Partial Adrenalectomy in Patients with Primary Aldosteronism

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SUMMARY

Patients with primary aldosteronism due to unilateral and solitary adrenocortical aldosterone-producing adenoma (APA) underwent unilateral adrenalectomy or enucleation of adenoma (partial adrenalectomy). Five years after respective operations, the possibility of tumor recurrence from remnant adrenal tissues, hypothalamic-pituitary-adrenal axis function, and urinary concentrating ability were investigated to determine which method is preferable.

Hypertension, hypokalemia and impaired urinary concentrating ability were improved to the same extent in the two groups. Mineralo-and glucocorticoid functions were well preserved in partially adrenalectomized patients. Remarkably low level of aldosterone production, but not cortisol production was noted in APA-adjacent tissues. Abnormal mineralocorticoid receptor-binding sites were normalized by each operation.

These findings support the notion that partial adrenalectomy appears to be preferable in patients with primary aldosteronism. The likelihood of tumor recurrence from remnant ipsilateral adrenal gland appears to be lower in this operation method.

Key words: partial adrenalectomy, aldosteronism, mineralocorticoid function

I. Introduction

Primary aldosteronism is a volume-dependent form of hypertension and exhibits metabolic alkalosis, hypokalemia and slight polyuria[1,2]. Earlier investigators reported that more than 90% of APAs were unilateral and solitary with the majority being less than 2 cm in diameter[3]. APAs are usually round to ovoid and sharply demarcated from adjacent parenchyma. Given the anatomical configuration and peculiar macroscopic appearance of this neoplasm, we have performed partial adrenalectomy, and this operative technique appeared in some respects to be more desirable than unilateral adrenalectomy[4]. In this paper, we endeavor to clarify whether remnant adrenal parenchyma contributes to maintain the normal hypothalamic-pituitary-adrenal axis function, and whether the urine concentrating defect in this disorder can really be improved by this surgical method, since these important variables were

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not examined in our previous study[4].

II. Patients and Methods

Forty-eight patients with primary aldosteronism due to unilateral adrenal adenoma (APA) (26 adrenalectomized group, 41±3 years, 11 men and 15 women; 22 partial adrenalectomized group, 44±4 years, 8 men and 14 women), 12 patients with essential hypertension (41±4 years, 8 men and 4 women) and 11 normal subjects (46±5 years, 7 men and 4 women) were studied. Specimens of normal adrenal cortexes removed from 11 patients with renal cell carcinoma were also included in this study. The diagnosis of primary aldosteronism was made by high levels of plasma aldosterone concentration (PAC) and urinary aldosterone excretion, suppressed plasma renin activity (PRA), and normal levels of urinary excretion of 17-hydroxycorticosteroids (17-OHCS) and urinary 17-ketosteroids (17-KS). Hypertension, hypokalemia and peculiar symptoms of this disease were noted. Computed tomographic examination, adrenocortical scintigraphy and occasional measurements of plasma aldosterone and plasma cortisol in adrenal venous tributaries were performed. Each patient received operation and the final diagnosis was confirmed. Methods of adrenalectomy and partial adrenalectomy were described previously[4]. Patients were randomized for either operative method and followed for 5 years. Blood pressure was determined repeatedly. None of these patients had hepatic dysfunction and none had been receiving drugs prior to the study. Blood collections were done at 7 to 8 a.m. from patients who had been kept in a supine position for 30 minutes before blood sample withdrawal. Angiotensin II was infused at a rate of 0.5, 1 or 2 ng/kg per minute during 3 consecutive 40-minute periods via the slightly modified method of Wisgerhof et al[5]. Some patients were given 0.25 mg adrenocorticotropic hormone (ACTH) intravenously and blood was withdrawn at 30-minute intervals from 0 to 2 hours. A 100 ug portion of corticotropin-releasing hormone (CRH) was intravenously injected in each patient, and plasma ACTH and plasma cortisol concentrations were determined every 30 minutes for 2 hours. The angiotensin II infusion, rapid ACTH and CRH tests were performed in subjects given diets containing 150 mEq sodium and 100 mEq potassium daily.

