Hypertensive Nephrosclerosis as a Relevant Cause of Chronic Renal Failure

Edna Regina Silva Pereira Caetano, Roberto Zatz, Luís Balthazar Saldanha, José Nery Praxedes

Abstract—It is currently unclear whether hypertensive nephrosclerosis (HN), usually diagnosed solely on clinical grounds, is a relevant cause of end-stage renal disease. We biopsied 81 hypertensive outpatients (blood pressure $\geqslant 160/95$ mm Hg) with moderate renal insufficiency, who were referred to our service from 1988 to 1998. Patients with known causes of hypertension, systemic disorders, rheumatic disease, or nephrotic syndrome were excluded. In 65% of patients, HN was the sole histological abnormality associated with renal dysfunction. Benign nephrosclerosis (BN), defined as isolated arteriolar hyalinosis and/or intimal fibrosis, was found in 18 HN patients (22%), whereas malignant nephrosclerosis (MN), denoted mainly by myointimal cell proliferation, appeared in 35 HN patients (43%). Previously undiagnosed primary nephritis (PN) was found in 13 patients (16%), whereas focal and segmental glomerulosclerosis, which might be either primary or secondary to hypertension, appeared in 15 patients (19%). These findings suggest that HN, in both its BN and MN forms, can be a definite cause of chronic renal insufficiency and that a substantial fraction of patients with renal insufficiency and clinical diagnosis of HN may actually have PN. (Hypertension. 2001;38:171-176.)

Key Words: nephrosclerosis $\bullet$ hypertension, essential $\bullet$ kidney $\bullet$ renal disease

Malignant nephrosclerosis (MN) is widely regarded as a definite, though increasingly rare, cause of end-stage renal disease (ESRD). In contrast, it remains uncertain whether benign nephrosclerosis (BN) consequent to essential hypertension can also cause ESRD. Recent data reported by the United States Renal Data System (USRDS) and by European and Latin American registries indicate that hypertensive nephrosclerosis (HN) is a frequent and growingly important presumed cause of ESRD among patients initiating replacement therapy. Although early epidemiological data indicated that few hypertensive patients eventually develop renal injury, more recent clinical observations revealed that the relative risk of developing ESRD is increased by up to 20 times in hypertensive patients.

Usually, the diagnosis of HN is entirely made on clinical grounds, without renal biopsy or any evidence that hypertension actually preceded renal disease. Thus, HN can be easily mistaken for primary or ischemic nephropathies, which may also exhibit an insidious nature. Only 2 large biopsy-based studies of HN have been reported so far. Zucchelli and Zuccala showed “true” HN in only 48% of 56 white patients clinically diagnosed as such. Fogo et al showed an 85% agreement between clinical and histological diagnoses of HN in African Americans.

We performed a 10-year follow-up of 81 hypertensives with impaired renal function and no clinical evidence of primary or ischemic renal disease. We could thus evaluate the frequency of HN among them and whether HN can be safely diagnosed on a clinical basis.

Methods

Patients

Between 1988 and 1998, a selected, nonsystematic cohort of 90 hypertensive patients, referred to the Hypertension Clinic of the Renal Division, Department of Clinical Medicine, University of São Paulo, was investigated. Inclusion criteria were arterial hypertension and renal insufficiency. A patient was determined to have arterial hypertension if (1) systolic blood pressure (SBP) was $\geqslant 160$ mm Hg and/or diastolic blood pressure (DBP) was $\geqslant 95$ mm Hg, following the then most recent World Health Organization guidelines, or (2) there was a persistent need for antihypertensives. Blood pressure was determined as the average of 2 sphygmomanometric measurements, taken in the seated position after a 5-minute rest. Renal insufficiency was defined by serum creatinine concentration ($S_{\text{crea}}$) $>133$ $\mu$mol/L (1.5 mg/dL). Exclusion criteria were (1) renal artery stenosis (diagnosed by renal arteriography); (2) other definite causes of hypertension; (3) diabetes mellitus; (4) immune-mediated disease; (5) heart failure (stages III and IV); (6) liver disease; (7) nephritic syndrome, defined by proteinuria $>3.5$ g/d; hypoaalbuminemia, edema, and hypercholesterolemia; (8) polycystic nephropathy; (9) urinary obstruction; (10) pregnancy; and (11) impaired hemostasis or continuous need for anticoagulants. The protocol was approved by

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the local ethics committee, and informed consent was obtained from each patient.

