CONCISE REPORT

Renal artery stenosis in the antiphospholipid (Hughes) syndrome and hypertension

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Background: Hypertension is common in the antiphospholipid (Hughes) syndrome (APS) and its cause is poorly understood. Anecdotal evidence suggests that renal artery stenosis (RAS) may be a relevant and treatable cause of hypertension.

Objective: To investigate the prevalence of RAS in patients with APS and hypertension.

Patients and methods: Three groups of patients were evaluated: (1) 77 patients with positive antiphospholipid antibodies (aPL) (60 secondary APS, 11 primary APS, and 6 with aPL only) and uncontrolled hypertension who were receiving two or more antihypertensive drugs; (2) 91 patients (≤ 50 years) attending hypertension clinics; (3) 92 normotensive healthy, potential renal transplant donors. Magnetic resonance renal angiography was used to image the renal arteries in all three groups.

Results: Group 1: 20/77 (26%) patients had evidence of RAS (16 unilateral and 4 bilateral). Sixteen patients (80%) had smooth well defined stenoses in the proximal third of the renal artery. Three further patients had irregular arteries without distinct stenosis. Group 2: 7/91 (8%) hypertensive patients had RAS ($\chi^2=10.3$, $p<0.001$ v group 1). Group 3: 3/92 (3%) healthy donors had RAS ($\chi^2=18.2$, $p<0.0001$ v group 1).

Conclusion: A significantly increased prevalence of RAS (26%) was found in patients with APS and hypertension, compared with relatively young (≤ 50 years) hypertensive controls and healthy potential donors.

In 1934 Goldblatt and Lynch demonstrated that hypertension could be produced in dogs by constricting both renal arteries or removal of one kidney.¹ In 1938 Houssay and Taqueni provided evidence for the role of renin in the development of hypertension in the ischaemic kidney.² Since then extensive clinical experience has linked renal artery stenosis (RAS) or occlusion with hypertension. Recently a "new" and possibly major cause of renovascular hypertension—the antiphospholipid syndrome (APS, Hughes syndrome), has been added to the list.^{3–6} Hypertension was noted in the original descriptions of APS, and was thought to be secondary to renovascular changes.³ We considered that renal artery occlusion, as in other arteries, might be a feature of APS.³ In 2000 we published an account of a small series of patients with RAS in patients with APS associated with hypertension.⁶ We considered it important, therefore, to establish the prevalence of RAS in a group of patients with APS with uncontrolled hypertension. Ethical approval was obtained for this preliminary study from the St Thomas' Hospital ethics committee.

PATIENTS AND METHODS

We evaluated three groups:

Group 1: 77 patients with positive antiphospholipid antibodies (aPL) (60 with systemic lupus erythematosus (SLE) and APS,

11 with primary APS, and 6 with aPL only) and uncontrolled hypertension. All patients had attended the St Thomas' Hospital Lupus Unit over the previous five years. Patients with SLE were classified by the American College of Rheumatology classification criteria for SLE.⁷ Patients with APS had a history of thrombosis or pregnancy morbidity, or both, in addition to positive aPL on two separate occasions at least six weeks apart, as defined by the preliminary classification criteria established in Sapporo.⁸ Six patients had only positive aPL antibodies.

Group 2: 91 hypertensive patients attended the hypertension and renal clinics in St Thomas' and Guy's Hospital and were investigated for their uncontrolled hypertension.

Group 3: 92 healthy, normotensive, aPL antibody negative patients, who were assessed before considering donation of a kidney for transplantation.

Patients in group 1 were assessed prospectively and groups 2 and 3 were assessed in the previous three years.

Blood pressure was measured at every clinic visit (three months) in groups 1 and 2. All patients with APS had had repeated blood pressure measurements $>150/100$ mm Hg despite receiving two or more antihypertensive agents. Magnetic resonance imaging angiography (MRA) was used non-invasively to image the renal arteries in the St Thomas' Hospital radiology department. A bolus of contrast medium gadolinium 0.3 ml/kg body weight was injected into the antecubital vein. The image acquisition was performed after visualisation of the aorta and its renal branches using the bolus track. T₁ and T₂ weighted images were processed with maximum intensity projection construction by an experienced radiologist at a workstation. MRA (73 patients) was used to study the renal arteries, two patients had contrast computed tomography (CT) angiography, and two underwent intravenous contrast angiography, as MRA was not possible. In groups 2 and 3, all patients had MRA of the renal arteries using the same protocol.