Urine concentrating ability was determined in some patients by a routine method[6-8]. Creatinine clearance (Cr), sodium clearance (CNa) and osmolar clearance (Cosm) were measured by conventional formulae [7]. Clearance of free water (CH2O) and the fractional filtrate delivery of sodium reabsorption at the distal tubule were calculated as described previously[6].

Some fragments of APAs, APA-surrounding adrenocortical tissues and normal adrenocortical tissues obtained from patients with renal cell carcinoma were used to determine hormone concentration study. Tissue preparation and hormone analysis were performed by the method by Brown et al with slight modifications [9,10].

III. Results

Figure 1 shows the changes in systolic blood pressure and diastolic blood pressure in patients with primary aldosteronism who underwent unilateral adrenalectomy and partial adrenalectomy. Preoperative systolic and diastolic blood pressures were similar in the two groups. Each adrenal operation gradually improved hypertension, and the blood pressure-lowering effects of the two operations were almost equivalent for 5 years except at 3 months after operation (143±4/85±4 mm Hg in adrenalectomy group versus 156±4/99±4
mm Hg in partial adrenalectomy group).

Figure 2 shows the effects of adrenal operations on serum potassium, urinary sodium-to-potassium ratio, PAC, urinary aldosterone excretion and PRA in patients with APA. The level of serum potassium in the partial adrenalectomy group just before the operation (2.4 ± 0.2 mEq/L) increased gradually after the operation, reaching 4.1 ± 0.4 mEq/L 3 months postoperatively. A similar pattern of increase in serum potassium was also noted in the adrenalectomy group. Urinary sodium-to-potassium ratio in both groups increased by degrees after operation. High levels of preoperative PAC and urinary aldosterone excretion in the adrenalectomy group and partial adrenalectomy group (792 ± 74 pg/mol, 19.9 ± 1.8 ug/day and 801 ± 75 pg/mol, 22 ± 2.0 ug/day, respectively) were reduced one month after the operation and fluctuated slightly thereafter. There were no significant differences between the groups 7 months after operations. The low levels of PRA in the preoperative period in both groups gradually increased after operation, and there were no significant differences in PRA throughout the study.

Figure 3 shows the effect of adrenal surgery on plasma cortisol and plasma ACTH levels. Three months after operation, plasma cortisol level in adrenalectomized group (7.8 ± 0.6 versus 9.8 ± 0.5 ug/dl) and plasma ACTH level in the former group was slightly higher (P < 0.05) than that in the latter group. Except at this time point, these hormone levels were similar in the two groups at each timepoint during the study.

Figure 4 shows the response of the renin-angiotensin-aldosterone system in subjects given a low-sodium diet (15-20 mEq/day) for one week previously. After 2 hours of ambulation, 20

Fig. 1 Effects of unilateral adrenalectomy (AX) and partial adrenalectomy (part.AX) on systolic blood pressure (Syst BP) and diastolic blood pressure (Diast BP) in patients with primary aldosteronism. Each bar represents the standard error of the mean. Significance of differences from other patients in the same postoperative month: *P < 0.05.

Fig. 2 Effects of AX and part AX on serum K (mEq/L), urinary sodium-to-potassium ratio (Na/K), plasma aldosterone concentration (PAC) excretion (ug/day) and plasma renin activity (PRA) (ng/ml/hr) in patients with primary aldosteronism. Each bar represents the standard error of the mean. Asterisk indicates *P < 0.05.

Fig. 3 Effects of AX and part. AX on plasma cortisol (ug/dl) and plasma ACTH (pg/ml) in patients with primary aldosteronism. *P < 0.05.
mg of furosemide was intravenously injected in some subjects. In normal subjects, normal levels of PAC and PRA were remarkably increased \((P < 0.001)\) following this treatment. In preoperative patients with APA, this response was significant \((P < 0.05)\) but not as remarkable as those of PAC \((618 \pm 56 \text{ to } 928 \pm 90 \text{ pmol/L})\) and PRA \((0.11 \pm 0.01\) to \(0.16 \pm 0.02\)). Five years after operation, patients with APA who underwent partial adrenalectomy responded more notably following this test than patients who had undergone adrenalectomy in respect to PAC \((187 \pm 18 \text{ to } 487 \pm 42, P < 0.001\) versus \(179 \pm 18 \text{ to } 295 \pm 30 \text{ pmol/L, } P < 0.05\)) and PRA \((3.9 \pm 0.3\) to \(8.4 \pm 0.5 \text{ ng/ml/hr, } P < 0.001\) versus \(3.9 \pm 0.4\) to \(6.1 \pm 0.4 \text{ ng/ml/hr, } P < 0.01\)).