### Study Protocol

Soon after enrollment, and after adequate blood pressure control, patients underwent renal biopsy. Biopsy-related untoward events were limited to a single case of intense hematuria, which subsided after 3 days. Other clinical and laboratory data taken at biopsy time were fundoscopy at the Ophthalmology Division, using Keith-Wagener-Barker criteria,11 echocardiography, renal ultrasonography, creatinine clearance, 24-hour proteinuria, urinary sediment analysis, hemogram, and routine serum biochemistry.

### Histological Techniques

The renal tissue was fixed by immersion in Duboscq-Brazil solution for 2 hours, postfixed in 10% formaldehyde, and included in paraffin by conventional techniques. Sections 3 to 4 μm thick were stained by hematoxylin-eosin, periodic acid–Schiff, Masson trichrome, and methenamine-silver. For immunofluorescence, renal fragments were snap-frozen in liquid nitrogen, and 4- to 5-μm-thick cryostat sections were incubated with antibodies against human IgG, IgM, IgA, C1q, C3, or fibrinogen. Only biopsy specimens comprising both cortical and juxtamedullary areas were reviewed. Specimens containing <5 glomeruli were discarded.9 The number of glomeruli per patient averaged 19.2±1.5 SE. Each section was examined by 2 renal pathologists who were unaware of the respective clinical background. In a few cases (5%) in which the diagnoses were discordant, the sections were reevaluated until a consensus was reached.

### Techniques of Semiquantitative Analysis

The extent of glomerulosclerosis was expressed as the percentage of globally sclerotic glomeruli. Wrinkling of the glomerular basement membrane (denoting glomerular ischemia), tubulatry atrophy, and interstitial fibrosis were quantitated by attributing to each case a score varying from 0 to 3, with 0 denoting no change; 1, slight injury; 2, moderate injury; and 3, severe injury. Arterial and arteriolar lesions, comprising medial hypertrophy, intimal fibrosis, myointimal cell proliferation (denoting glomerular ischemia), tubular atrophy, and interstitial fibrosis were quantitated by attributing to each case a ground. In a few cases (5%) in which the diagnoses were discordant, the sections were reevaluated until a consensus was reached.

### Groups

Patients were distributed among 3 groups according to histological diagnosis: HN, PN, and focal and segmental glomerulosclerosis (FSGS). HN is the group in which vascular injury dominated the histologic picture, with no specific parenchymal lesions except those attributable to ischemia, such as wrinkling of the glomerular basement membrane and global tuft collapse.12 The HN group was in turn divided into 2 subgroups: BN, characterized by arterial and arteriolar hyalinosis, medial hypertrophy, and intimal fibrosis; and MN, showing myointimal cell proliferation (usually with an "onion skin" aspect), mucinous intimal thickening, or fibrinoid necrosis.12–14 PN was the group in which primary glomerulonephritis and/or tubulointerstitial nephritis was seen rather than, or in addition to, vascular injury. FSGS was the group in which classical FSGS lesions were the main structural abnormality. These patients were classified as a separate group because it was indiscernible, based on our data, whether FSGS resulted from hypertension itself or rather represented primary renal disease.

### Statistical Analysis

Differences among the groups HN, PN, and FSGS were assessed using 1-way ANOVA with posttest pairwise comparison according to the Newman-Keuls formulation. The unpaired Student’s t test was used to assess the statistical significance of differences between subgroups BN and MN. Differences between groups for qualitative variables (gender, race, and familiar antecedents) were assessed by the χ2 test. P<0.05 was significant.

