



Clinical Significance of Associated Nodular Lesions of the Adrenal in Patients with Aldosteronoma

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Thirty-seven patients with primary aldosteronism were treated by unilateral total adrenalectomy during a 7-year period (1981-1987). The 37 patients were classified into 3 groups on the basis of adrenal pathology: unilateral solitary adenoma, 23 cases (group 1); unilateral adenomas, 3 cases (group 2); and adenoma with multiple macro- or microscopic nodules, 11 cases (group 3). The preoperative conditions of the patients (age, duration of hypertension, plasma renin activity, plasma aldosterone concentration, and serum potassium concentration), postoperative sequential changes of hormone levels, and outcome of hypertension were compared among the groups in order to determine whether the differences of adrenal pathology would affect the postoperative course. The preoperative parameters excluding age at surgery did not differ significantly among the 3 groups. The mean age in group 3, however, was slightly higher than in groups 1 and 2 (47.8 versus 42.8 versus 42.7 years).

Postoperative hormonal changes were also similar, particularly in groups 1 and 3, staying within the normal range throughout the follow-up period (mean, 31 months; range, 3-86 months). However, postoperative improvement of hypertension showed marked differences, being significantly retarded in patients with multinodular lesions (group 3), about half of whom remained hypertensive even after 1 year. Nodular lesions other than adenoma(s) were, therefore, thought not to contribute to hormonal excess but to result from intractable hypertension.

Primary aldosteronism is known to be caused by aldosterone-producing tumors, mainly adenoma (APA), or bilateral adrenocortical hyperplasia [1, 2]. Surgical treatment is very effective in cases due to APA, whereas it is not the choice of treatment in cases of underlying hyperplasia [3]. Unilateral total adrenalectomy is the standard procedure for surgical management [4].

The resected adrenal sometimes contains macro- or micronodular lesions in addition to APA [5]. These nodules are reported to be multiple and generally bilateral [6]. Although the histopathological and biological nature of these nodules has been widely studied, their clinical significance in the management of patients with primary aldosteronism has not been fully discussed [7].

In this study, we analyzed 37 patients treated by unilateral total adrenalectomy and attempted to determine whether the

clinical course of patients with primary aldosteronism differs according to whether they have a multinodular adrenal.

Material and Methods

In the period from April, 1981 to March, 1987, a total of 37 patients were diagnosed as having APA and were treated by unilateral total adrenalectomy. Preoperatively, adenoma was demonstrated in 35 patients by computed tomography, and subsequently, hyperfunction of the tumor-bearing adrenal was revealed by adrenal scintigraphy using NP-59 with dexamethasone suppression and/or adrenal venous sampling. In the remaining 2 patients, tumors were not demonstrated, but scintigraphy and venous sampling showed significant unilateral hyperfunction, necessitating adrenalectomy. In all cases, the diagnosis of APA was confirmed at surgery and by pathologic examination.

These 37 patients were classified into 3 groups on the basis of the pathologic features of the resected adrenal. Group 1 comprised 23 patients, each with a solitary adenoma only. Group 2 comprised 3 patients with multiple adenomas in the unilateral adrenal. Group 3 comprised 11 patients with one or more macro- or microscopic nodule in the attached adrenal in addition to a solitary adenoma (Fig. 1).

In group 2, two patients were diagnosed as having multiple aldosterone-producing adenomas (Fig. 2). One patient had a single APA and a nonfunctional adrenocortical adenoma, which was proven measuring hormonal content of the resected tissue (Fig. 3).

The preoperative parameters for the patients in each group included age at surgery, duration of hypertension, serum potassium concentration (serum K), plasma renin activity (PRA), and plasma aldosterone concentration (PAC).

Postoperative sequential changes in the levels of serum K, PRA, and PAC, and outcome of hypertension in each group were reviewed.

These preoperative conditions and postoperative results for the 3 groups were compared in order to determine whether the differences in adrenal pathology would result in different pre- and postoperative clinical courses in patients with primary aldosteronism.