Table 1 shows the effect of angiotensin II on PAC in normal subjects and patients with APA. Five years after partial adrenalectomy, PAC in this group increased 107\% \((P < 0.001)\) an increment of similar degree to that in normal subjects \((105\% \text{ increase, } P < 0.001)\), while PAC in patients with APA who had undergone adrenalectomy increased only 25\% \((P < 0.05)\) following the same dosage of angiotensin II infusion.

The post operative plasma cortisol response to ACTH administration in patients with APA who had undergone different adrenal operations and normal subjects showed different reactions. Plasma cortisol in patients with APA who had received partial adrenalectomy increased 118\% at 30 minutes and 64\% at 60 minutes following ACTH injection. This response of plasma cortisol was almost identical to that in normal subjects following ACTH treatment. However, the increment ratio of plasma cortisol in patients with APA who had undergone adrenalectomy was the lowest after this evaluation.

Figure 5 shows the post operative plasma

<table>
<thead>
<tr>
<th>Operation</th>
<th>Before Operation</th>
<th>After Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC (p mol/L)</td>
<td>0 min</td>
<td>120 min</td>
</tr>
<tr>
<td>Normal subjects ((n = 11))</td>
<td>190 (\pm) 12</td>
<td>389 (\pm) 29</td>
</tr>
<tr>
<td>APA + AX ((n = 14))</td>
<td>628 (\pm) 51</td>
<td>651 (\pm) 34</td>
</tr>
<tr>
<td>APA + part. AX ((n = 14))</td>
<td>601 (\pm) 42</td>
<td>648 (\pm) 53</td>
</tr>
</tbody>
</table>

APA: Aldosterone-producing adenoma
AX: Unilateral adrenalectomy
Part AX: Partial adrenalectomy

CRH TEST

Fig. 5 Response of plasma ACTH (pg/ml) and plasma cortisol (ug/dl) following 100 ug CRH administration in N and patients with primary aldosteronism who had undergone AX or part.AX. *\(P < 0.05\).
ACTH and plasma cortisol responses following CRH administration in patients with APA and normal subjects. Levels of plasma ACTH similarly increased in patients with APA who had undergone adrenalectomy and patients with APA who had undergone partial adrenalectomy. Plasma cortisol in patients with APA who had undergone partial adrenalectomy increased following CRH administration to the same extent as in normal subjects. However, the minimum plasma cortisol response was noted in adrenalectomized patients at 60 minutes following CRH administration.

Table 2 shows the concentration of aldosterone in normal adrenocortical tissues. APA, APA-adjacent tissue and APA-uninvolved adrenal cortex. Aldosterone concentration was the highest in APA among examined tissues. The aldosterone content of the APA-adjacent tissue was the lowest. Aldosterone concentration in APA-uninvolved adrenal cortex was approximately 46.7% lower \( (P < 0.001) \) than that in normal adrenal cortex.

Table 3 shows the concentration of cortisol in normal tissues. APA, APA-adjacent tissue and APA-uninvolved adrenal cortex were almost identical.

Figure 6 shows results of clearance studies in each group of patients during water diuresis.