### Results

#### Baseline Clinical Data

Nine patients (10%) were excluded because too few (<5) glomeruli were present in the biopsy material. Baseline clinical data concerning the remaining 81 patients are shown in Table 1. Males predominated over females (53/28). The ratio of whites to nonwhites (the latter comprised almost exclusively of subjects of African descent) approached unity. Most patients (68%) reported familial antecedents of hypertension. Severe hypertension (DBP $\geq 110$ mm Hg) occurred in 52% of patients. Accordingly, 45% exhibited grade III or grade IV retinopathy (however, the severity of hypertension did not always agree with that of retinopathy; see Table 5). Mean S\textsubscript{creat} was 353±27 μmol/L, indicating moderate renal insufficiency.

#### Histological Diagnosis

HN, diagnosed in 53 patients (65%), was the most frequent renal abnormality (Table 2). MN was found in 35 HN patients (43% of total), whereas BN was diagnosed in 18 HN patients (22% of total). One MN patient had superimposed cholesterol microembolism. PN was seen in 13 (16%) of all patients. Of these, 9 (11% of total) exhibited IgA nephropathy, 2 had membranous glomerulonephritis, one had mesangiocapillary
glomerulonephritis, and one had chronic interstitial nephritis.
FSGS was seen in 15 patients (19% of total). Associated
microvascular injury appeared systematically in PN and
FSGS patients.

Clinical and Histological Data: HN Versus PN
Versus FSGS
Clinical data obtained in HN, PN, and FSGS patients are
given in Table 3. Group HN exhibited lower \( S_{\text{c mote}} \), higher
hematocrit (Hct), and less renal contraction than that of group

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HN</td>
<td>53 (65)</td>
</tr>
<tr>
<td>BN</td>
<td>18 (22)</td>
</tr>
<tr>
<td>MN</td>
<td>35 (43)</td>
</tr>
<tr>
<td>Primary nephritis</td>
<td>13 (16)</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Membranous glomerulonephritis</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Mesangiocapillary glomerulonephritis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Chronic interstitial nephritis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>FSGS</td>
<td>15 (19)</td>
</tr>
</tbody>
</table>

PN. Group FSGS resembled group HN regarding blood
pressure, \( S_{\text{c mote}} \), and Hct but approached group PN as to
proteinuria (Figure 1) and renal size.

Histological findings are shown in Table 4. The frequency
of globally sclerotic glomeruli was significantly greater in PN
than in HN or FSGS, whereas the mean tubular atrophy score
was higher in PN versus HN. The severity of vascular injury,
assessed by the myointimal proliferation score, was higher in
HN versus FSGS.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HN (n=53)</th>
<th>PN (n=13)</th>
<th>FSGS (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>37/16</td>
<td>6/7</td>
<td>10/5</td>
</tr>
<tr>
<td>White/nonwhite</td>
<td>26/27</td>
<td>7/6</td>
<td>5/10</td>
</tr>
<tr>
<td>Age, y</td>
<td>42.6±1</td>
<td>39.6±3.3</td>
<td>38.8±3.4</td>
</tr>
<tr>
<td>Hypertension familiar antecedents, %</td>
<td>75</td>
<td>62</td>
<td>47</td>
</tr>
<tr>
<td>Hypertension duration, y</td>
<td>8.3±1.0</td>
<td>3.8±1.2</td>
<td>6.6±2.2</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>183±4.7</td>
<td>171±8.9</td>
<td>192±9.9</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>117±2.9</td>
<td>106±5.6*</td>
<td>130±7.7</td>
</tr>
<tr>
<td>Classes of hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP &lt;110 mmHg, %</td>
<td>36</td>
<td>54</td>
<td>27</td>
</tr>
<tr>
<td>DBP ≥110 mmHg, %</td>
<td>64</td>
<td>46</td>
<td>73</td>
</tr>
<tr>
<td>Grades of retinopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O–II, %</td>
<td>54</td>
<td>73</td>
<td>43</td>
</tr>
<tr>
<td>III–IV, %</td>
<td>46</td>
<td>27</td>
<td>57</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.8±0.6</td>
<td>23.7±1.3</td>
<td>25.4±1.5</td>
</tr>
<tr>
<td>( S_{\text{c mote}} ), μmol/L</td>
<td>290±18†</td>
<td>537±106</td>
<td>415±70</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>34±2.7</td>
<td>24±5.2</td>
<td>35±7.4</td>
</tr>
<tr>
<td>Protein excretion rate, g/24 h</td>
<td>1.1±0.1*</td>
<td>1.5±0.3</td>
<td>1.7±0.3</td>
</tr>
<tr>
<td>Frequency of hematuria, %</td>
<td>4</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.40±0.01†</td>
<td>0.32±0.02*</td>
<td>0.38±0.01</td>
</tr>
<tr>
<td>Uric acid, μmol/L</td>
<td>517±12</td>
<td>494±30</td>
<td>523±48</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.4±0.2</td>
<td>5.4±0.3</td>
<td>5.7±0.4</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.0±0.0</td>
<td>1.0±0.1</td>
<td>0.9±0.1</td>
</tr>
<tr>
<td>Left kidney size, mm</td>
<td>98±1‡</td>
<td>88±4</td>
<td>79±3</td>
</tr>
<tr>
<td>Interventricular septum, mm</td>
<td>13.4±0.4</td>
<td>11.5±0.8</td>
<td>12.0±0.7</td>
</tr>
<tr>
<td>Left ventricular mass, g</td>
<td>357±29</td>
<td>264±40</td>
<td>315±36</td>
</tr>
</tbody>
</table>