Baseline clinical parameters

Group 1 comprised 65 women and 12 men with a median age of 45 years (range 19–72). The racial distribution included 61 white, 9 black, and 7 patients of Asian origin. The median duration of disease was 16 years (range 4–23). The median creatinine concentration was 184 $\mu\text{mol/l}$. Eleven patients were diabetic and 10 hyperlipidaemic, for which they were receiving lipid lowering agents. The mean systolic blood pressure of all the patients was 160 mm Hg and diastolic 100 mm Hg. Three patients were overweight (body mass index (BMI) >28) and 11 were chronic smokers (table 1). These results refer to the whole of group 1 not just the patients with RAS.

Abbreviations: aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; BMI, body mass index; CT, computed tomography; INR, international normalised ratio; MRA, magnetic resonance imaging angiography; ox-LDL, oxidised low density lipoprotein; RAS, renal artery stenosis; SLE, systemic lupus erythematosus

Table 1 Baseline parameters of patients with APS and hypertension

Patients (n=77)	Patients with no RAS (n=57)	Patients with RAS (n=20)
Primary APS	9	4
Secondary APS	48	16
Median age (years)	45	43
Mean systolic BP (mm Hg)	160	155
Mean diastolic BP (mm Hg)	100	104
Median creatinine ($\mu\text{mol/l}$)	184	185
Diabetes	11	2
Smoking	10	1
Steroids (prednisolone)	26	10
Hyperlipidaemia	10	2
Obesity/overweight	2	1
Nephritic/nephrotic syndrome	11	2
Past thrombotic events (arterial/venous)	55	18
Pregnancy related morbidity	41	4

APS, antiphospholipid syndrome; RAS, renal artery stenosis.

All except 12 patients had had other arterial/venous thrombotic episodes such as cerebrovascular accident, deep venous thrombosis, pulmonary embolism, ischaemic heart disease, and gangrene. Forty two patients had pregnancy related complications. Six patients were positive for aPL only, without any vascular occlusions or pregnancy related morbidity.

In group 2, 91 hypertensive (≤ 50 years) patients were investigated for their uncontrolled hypertension. Their mean age was 42 years (18–50) and 46 were female. Group 3 consisted of 92 healthy subjects, who were investigated as prospective kidney donors. Their mean age was 52 years (22–59).

Statistical analysis

Categorical data were assessed non-parametrically with the χ^2 test with Yates's correction for small numbers where appropriate.

RESULTS

Imaging of renal arteries

Examination of the renal arteries in group 1 (77 patients) showed RAS in 20 patients (26%). In 16 the lesions were unilateral, while four had bilateral RAS. Sixteen patients had smooth well delineated stenoses situated in the proximal one third of the artery from the ostium (figs 1 and 2). In these 16 patients, the aorta above and below the renal arteries was uniformly smooth and regular. The remaining four had irregular, tortuous renal arteries and aorta, suggesting atherosclerotic lesions. Three further patients had irregular renal arteries, without evidence of distinct stenosis. Fifteen of the 20 patients had secondary APS and three had primary APS. Two patients with RAS were aPL positive only. In group 2 of young hypertensive patients, 7/91 (8%) patients had RAS and in five the appearance was suggestive of fibromuscular dysplasia. In group 3, only 3/92 (3%) subjects had RAS. The prevalence of RAS was significantly higher in group 1 than in both control groups ($\chi^2=10.3$, $p=0.001$ v group 2 and $\chi^2=18.2$, $p<0.0001$ v group 3).

Patients with APS with RAS

Renal parameters

In the patients with APS, the median creatinine level was 185 $\mu\text{mol/l}$ (range 64–350). Two patients had had significant proteinuria (>3.0 g/day) and microangiopathic lesions on renal biopsy. None of the patients had fragmented red blood cells or granular casts on urine analysis.

Other parameters

The mean systolic and diastolic blood pressure of these patients with RAS was 155 mm Hg and 104 mm Hg,

Figure 1 Magnetic resonance angiography showing renal artery stenosis in a patient with APS and hypertension.

Figure 2 RAS confirmed on arteriography. The lesion is a long smooth stenosis with no evidence of atheroma.

respectively. Two were diabetic and two had hypercholesterolaemia. Their median age was 43 years (19–62). One patient had had dissection of the descending aorta. One of these patients was obese and all were Caucasian in origin. Eighteen of these patients had had venous or arterial thrombotic events. Four patients had pregnancy related morbidity.

Therapy

All but two patients with RAS were treated with anticoagulants (recommended international normalised ratio (INR) 3.0–4.0).