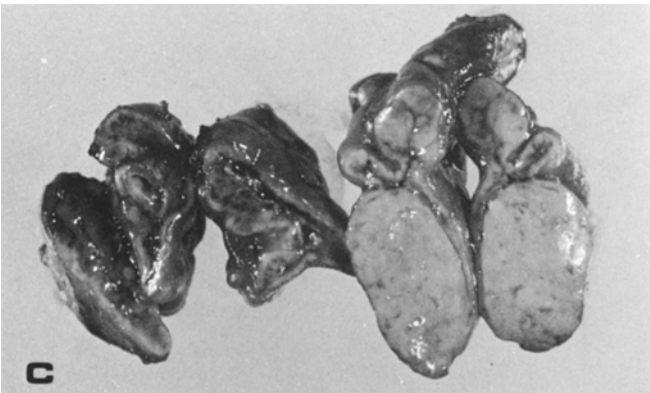
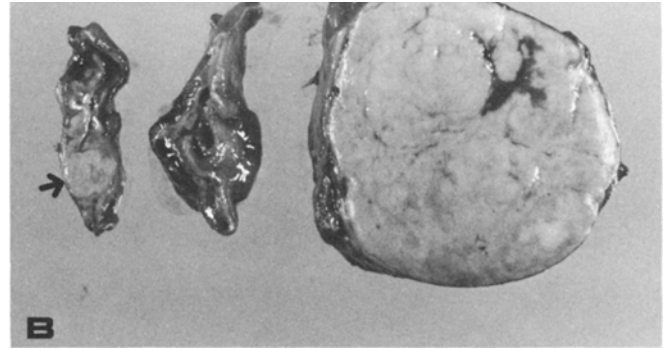
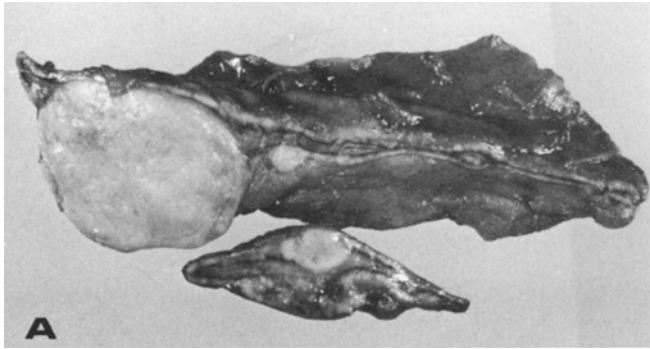


Fig. 1. Cut surfaces of adrenals containing a solitary adenoma and macro- and micronodules. **A.** Macronodules and cortical thickening are moderately prominent. Patient hypertensive 4 years after surgery. **B.** A macronodule (*arrow*) and mildly thickened adrenal cortex. Patient normotensive at 3 months after surgery. **C.** Macronodules and highly thickened adrenal cortex. Patient hypertensive at 5 years after surgery.

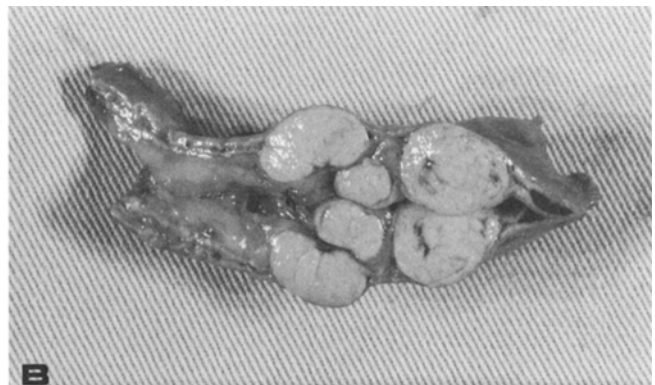
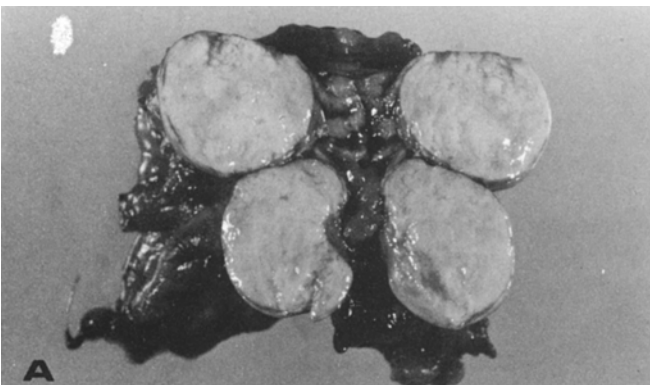


Fig. 2. Cut surfaces of adrenals containing multiple APA. **A.** Two equal-sized APA: Congregated but each clearly circumscribed. **B.** Three APA: Attached adrenal shows no nodular changes.