Values are mean±SE.
\*P<0.05 vs FSGS, †P<0.05 vs PN.
Clinical and Histological Data: BN and MN

Comparisons between BN and MN are given in Table 5. BN predominated in males (89%). Mean age was higher in BN versus MN. DBP (Figure 2) was significantly higher in MN versus BN. In addition, DBP ≥110 mmHg was more frequent in MN versus BN (63% versus 28%).

Clinical data of BN versus HN patients are shown in Table 5. Four out of 16 patients (25%) with BN had grade III hypertensive retinopathy (exudates and/or hemorrhages, considered markers of accelerated hypertension). No patient had papilledema (grade IV retinopathy). Conversely, 14 out of 32 (44%) MN patients showed only mild fundoscopic alterations (grades I and II), consistent with a clinical diagnosis of BN. MN patients exhibited more severe renal injury, indicated by higher S creat, and smaller kidneys, compared with BN patients (Table 5). However, proteinuria was similar between BN and MN (Figure 3). Hematuria appeared in 2 MN patients but was absent in group BN.

Table 6 shows histological data obtained in BN versus MN. Myointimal proliferation (Figure 4A) defined the diagnosis of MN. Hypertrophy of the tunica media was most frequent in MN. Mucinous intimal thickening appeared in 9 (35%) MN patients, whereas only 1 had fibrinoid necrosis. Interstitial fibrosis was more severe in BN versus MN (Table 5 and Figure 4B).

Discussion

In 22% of our patients, the predominant histological findings were arterial and arteriolar lesions, such as hyaline deposits, intimal fibrosis, and hypertrophy of the tunica media. These patients also exhibited glomerular ischemia, tubular atrophy, and variable interstitial fibrosis. In the absence of specific evidence of primary glomerular or tubulointerstitial disease, these findings indicate that BN was the sole cause of renal injury in these patients.
insufficiency. Thus, this study provides new histological evidence that pure BN can occur in a substantial fraction of hypertensives presenting with moderate renal insufficiency, suggesting that longstanding essential hypertension may indeed cause chronic renal injury. We did not evaluate the epidemiological risk that hypertensive subjects will develop renal insufficiency. Nevertheless, given the high prevalence of hypertension, even an apparently negligible risk will result in a substantial incidence of renal insufficiency and ESRD in the long run. Indeed, the prevalence of HN is steadily increasing with time, leading a growing number of hypertensives to eventually need replacement therapy. Accordingly, the mean age of patients entering chronic dialysis programs has increased in the past 2 decades. Several factors are likely to contribute to this picture: (1) life expectancy has increased in most countries, augmenting the prevalence of hypertension and of its long-term complications; (2) the incidence of potentially lethal cardiac and cerebral vascular complications has been reduced by better clinical management of hypertension; and (3) for the same reason, the incidence of malignant hypertension has declined markedly.

