Proc EDTA (1982) Vol 19

BERGER'S NEPHROPATHY: RELATIONSHIP BETWEEN HISTOLOGICAL PATTERN, BLOOD PRESSURE AND RENIN

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Summary

Vascular damage (VD), glomerular sclerosis (GS), renin (PRA) and blood pressure were assessed in 50 patients with Berger's nephropathy. GS was present in 5/15 patients without VD and affected more than 15 per cent of glomeruli in seven patients with minimal VD. Nine out of 19 patients with GS were normotensive. VD was present in 35 patients: 16 were hypertensive and 19 normotensive. Therefore hypertension is not the only mechanism responsible for VD. In the seven normotensive patients with high PRA, GS was not present while VD was absent or minimal.

Introduction

Hypertension is frequently found in patients with renal disease. The kidney affects blood pressure by a variety of mechanisms ranging from the regulation of sodium-water homeostasis to the release of pressor and depressor substances. Since these mechanisms are traditionally altered in end-stage renal disease, they have been extensively studied in patients on chronic haemodialysis. However, little is known about the genesis of hypertension in patients with glomerulonephritis with no impairment of excretory renal function. In these diseases, hypertension generally occurs many years after the onset of the nephropathy [1]. This would suggest that the mechanism responsible for the onset of hypertension is related to progressive renal damage. The morphologic indices of chronicity are glomerular sclerosis (GS) and intrarenal vascular damage (VD), which in turn could play a role in the development of hypertension by causing ischaemia and an increase in renin release [2]. GS, VD and hypertension have been reported in glomerulonephritis with IgA mesangial deposits (IgA GN) [3]. This study investigates the relationship between histology, renin release and blood pressure in patients with IgA GN and normal excretory renal function.

Material and methods

From 1973 to 1981, 101 patients were diagnosed as having IgA GN. The incidence of hypertension was 24.7 per cent. Fifty patients (39 males and 11 females), with an age-range of nine to 66 years (mean 35.2 years) were selected. Four subjects were over 50 and one less than 15 years of age. In all the patients the diagnosis was made by renal biopsy examined by light and immunofluorescence microscopy, obtained one month to 21 years after the onset of glomerulonephritis. Eight or more glomeruli were present in all biopsy specimens analysed. Mesangial deposits, predominantly IgA, were present in all glomeruli. No patients had systemic lupus erythematosus, Henoch-Schönlein syndrome or chronic hepatic disease. None had been previously treated with anti-inflammatory, steroid, cytotoxic or antihypertensive therapy. At the time of the observations, 18 patients were hypertensive (blood pressure greater than 140/90 mmHg). None of the patients were nephrotic. Serum creatinine was 1.5mg/dl or less in all.

In 34 patients, plasma renin activity (PRA), plasma aldosterone (PA), plasma noradrenaline (NA) and exchangeable sodium (ES) were determined at 8–9 a.m. after a night recumbent and fasting, after four days on a controlled diet (sodium 130–140mEq/day and potassium 60mEq/day). In our laboratory, normal PRA, evaluated in the same conditions in 80 healthy normotensive subjects aged 15–68 years, ranged from 0.2 to 0.9ng/ml/h of angiotensin I. PRA, NA and ES were determined as previously described [4,5]. PA was measured by radioimmunoassay methods [6].

GS was arbitrarily defined as absent, present in less than 15 per cent of glomeruli, or present in more than 15 per cent of glomeruli. VD was evaluated with the semiquantitative method of Pirani et al [7].

Results are expressed as mean ± standard error. Statistical analysis employed Student's t test and linear regression.

Results

Comparing the 32 normotensive and 18 hypertensive patients, no significant differences were found in the mean value of duration of nephropathy, total plasma proteins, daily protein excretion, and plasma IgA concentrations. On light microscopy six patients were classified as having minimal change, 27 as having focal proliferation (21 with GS) and 17 as having diffuse proliferation (10 with GS). VD was absent in 15 patients, mild (graded 1–2) in 28 patients and severe in seven patients (Figure 1). Of the 35 patients with VD 16 were hypertensive and 19 normotensive. VD was not related to either the duration of nephropathy or the patient's age, even if patients without VD were significantly younger than patients with a VD grade 3–4 (22 ± 2 vs 46 ± 5 years, $p < 0.01$). GS was present in 31 patients and affected more than 15 per cent of the glomeruli in 19 patients. GS did not correlate with VD:GS was present in 5/15 patients without VD and affected more than 15 per cent of glomeruli in seven patients with minimal VD (grade 1). GS and VD occurred together in 26 patients (11 normotensive and 15 hypertensive).