Results

Preoperative parameters in these 3 groups are summarized in Table 1. The mean age in group 3 was higher than in the other 2 groups, but, the difference was not significant.

Duration of hypertension in group 2 was shorter than in the other groups, although the number of patients in this group is too small for this to be significant.

There were no significant differences in the preoperative values of serum K, PRA, and PAC among the 3 groups.

The serum K recovered unequivocally to the normal range within 1 week after surgery in all patients.

Postoperative sequential changes in PRA and PAC in groups 1 and 3 are demonstrated in Fig. 4. Plasma renin reactivity in

group 3 showed slower recovery from preoperative suppression than that in group 1 in the early postoperative period. At 6 months and thereafter, the levels of PRA were almost identical in both groups.

The level of PAC fell to near the lower end of the normal range immediately after surgery and stayed normal throughout the follow-up term (mean, 31 months; range, 3–86 months) in both groups, and there was no difference between the postoperative level of PAC in group 1 and that in group 3. In group 2, the value of PAC was almost identical to those in the other groups, but PRA fluctuated in comparison with the other 2 groups. As a result, all patients were considered to recover from primary aldosteronism and no patient seemed to show



Fig. 3. Cut surface of APA (*small arrow*) and nonfunctional adenoma (*large arrow*). APA is golden-yellow whereas adenoma is mixed black and yellow.

recurrence after surgery. Normalization of hypertension was not as uniform as that of hormonal overproduction (Table 2). Hypertension was cured in half of the patients in group 1 immediately after surgery, but only 1 of 11 patients in group 3 became normotensive in the same period ($p < 0.025$). In group 3 patients, hypertension still remained at 3 months after surgery compared with group 1 patients ($p < 0.05$). More than 1 year after surgery, the percentages of normotensive subjects were increased in all groups, the figure being higher in group 1, but not significantly. The overall cure rate of hypertension by unilateral total adrenalectomy was 70%.

Discussion

Unilateral adrenalectomy for patients with APA is effective for correction of metabolic abnormalities or improvement of hypertension. The serum K usually normalizes immediately after surgery. Hypertension is cured in 60–80% of patients with APA, and the rest achieve some improvement of hypertension postoperatively [8–10]. It is also true that some patients cannot acquire normal blood pressure after surgery.

The predictive factors for identifying those patients who will respond well after surgery have been evaluated. Preoperative blood pressure, age at surgery, and duration of hypertension prior to surgery do not seem to be of prognostic importance [10]. In our present review, none of the above—not serum K, PRA, or PAC—had predictive importance. A positive family history of hypertension also does not seem to be useful in this respect [10, 11].

Preoperative response to spironolactone administration is

reported to have prognostic value [12, 13]. We routinely administer 75–100 mg spironolactone per day for about 2 weeks before surgery in order to correct hypokalemia. Other antihypertensive agents such as calcium antagonists or beta blockers are also administered. Consequently, it is difficult to evaluate the isolated response to spironolactone.

Normalization of blood pressure is reported to be achieved early in the postoperative course. This can take 1 month, but is usually achieved within 1 week after surgery [3, 14]. In some subjects, the full effect of adrenalectomy is not complete for several months [11, 14]. In our present study, 50% of patients with solitary adenoma became normotensive within 1 week, whereas it took 1 year or more for patients with multinodular adrenal lesions in addition to APA to become normotensive. At final follow-up, 80% of the former had normal blood pressure, whereas over 40% of the latter patients remained hypertensive. There was no difference in the postoperative hormonal levels in these 2 groups, implying that nodular lesions were not the cause of the hormonal excess because they were known to be bilateral, and remaining contralateral adrenal would have contained the same type of lesions. Multinodular lesions are, thus, not a cause of hypertension, but may result from it [7]. As a result, multinodular lesions in the attached adrenal gland seem to have significant value for predicting the postoperative time course of blood pressure normalization. Multinodular lesions associated with APA were found previously in 21 of 38 patients with APA [3]. In that study, however, no prognostic or predictive importance of such multinodular lesions was demonstrated. The cure rate of hypertension was low—40–50% in both groups—and the overall cure rate after surgery was 44%, which was significantly lower than in other studies or in ours.