A conspicuous finding of this study was that DBP >110 mmHg appeared in 52% of patients, whereas fundoscopic abnormalities consistent with malignant hypertension appeared in 45%. Accordingly, renal vascular lesions (mostly “onion skin” proliferation) characteristic of MN were found in 43% of these subjects, a much higher frequency than reported previously. It should be noted that unlike in other studies, we did not exclude patients with severe hypertension or moderate-to-severe proteinuria. Moreover, fundoscopic injury was limited to grades I and II in almost half of these patients, whereas in nearly 40%, DBP was below 110 mm Hg. These findings suggest that a large fraction of our patients, most of which are of poor socioeconomic condition, may have undergone previous undiagnosed, subclinical episodes of malignant hypertension. This view is consistent with the very low frequency of fibrinoid necrosis observed in this and other studies of MN.

Only a few clinical differences between BN and MN were observed in this study. In BN, males predominated over females, whereas the mean age was 10 years higher than in MN. Although younger, MN patients exhibited higher $S_{\text{crea}}$ and smaller kidneys than those of BN patients. Proteinuria, expectedly higher in MN, was similar between the 2 subgroups. The extensive overlap between groups makes the clinical detection of MN in hypertensives with moderate-to-advanced renal insufficiency an extremely difficult task.

The mechanisms by which hypertension could cause renal injury are incompletely understood and may include glomerular ischemia secondary to vascular narrowing, glomerulosclerosis due to intracapillary hypertension, and interstitial fibrosis. Two recent preliminary reports have stressed the importance of renal inflammatory phenomena, such as leukocyte infiltration, in experimental hypertension.

About one sixth of all patients exhibited primary nephropathies unsuspected on clinical evaluation, mainly IgA nephropathy (group PN). $S_{\text{crea}}$ proteinuria, and kidney size indicated more severe renal disease in this group than in HN. Accordingly, PN patients exhibited a higher frequency of globally sclerotic glomeruli and more severe tubular atrophy. Because the severity and known duration of hypertension were similar between PN and HN, as were cardiac hypertrophy and retinal injury, the more severe renal deterioration in the former must reflect a more aggressive nature of PN versus HN.

Despite the functional and morphological differences between HN and PN, no clinical parameter helped to discern between these groups. It has been suggested that proteinuria $>$1 g/24 hours could be used as a clinical criterion to exclude HN. In our series, however, 36% of HN patients exhibited...
proteinuria >1 g/d, in 7.4%, this value exceeded 3 g/d), in agreement with a previous retrospective, biopsy-based multicentric study, in which proteinuria exceeded 1.5 g/24 hours in 40% of patients with the diagnosis of BN. Given the difficulty to discern between HN and PN, and because patients with PN may need specific therapeutic measures, our findings suggest that renal biopsy should be indicated in hypertensives with moderate renal insufficiency.

The exact relationship between hypertension and renal injury in PN is unclear. Hypertension may result from the loss of renal mass caused by primary glomerular disease. Several mechanisms might mediate this effect, including salt retention, sympathetic activation, and inappropriate activity of the renin-angiotensin system. Alternatively, the association between hypertension and PN may have been coincidental in some patients. In either case, hypertension likely contributed to hasten the progression of renal disease. Indeed, hypertension is now regarded as a strong risk factor for ESRD, regardless of the initial renal insult.

Of interest, 19% of our cohort received a diagnosis of FSGS. There is currently no consensus as to whether primary and secondary FSGS can be unequivocally discerned by histology, and this is the reason why these patients were classified as a separate group. It must be noted that FSGS may represent a distinct manifestation of renal hypertensive injury. The FSGS group exhibited characteristics of both HN and PN, suggesting that renal injury may have resulted from either primary renal disease or long-standing hypertension. Therefore, the proportion of patients with hypertensive renal disease may have been even higher than inferred from the size of group HN.

In summary, our results suggest that (1) HN, in both its benign and malignant forms, can indeed represent a definite cause of chronic renal failure, and (2) conversely, a substantial fraction of patients with clinical diagnosis of HN may actually have primary renal disease. Further biopsy-based studies are necessary to establish the true dimension of HN as a cause of renal insufficiency.

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