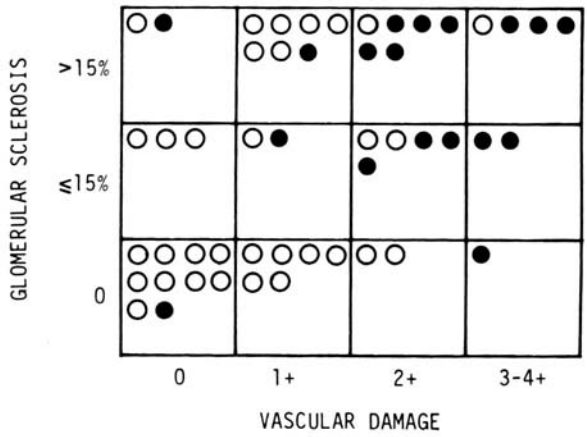

Figure 1. Relationship between vascular damage and glomerular sclerosis in normotensive (o) and hypertensive (•) patients with IgA GN

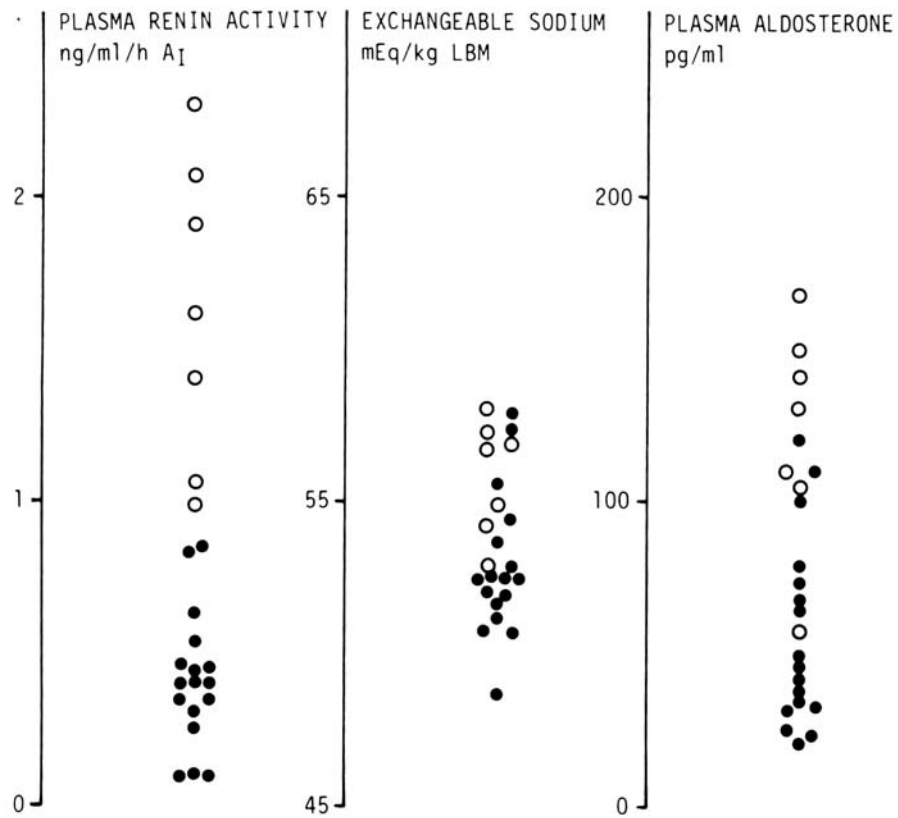

Figure 2. Individual values of PRA, plasma aldosterone and exchangeable sodium in normotensive patients with IgA GN classified as having normal (•) or high (o) PRA levels