Five subjects with multiple adenomas were reported in a series of 50 patients who were operated on for primary aldosteronism [15]. In that report, 27 patients had solitary adenoma. The size of the multiple adenomas ranged from a few millimeters to 6 cm in diameter. In 3 of 5 patients with multiple adenomas, blood pressure returned to the normal range after surgery, and the same response rate was obtained in patients with a single adenoma.

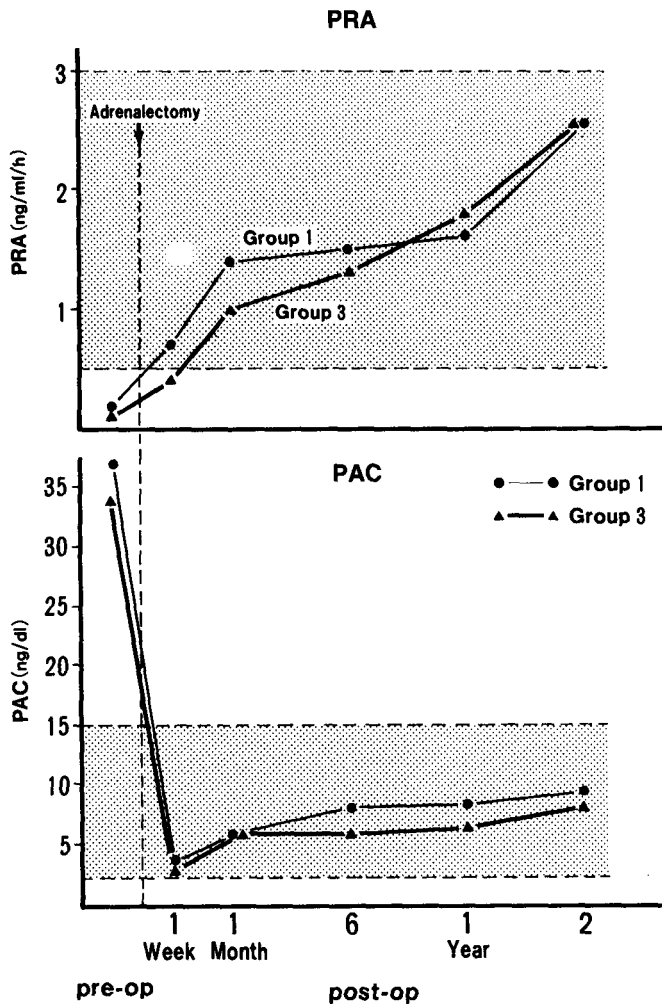
Neville urged caution in the diagnosis of multiple adenomas because of the difficulty in differentiating adenomas from macronodules [5]. We diagnosed 2 cases as aldosterone-producing multiple adenomas. The characteristics of unilateral multiple adenomas included similarity in size, a typical golden-yellow color, localization and congregation in one portion of the adrenal, and lack of other macro- or micronodular lesions in the attached adrenal.

In the present review, all patients underwent unilateral total adrenalectomy; however, it is debatable whether a tumor-bearing adrenal gland should be removed totally or whether partial removal is sufficiently curative.

Macro- or micronodular lesions are not a cause of hormonal excess, and, therefore, they need not be removed if they are correctly diagnosed intraoperatively. The possibility of multiple adenomas must also be considered and it may be difficult to differentiate large nodules from adenomas specifically when the adrenal remains in situ. According to the clinical characteristics of our present series of multiple adenomas and multinodular lesions, it seems reasonable to recommend that micronodular lesions need not be removed completely.

Table 1. Preoperative conditions in the 3 groups.

Group	No.	Age (yr)	Duration of hypertension (yr)	Serum K (mEq/L)	PRA (ng/ml/hr)	PAC (ng/dl)
1	23	42.8 ± 10.6	6.6 ± 6.7	2.6 ± 0.4	0.17 ± 0.10	37.0 ± 24.3
2	3	42.7 ± 3.8	4.3 ± 1.2	2.5 ± 0.2	0.1	36.5 ± 9.2
3	11	47.8 ± 6.7	7.8 ± 6.3	2.5 ± 0.5	0.11 ± 0.08	33.9 ± 13.2

**Fig. 4.** Pre- and postoperative sequential changes in plasma renin activity (PRA) and plasma aldosterone concentration (PAC) in groups 1 and 3. The shaded areas are normal ranges.