Table 2 Concentration of aldosterone in normal adrenocortical tissues, APA, APA-adjacent tissue and APA-uninvolved adrenal cortex

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Concentration of aldosterone (ng/l(^{10^{9}}) cell)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal adrenal cortex ( (n = 11) )</td>
<td>89.1 ± 5.9 ( P &lt; 0.001 )</td>
</tr>
<tr>
<td>APA ( (n = 12) )</td>
<td>302.5 ± 19.5 ( P &lt; 0.001 )</td>
</tr>
<tr>
<td>APA-adjacent tissue ( (n = 12) )</td>
<td>123.8 ± 16 ( P &lt; 0.001 )</td>
</tr>
<tr>
<td>APA-uninvolved adrenal cortex ( (n = 12) )</td>
<td>48.4 ± 4.1 ( P &lt; 0.001 )</td>
</tr>
</tbody>
</table>

Table 3 Concentration of cortisol in normal tissues, APA, APA-adjacent tissue and APA-uninvolved adrenal cortex

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Concentration of aldosterone (ng/l(^{10^{9}}) cell)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Normal adrenal cortex ( (n = 11) )</td>
<td>2457 ± 15 ( P &lt; 0.001 )</td>
</tr>
<tr>
<td>APA ( (n = 12) )</td>
<td>56 ± 7 ( P &lt; 0.001 )</td>
</tr>
<tr>
<td>APA-adjacent tissue ( (n = 12) )</td>
<td>2611 ± 117 ( P &lt; 0.001 )</td>
</tr>
<tr>
<td>APA-uninvolved adrenal cortex ( (n = 12) )</td>
<td>2350 ± 148 ( P &lt; 0.001 )</td>
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Fig. 6 Renal clearance study in normal subjects \( (N) \), patients with essential hypertension \( (EH) \) and patients with primary aldosteronism who had undergone APA+AX or APA+part. AX under water diuresis. \*\( P < 0.05 \), \**\( P < 0.01 \), \***\( P < 0.001 \).

Before treatment, urine volume in patients with APA was reduced after adrenalectomy \( (P < 0.01) \) or partial adrenalectomy \( (P < 0.05) \). The values of urine osmolarity were similar in all groups. Adrenalectomy increased Uosm before treatment \( (103 ± 4 \text{ to } 134 ± 6 \text{ mOsm/kg}) \) significantly \( (P < 0.01) \). Partial adrenalectomy also increased this parameter to the same extent \( (107 ± 5 \text{ to } 141 ± 7 \text{ mOsm/kg}) \). The values of CNa in patients with APA were greater than those in normal subjects and patients with EH. This parameter in patients with APA was decreased \( (P < 0.001) \) following adrenalectomy \( (7.2 ± 0.4 \text{ to } 4.6 ± 0.3 \text{ ml/dl GFR}) \) or partial adrenalectomy \( (7.1 ± 0.4 \text{ to } 4.6 ± 0.3 \text{ ml/dl GFR}) \).
4.3 ± 0.3 ml/dl GFR). The values of Cosm in preoperative patients with APA were greater than those in normal subjects (5.9 ± 0.6 ml/min) and patients with EH (5.8 ± 0.5 ml/min). These values decreased (P<0.01) by adrenalectomy or partial adrenalectomy. The higher values of CH2 in patients with APA than those in normal subjects (8.7 ± 0.7 ml/dl GFR) or patients with EH (8.8 ± 0.9 ml/dl GFR) were decreased by adrenalectomy or partial adrenalectomy. The fraction of delivered sodium in patients with APA was lower than that in normal subjects (19.6 ± 0.8) and patients with EH (17.5 ± 2.0). This parameter in patients with APA was increased after adrenalectomy (P<0.05) or partial adrenalectomy (P<0.001).

In the follow-up period, no recurrence was noted.

IV. Discussion

Gradual improvement of hypertension in patients with APA was confirmed in this study (Fig. 1). Abnormal values of vasoactive substances were similarly improved by either adrenalectomy or partial adrenalectomy (Figs. 2 and 3). Two questions may be raised, concerning the possibility of tumor recurrence from remnant adrenal cortical tissues with APA, and definite advantage of partial adrenalectomy.

