A CASE OF RENOVASCULAR HYPERTENSION WITH HIGH URINARY NORADRENALINE EXCRETION

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TOSHIAKI SHIRATSUCHI, MICHIKOBU HATANO

A case report of a 32-year-old male with renovascular hypertension, suspected to be pheochromocytoma as a result of a tentative diagnosis, is given. The suspicion was based on the observation of high levels of urinary noradrenaline on several occasions with the sign of hyperreninemia. Reduction of the urinary noradrenaline levels by the administration of angiotensin converting enzyme inhibitor (SQ-14225) suggested that the high urinary noradrenaline probably resulted from hyperreninemia which reflected high plasma levels of angiotensin II.

Radioisotope renography and intravenous urography strongly suggested a reduction of the right renal blood flow, and the final diagnosis of renovascular hypertension was obtained on the basis of renal arteriography. On the other hand, the possibility of a catecholamine releasing tumor was carefully excluded by angiography before undertaking surgical treatment.

The affected kidney was transplanted autogeneously into the abdominal cavity. The successful operation led to a decrease in plasma renin activity, blood pressure and urinary noradrenaline excretion.

In the present case, we were thus unable to define at first whether the primary genesis of hypertension was related to the hyperactivity of the renin-angiotensin system caused by renovascular stenosis or a noradrenaline releasing tumor.

THE concept of angiotensin-catecholamine interaction has received partial acceptance in the pathogenesis of high blood pressure. Two main ways of investigating this interaction have been adopted. One is concerned with the effect of the renin-angiotensin system on the sympathetic nervous system, and the other is concerned with the effect of the sympathetic nervous system on the renin-angiotensin system. Green suggested that overactivity of the sympathetic nervous system or increased circulating catecholamine could result in a release of constricting substances from the kidney. Noradrenaline has been identified as an important substance among several catecholamines to potentiate the renin-angiotensin system. Among clinical examples reported hitherto there are cases of neurogenic hypertension with increased secretion of noradrenaline and adrenaline from chromaffin tumors, namely,
TABLE I  THE 24h EXCRETION OF URINARY CATECHOLAMINES FOR 3 CONSECUTIVE DAYS UNDER CONDITIONS OF NO TREATMENT, CEI ADMINISTRATION, AND AFTER THE OPERATION.

<table>
<thead>
<tr>
<th></th>
<th>No treatment</th>
<th>CEI</th>
<th>Post-operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>9.8</td>
<td>15.3</td>
<td>13.0</td>
</tr>
<tr>
<td>NA</td>
<td>217.6</td>
<td>691.9</td>
<td>87.9</td>
</tr>
</tbody>
</table>

AD: adrenaline (μg/day), NA: noradrenaline (μg/day)

pheochromocytoma. Renin release was enhanced in this disease by the hypersecretion of catecholamine, but not in all cases. DeQuattro et al indicated that the increased renin might be a biochemical marker of sympathetic nervous hyperactivity in high renin hypertensive patients without renal dysfunction.

On the other hand, clinical cases of angiotensin-enhanced catecholamine have not yet been reported, although experimental examples have been described. It is indicated that hyperreninemia caused by experimental renovascular stenosis resulted in an increase in plasma noradrenaline. In the present clinical case with renovascular hypertension, angiotensin-enhanced noradrenaline secretion was detected in which converting enzyme inhibitor (CEI) (SQ-14225) administration and autotransplantation of the affected kidney normalized the urinary noradrenaline secretion and blood pressure.

CASE REPORT

A 32-year-old male was referred to Nihon University Hospital from another hospital on May 14, 1979, for complete medical examination regarding hypertension accompanied by a persistent headache and general fatigue. The onset of the headache and general fatigue had occurred 3 months previously, and repeated measurements before admission showed a blood pressure of 230/140 mmHg in the arm.

The patient's history revealed a slight hypertension at the ages of 15 and 17 years. His father had suffered from diabetes and hypertension, but no other remarkable findings were noted in the family history. The grand parents enjoyed an uneventful long life and died.