The indication for anticoagulation in 14 patients was recurrent arterial/or venous thrombosis. Four patients were anticoagulated as it was thought that RAS as a potential thrombotic event might compromise renal function.

Progress of patients

MRA/CT contrast angiography was repeated in five patients for suspected re-stenosis (renal bruit 3, impaired renal function 3, uncontrolled blood pressure 2). All five had previously undergone angioplasty of stenosed renal arteries and stents were inserted in three. All these patients were anticoagulated after angioplasty.

On re-imaging two of the five showed evidence of renal arterial re-stenosis. Interestingly, one patient who was not anticoagulated and the other, who was inadequately anticoagulated (mean INR <2.3), were the two patients who

re-stenosed. The remaining three patients whose INR was maintained at >3.0 showed no evidence of re-stenosis. All other patients with RAS and a mean INR maintained at >3.0 showed good control of blood pressure and stable renal parameters, suggesting that adequate anticoagulation may be important in maintaining the patency of the renal arteries.

DISCUSSION

The most common primary renal diseases of the renal arteries are atherosclerotic RAS and fibromuscular dysplasia. These lesions are associated with two common syndromes—namely, hypertension and ischaemic nephropathy. Fibromuscular dysplasia accounts for 10% of these stenoses, the rest being atherosclerotic. The prevalence of RAS in atherosclerotic patients increases with age, particularly in patients with diabetes, peripheral arterial occlusive disease, atherosclerosis, and coronary artery disease.⁹ The existing data on the prevalence of renovascular hypertension are based on necropsy findings and angiography carried out owing to renovascular hypertension. Renovascular hypertension accounts for about 5% of the American hypertensive population.² Several studies have shown a correlation between increasing age and the presence of renal artery atherosclerosis.^{2–10} Bacha *et al* described an increased prevalence of renovascular disease (20%) in patients with diabetes and hypertension.^{11–12} The mean age of these patients was >61 years.¹¹ Similarly Jean *et al* found a high prevalence of RAS in elderly patients (mean age >63 years) with coronary heart disease.¹³ RAS was also an independent feature in patients with peripheral vascular disease, and its prevalence increased with the severity of the peripheral vascular disease.¹⁴ The mean age of these patients was 73 years.

We have demonstrated a significantly higher prevalence of RAS (26%) in patients with APS who have difficult to control hypertension than in a hypertensive group and otherwise healthy potential renal donors. Ideally, a group of patients with SLE without APS should be compared with the patients with SLE and APS. However, ethical and economic reasons made this difficult. Nevertheless, we managed to compare our results with relatively young hypertensive (≤ 50 years) patients without APS and another control group of normotensive, healthy potential kidney donors.

This study suggests that RAS may be an important cause of hypertension in APS. In 1991 we reported a single patient with hypertension, RAS, and primary APS,³ and in 2000 followed with a series of five patients with APS and hypertension who had RAS.⁶ This study considerably extends and confirms these findings.

The type of stenotic lesions observed in 16 patients with APS is rather unusual. Most were in the proximal segment of the renal arteries and they are smooth and well delineated (figs 1 and 2). These lesions appear to be quite different from those seen in the stenoses of atherosclerosis and fibromuscular dysplasia and potentially constitute a lesion that is unique to this syndrome. Our findings extend to patients with both primary and secondary APS. Indeed, two patients with RAS and uncontrolled blood pressure only had aPL without previous thrombosis and morbidity. This has diagnostic and therapeutic implications. Thus when any aPL positive patient develops hypertension, the doctor should look beyond the traditional risk factors such as corticosteroid treatment and underlying lupus nephritis and consider investigation for renovascular disease.

The high prevalence of RAS in our patients with APS suggests that there might be a pathophysiological relationship. APS is by definition a prothrombotic state, and both arterial and venous thromboses are typical features. Thrombosis in the renal arteries and veins has been reported.^{15–16} Beyond this propensity to thrombosis there is also mounting evidence that patients with APS may develop accelerated

atherosclerosis,¹⁷ and that aPL are the biggest single risk factor.¹⁸ At a molecular level, anticardiolipin antibodies (aCL) have been shown to have atherogenic properties. For example, aCL can cross react with oxidised low density lipoprotein (ox-LDL), and may enhance the in vitro uptake of ox-LDL by monocytes.^{19–20} Ox-LDL is considered to be a major antigen in the development of the atherosclerotic plaque, and its enhanced uptake into monocytes/macrophages may play a part in the progression from fatty streak to plaque. There is also a possibility that a third factor, “endothelin” has a role in vasoconstriction in these patients. Atsumi *et al* described increased endothelin levels in patients with APS and arterial occlusions.²¹ Endothelial cell activation, which may occur in early atherosclerosis, may be induced in vitro by aCL.¹⁸