Very few data are available on aldosterone content in APA and the in vivo cellular homeostasis of angiotensin, aldosterone or cortisol in adrenal tissues[10]. The present study demonstrated that concentration of aldosterone in APA-adjacent tissues was extremely low (Table 2). APA-uninvolved adrenal cortex also possessed only 13.8% (P <0.001) of the aldosterone content of normal adrenal cortex. Similar findings were also demonstrated by Brown et al[9]. According to previous investigators[11-13], the low level of mineralocorticoid receptors in patients with APA and patients with pseudoaldosteronism was the consequence of high plasma aldosterone concentration. Indeed, high values of PAC in patients with APA were normalized after each type of operation (Fig. 2). We have never experienced recurrent patients in this study. These results suggest that recurrence of tumor from remnant adrenal cortex is less likely. In earlier studies of essential hypertensives, a blunted adrenal response to volume change was attributed to reduced reaction to angiotensin II[12-14]. We did not examine this problem. Further studies are necessary. In patients with APA, angiotensin infusion nearly failed to increase PAC before operation (Table 1). Five years after operation, we stimulated the renin-angiotensin-aldosterone system of the examined groups by 2 hours of ambulation, furosemide injection and a low-sodium diet, and found that this system was well preserved in patients with APA received partial adrenalectomy. In removed specimens, concentrations of cortisol in APA-adjacent tissue, APA-uninvolved adrenal cortex and normal cortex were nearly identical (Table 3). Secretion of ACTH is controlled by the hypothalamic pituitary-adrenal axis. Hypothalamic CRH is the most dominant stimulator of ACTH secretion. It is well known that CRH sensitizes cyclic AMP production and increases POMC gene as well as ACTH secretion[16]. Chronic stimulation by CRH also induces corticotrophic cells hyperplasia[16]. In the present study, infusion of CRH increased plasma ACTH concentration in patients with APA who had undergone adrenalectomy and patients with APA who had received partial adrenalectomy at the same extent (Fig. 5). The same dosage of CRH infusion similarly increased plasma cortisol in all groups except patients with APA who had undergone adrenalectomy after 60 minutes of CRH administration (Fig. 5). The rapid ACTH test evoked reduced responses of plasma cortisol in patients with
APA who had undergone adrenalectomy. These findings indicate that reversed adrenocortical glucocorticoid function is well preserved in patients with APA received partial adrenalectomy.

Another point of interest in this study is the results of clearance study (Fig. 6). Polyuria and polydipsia are occasional complications of prolonged potassium depletion. This study definitely demonstrated that impairment of urinary concentrating ability resulted in high urinary output and low urinary osmolarity. Although polydipsia plays a role in the polyuria associated with hypokalemia high water intake alone is not responsible for urinary concentration, which is probably mediated by an intrarenal mechanism. A high value of CH2O was observed in patients with APA during water diuresis. This finding suggests that an impairment of proximal tubular reabsorption influences the absolute value of CH2O under water diuresis. Subsequently, the ratio of CH2O to distal delivery of sodium was lower in patients with APA than that in normal subjects and patients with EH at all levels of water intake. Low level of CH2O is thought to be a manifestation of defective transport of Henle’s loop, since most free water is generated by the loop of Henle[8]. In this study, the large amount of sodium delivery to the ascending limb of Henle’s loop probably increased the absolute CH2O concomitant with lowering of the fractional CH2O. The present results are almost compatible with those of patients with normokalemic primary aldosteronism by Conteal[8]. Exchange of sodium for potassium is believed to decrease CNa without altering the level of CH2O[7]. In this study, the reason for the elevation or reduction of CNa in patients with APA following adrenal operation during water diuresis is unclear. However, any exchange of sodium for hydrogen, including bicarbonate reabsorption, has been shown to result in a decrease in CNa concomitant with increase in CH2O[7]. The real effect of adrenal surgery on CNa is thus still unclear.

Contrary to our speculation, the two methods of adrenal operation improved urine concentrating ability to the same extent. Adrenal surgery is probably essential for patients APA to improve renal function, though hypertension or hypokalemia can be partially controlled by various medications. Since administration of 3beta-hydrogenase inhibitor alone could not improve the concentrating ability in aldosteronism[6]. Laparoscopic partial adrenalectomy is probably reasonable for the treatment of unilateral APA and is now being performed[17,18].

References