Physical examination on admission revealed nothing to suggest an abnormal status. The body weight was 65 kg and the height, 173 cm. The blood pressure was 184/110 mmHg in the arm with the patient supine. The pulse rate was 72/min with a regular rhythm. The heart sound were clear and the rhythm was regular without audible murmurs. The abdomen was flat and soft, and revealed no abnormal mass or vascular murmur. Funduscopy indicated Stage I hypertensive retinopathy (Keith-Wagener classification). Routine determinations of the blood count were within normal limits. The results of other laboratory tests were: Sodium, 140 mEq/litre; potassium, 3.9 mEq/litre; chloride, 106 mEq/litre; and total cholesterol, 200.4 mg/100 ml. The creatinine clearance was 81.1 ml/min/1.7 m² body surface area. The plasma renin activity (PRA) before and after 2 hours ambulation with intravenous injection of furosemide (0.7 mg/kg) were 7.7 and 29.4 ng/ml/h, respectively. Results for urinalysis, protein and sugar were negative, and the 24 hours excretion of vanillylmandelic acid, urinary 17-hydroxycorticosteroids, and 17-ketosteroids were within normal limits. The 24 hours catecholamine excretion values for 3 consecutive days are shown in Table I, and with blood pressure in Fig.1, including values for conditions of no treatment, CEI administration, and after the operation. Circadian rhythms in the PRA and blood pressure under these three conditions are indicated in Table II.

Chest X-ray films were within normal limits and an electrocardiogram indicated slight myocardial damage. Intravenous pyelography revealed a mild prolongation of excretion time in the right kidney as compared to the left kidney, while the calyces were defined and the ureters were within normal. Radioisotope renography demonstrated a reduction of renal blood flow in the right kidney compared to the left one. Selective renal arteriography with injection into the right renal artery indicated a stenotic lesion (Fig. 2A). The left renal artery was normal. Venous blood samples were collected from the right and left renal veins, and the inferior and superior venae cavae for determination of the PRA and

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catecholamines when the above angiographic study was performed. The results are given in Table III.

The high blood pressure did not respond to intravenous bolus injection of regitine (5 mg), angiotensin II infusion (8 ng/kg/min), and angiotensin II analogue (Sar-1-Ala-8-Angiotensin II) infusion (600 ng/kg/min). Figure 1 illustrates the changes in blood pressure and catecholamines for the conditions of no treatment, CEI (SQ-14225, 100 mg/day) administration, and after the operation.

After completion of the above studies, aortic angiography was again carried out to exclude the existence of pheochromocytoma which can sometimes lead to dangerous complications in the operation period. After excluding the possibility of pheochromocytoma, the right kidney was autotransplanted to the right lower intraperitoneal cavity. A postoperative arteriogram is given in Fig. 2B. The PRA, determined on a sample collected from the transplanted renal vein, was 1.3 ng/ml/h. As shown in Tables I and II, the blood pressure, PRA and 24 hours excretion of urinary noradrenaline decreased post-operatively. The PRA values before and after 2 hours ambulation with intravenous injection of furosemide (0.7 ng/kg) were 1.7 and 8.2 ng/ml/h, respectively.

PRA was measured by radioimmunoassay.

**Fig. 1.** Changes in blood pressure (BP) and urinary noradrenaline excretion (NA) during the period of admission, including those under conditions of no treatment, CEI administration, and after the operation.