Intra-arterial radiocontrast angiography is the traditional method for assessing renovascular disease. However, non-invasive assessment is now reliable and safe. Gadolinium enhanced MRA has been shown to be a sensitive (84%) and specific (91%) technique producing excellent images.⁹ Further, gadolinium is non-nephrotoxic and can be used in chronic renal failure—for example, secondary to lupus nephritis. There are, of course, restrictions to MRA—for example, in the presence of marked obesity, pacemaker implantation, intracranial metallic clips, claustrophobia, etc. In addition, in a few cases that we have observed, MRA suggested suspicious lesions, but angiography was required for a definitive diagnosis. In particular, distal segments and small accessory arteries are less reliably visualised with MRA.²² MRA has been shown to overestimate the prevalence of stenotic lesions by 15%.²³ However, the use of two control groups using the same protocol minimises this effect in our study.

Our findings also have therapeutic implications. The finding of RAS either by MRA or angiography necessitates a clinical decision about treatment. Our preliminary data, especially in the patients who developed re-stenosis of their renal arteries, suggest that anticoagulation may be a potential treatment. Furthermore, Remondino *et al* reported that anticoagulation with acenocumarol was successful in recanalising bilateral RAS in a patient with secondary APS.²⁴ Thus anticoagulation should be carefully considered to stabilise or improve the stenosis, to prevent re-stenosis after angioplasty, and as prophylaxis against thrombosis elsewhere.

Local treatment of the stenosis may involve percutaneous transluminal balloon angioplasty with or without stenting or surgery.⁹ Aizawa *et al* reported a patient with APS associated RAS treated successfully with angioplasty.²⁵ However, factors needing to be considered include (a) the nature of the stenosis—long and irregularly stenosed arteries suggestive of atherosclerosis are less amenable to angioplasty; (b) the patient's underlying renal function—patients who have chronic renal impairment are at risk of further deterioration of their renal function if they develop radiocontrast nephropathy; (c) the severity of hypertension—if the blood pressure is well controlled, albeit with two agents, then an invasive procedure may not be justified.

The alternative to angioplasty is, of course, surgical intervention, which is reserved for severe lesions not amenable to angioplasty. Anticoagulation is still essential even if local treatment is undertaken in order to prevent re-stenosis and extrarenal thrombosis. In this series we report the successful combination of renal artery angioplasty and anticoagulation in three patients.

Other risk factors for atherosclerosis are important, and clearly the hypertension resulting from RAS may itself exacerbate the process. RAS is common in patients with diabetes, coronary artery disease, peripheral vascular disease, and atherosclerosis.^{10–14} Its prevalence increases with age (mean age >60 years)^{2–10} and duration of diabetes.¹² Our patients were much younger than these previously reported series with a median age of 43 years (19–62). Only two of the

20 patients had relatively recent onset diabetes (4 and 6 years). Only one was overweight (BMI >28) and two had hyperlipidaemia (table 1). Ten patients (all secondary APS) were receiving long term steroids and two (primary APS) had nephrotic syndrome, which might have been secondary to microthrombi in the glomerular capillaries. Clinically there was no evidence of peripheral vascular occlusion in any patient. It is unlikely, therefore, that traditional atheromatous risk factors, other than corticosteroids, have a major role in the development of RAS in these patients. Our findings suggest that a prothrombotic tendency probably has a major role in the development of RAS in patients with APS. The role of accelerated atheroma needs further evaluation.

Although we have clearly defined renal arterial disease as occurring in patients with APS, it is important to note that renal microvascular disease is also a recognised feature of APS.²⁶ The pathological hallmark in the kidney is thrombotic microangiopathy. Renal microvascular disease in APS can present in a variety of ways, including haematuria, proteinuria, renal impairment, or hypertension. In fact, the most common clinical correlate of renal microvascular disease is hypertension as reported in 15/16 patients in the series of Nochy *et al.*²⁷ Thus, although we would suggest that the finding of hypertension in a patient with APS should certainly lead to an investigation of the renal arteries, there may also be a case for considering renal microvascular disease, particularly in the presence of other signs of intrinsic renal disease.

In summary, we report a significantly higher prevalence of RAS in patients with APS and hypertension compared with two control groups. These lesions appear to be quite different from those seen in atherosclerotic RAS or fibromuscular dysplasia and may be unique to this syndrome. Possibly, APS will prove to be an important cause of RAS in the younger age groups.

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