively. The commonest cause of death was cardiovascular. ‘Benign’ hypertensive nephrosclerosis may not be a ‘benign’ condition at all.

References