**TABLE II**

<table>
<thead>
<tr>
<th></th>
<th>No treatment</th>
<th>CEI</th>
<th>Post-operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRA</td>
<td>BP (mmHg)</td>
<td>PRA (ng/ml)</td>
</tr>
<tr>
<td>16:00</td>
<td>5.4</td>
<td>164/110</td>
<td>10.8</td>
</tr>
<tr>
<td>24:00</td>
<td>5.8</td>
<td>156/100</td>
<td>16.4</td>
</tr>
<tr>
<td>6:00</td>
<td>5.4</td>
<td>170/120</td>
<td>7.5</td>
</tr>
</tbody>
</table>
following the method of Haber et al. Plasma and urinary catecholamines were measured by the original method of Ueda et al.9

DISCUSSION

Both the renin-angiotensin system and the sympathetic nervous system have been considered as principal factors in the maintenance of blood pressure. The effects of angiotensin on the sympathetic nervous system to induce high blood pressure have been demonstrated in numerous experimental studies.10-14 Regoli et al.15 sum-
TABLE III  PRA (ng/ml/h) AND PLASMA LEVELS OF CATECHOLAMINES IN SAMPLES COLLECTED FROM THE RENAL VEINS, AND INFERIOR AND SUPERIOR VENAEC AVAE.

<table>
<thead>
<tr>
<th>Site</th>
<th>PRA</th>
<th>AD</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right renal vein</td>
<td>15.4</td>
<td>0.07</td>
<td>0.41</td>
</tr>
<tr>
<td>Left renal vein</td>
<td>7.8</td>
<td>0.07</td>
<td>0.26</td>
</tr>
<tr>
<td>Superior vena cava</td>
<td>8.6</td>
<td>0.2</td>
<td>0.28</td>
</tr>
<tr>
<td>Inferior vena cava</td>
<td>7.4</td>
<td>0.08</td>
<td>0.25</td>
</tr>
</tbody>
</table>

AD: adrenaline (ng/ml), NA: noradrenaline (ng/ml)

summarized that the most consistent data were related to the action of angiotensin on four components of the sympathetic nervous system: the central nervous system, adrenal medulla, sympathetic ganglia and sympathetic nerve terminals. Roth and Hughes suggested the possibility that angiotensin II may have a potent effect in accelerating noradrenaline biosynthesis in sympathetically innervated tissues. Furthermore, some investigators demonstrated that increased endogenous angiotensin following experimental renal arterial stenosis resulted in an enhancement of endogenous noradrenaline levels. In these studies, several courses were also considered to potentiate the release of noradrenaline.

On the other hand, potentiation of renin release by catecholamines has been reported by several investigators. Green suggested that a vasoconstricting substance from the kidney was released under conditions of overactivity of the sympathetic vasoconstrictor nerves or the circulating constrictor substances. Later, other investigators demonstrated that intravenous or intrarenal arterial infusion of noradrenaline induced a small increase in PRA in dogs. It may thus be suggested that noradrenaline is a more potential activator of renin release than adrenaline among exogenous sympathetic substances.

Clinical overproduction of catecholamines in pheochromocytoma does not always increase renin release. Gordon et al. observed a patient with pheochromocytoma producing sufficient catecholamine but having normal PRA values. However, Meyer et al. demonstrated elevated renin levels in this disease. Interestingly, Macbashi et al. found a progressive rise in PRA with a proportional increase in urinary excretion of noradrenaline in one case, although they found that PRA remained normal in other cases, in whom adrenaline excretion was dominant as compared with noradrenaline excretion.

Although clinical cases with pheochromocytoma producing sufficient catecholamine to cause hyperreninemia have been described, cases with renovascular hypertension stimulating overproduction of noradrenaline as in the previous experimental studies have not been reported. It is thought that if changes in catecholamine levels in renovascular hypertension before and after surgical treatment were determined, a slight reduction in the catecholamine levels might be observed after the operation.

In the present case, the elevated urinary excretion of noradrenaline could apparently be ascribed to a rise in angiotensin II resulting from renovascular stenosis, so that reduction of blood pressure and urinary noradrenaline were found under CEI administration. In addition, parallel decreases in blood pressure and urinary noradrenaline were observed after surgical treatment. In spite of the demonstration of a clinical case in which overactivity of the renin-angiotensin system influenced the sympathetic nervous system, further studies on the mechanisms are clearly necessary.

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REFERENCES


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