No significant differences were found in the mean values of PRA, PA, ES and daily sodium excretion between normotensive (24 cases) and hypertensive (10 cases) patients. PRA correlated significantly with PA ($r = 0.765$, $p < 0.001$) but not with ES ($r = 0.279$, p = NS) in the normotensive group. Seven out of 24 normotensive patients had raised PRA levels. The individual values of PRA, PA and ES of normotensive patients are reported in Figure 2. Taking the normotensive patients with 'high' PRA and 'normal' PRA as two distinct groups, the mean values of PA (123 ± 13.6 vs 56 ± 0.6pg/ml, $p < 0.001$) and ES (55.8 ± 0.75 vs 52.8 ± 0.5mEq/Kg of lean body mass, $p < 0.01$) were significantly higher in the former than in the latter group. However, no differences were found in the mean values of NA, daily sodium excretion, age, mean blood pressure and heart rate. The mean values of PA and ES found in 'normal' PRA patients were equal to the mean values found in our laboratory in healthy normotensive subjects. In Figure 3, we have related the PRA levels to the histological findings: in the seven patients with raised PRA, GS was totally absent, while VD was absent in five patients and minimal in two.

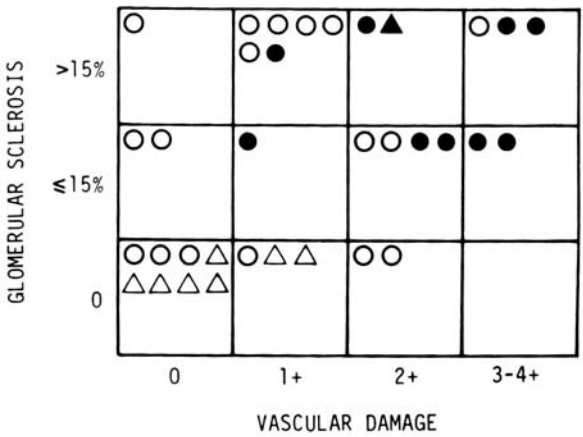

Figure 3. Relationship between vascular damage, glomerular sclerosis, renin and blood pressure in patients with IgA GN.
Normotensive patients with normal (o) or high (△) PRA levels.
Hypertensive patients with normal (o) or high (▲) PRA levels

Discussion

Intrarenal VD, which is frequently observed early in IgA GN both in hypertensive and in normotensive patients, could be considered either a consequence or a cause of hypertension.

Kincaid-Smith has suggested that arteriolar lesions could cause hypertension in glomerulonephritis by causing ischaemia and an increase in renin release [2]. Our results do not support this hypothesis in patients with IgA GN. The presence of VD, independently of its severity, is not accompanied by high PRA values either in normotensive or hypertensive patients. However, high PRA

concentrations are present in normotensive patients without VD and GS. This seems to confirm the observation made in essential hypertension that VD may lead to a reduction rather than to an increase in renin release [8]. In 'high renin' patients, metabolic situations which might explain the high PRA levels, are not apparently present. These findings suggest that the immunological damage of the mesangium may be responsible for the hypersecretion of renin. The mesangium is strategically located to modify blood flow and pressure within the glomerular capillary loops. Consequently, it is possible that a morphologic and/or functional lesion of the mesangium may influence the secretory function of the juxtaglomerular apparatus, as supported by experimental studies [9–11].

The hypersecretion of renin may explain a cause and effect relationship between renin and hypertension in IgA GN. It has been demonstrated in animals that the chronic infusion of small doses of angiotensin II, which, by itself has no pressor effect, can cause sustained hypertension. This is the result of a sodium retention mechanism linked to angiotensin II itself and/or to aldosterone [12].

The normal or low PRA values found in our hypertensive patients may be due to the high blood pressure physiologically reducing renin release.

All our hypertensive patients except one had severe VD, which confirms the role of hypertension in the causation and worsening of VD [1].

In these patients, moreover, there is a high incidence of GS and it is thus possible to speculate that VD may be a cause of GS. However, VD and GS, separately or together, are also present in the absence of hypertension, suggesting that there are other mechanisms responsible for VD and GS.

In conclusion, the inflammatory lesion of the mesangium seems to stimulate the release of renin in some normotensive patients with IgA GN. Those patients whose PRA is higher are probably most at risk for hypertension.

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