Résumé

Trente-sept patients ayant un hyperaldostéronisme primaire ont eu une surrénalectomie totale unilatérale entre 1981 et 1987. Ces 37 patients ont été classés en 3 groupes selon la pathologie surrénalienne: adénome solitaire unilatéral, 23 cas (groupe 1); adénome unilatéral, 3 cas (groupe 2); et adénome avec nodules micro ou macroscopiques multiples, 11 cas (groupe 3). On a comparé les données préopératoires (âge, durée de l'hypertension, activité rénine plasmatique, concentration d'aldostérone plasmatique et kaliémie), les changements hormonaux postopératoires, et l'évolution de l'hypertension afin de déterminer si

Table 2. Postoperative improvement of hypertension (percentages of normotensives).

Group	Within 1 wk	3 mo	>1 yr
1	48 ^a	57 ^b	78
2	33	66	66
3	9 ^a	18 ^b	56

^a*p* < 0.025.^b*p* < 0.05.

des différences de pathologie surrénalienne peuvent influencer l'évolution postopératoire. Les paramètres préopératoires (excepté l'âge) ne différaient pas de façon significative parmi les 3 groupes. L'âge moyen était plus élevé dans le groupe 3 que dans les groupes 1 et 2 (47.8 versus 42.8 versus 42.7 ans).

Les variations hormonales postopératoires étaient également similaires, surtout dans les groupes 1 et 3, restant dans les limites de la normale pendant la période de suivi (moyenne, 31 mois; extrêmes, 3 à 86 mois). Cependant l'amélioration de l'hypertension postopératoire était différente, retardée de façon significative chez les patients ayant des lésions multinodulaires (groupe 3), la moitié d'entre eux restant hypertendus après un an. Les lésions nodulaires, étant donné que les adénomes ne donnent pas d'hypersécrétion hormonale, peuvent traduire plutôt une hypertension prolongée.

Resumen

Treinta y siete pacientes con aldosteronismo primario fueron tratados mediante adrenalectomía total unilateral en un período de 7 años (1981–1987). Los 37 pacientes fueron clasificados en 3 grupos con base en la patología adrenal: adenoma solitario unilateral, 23 casos (grupo I); adenomas unilaterales, 3 casos (grupo 2); y adenoma con múltiples macro- o micronódulos, 11 casos (grupo 3). Las condiciones preoperatorias de los pacientes (edad, duración de la hipertensión, actividad de renina plasmática, concentración plasmática de aldosterona, y concentración sérica de potasio), los cambios postoperatorios sucesivos en los niveles hormonales, y el resultado de la hipertensión fueron comparados en los 3 grupos, con el objeto de determinar si las diferencias en la patología adrenal podrían afectar la evolución postoperatoria. Los parámetros preoperatorios, excluyendo la edad en el momento de la cirugía, no diferieron significativamente en los 3 grupos. La edad promedio en el grupo 3, sin embargo, fue ligeramente superior en los grupos 1 y 2 (47.8 versus 42.8 versus 42.7 años).

Los cambios hormonales postoperatorios también fueron similares, particularmente en los grupos 1 y 3, manteniéndose dentro del rango normal a través del seguimiento (promedio, 31 meses; rango, 3–86). Sin embargo, la mejoría postoperatoria de

la hipertensión exhibió diferencias marcadas, con aparición significativamente tardía en pacientes con lesiones nodulares (grupo 3); aproximadamente la mitad de éstos permanecieron hipertensos aún después de un año. Por consiguiente, se piensa que las lesiones nodulares diferentes del adenoma(s) no contribuyen al exceso hormonal sino que resultan de la hipertensión intratable.

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Invited Commentary

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Dr. Ito and his colleagues present a significant experience with the surgical management of primary aldosteronoma over a 7-year period. The hypothesis that outcome can be predicted in patients with primary aldosteronism presenting for operation is an important one. They conclude that because patients with multinodular glands do badly in terms of postoperative control of blood pressure, they may not be candidates for operation. Why gross pathology should predict outcome is unclear. A possibility is that the macronodular disease is an indicator of hyperplasia, a known factor not responsive to unilateral adrenalectomy. The authors must have this information, but it is not given. An argument against this hypothesis is that the plasma renin activity and plasma aldosterone concentration return to normal postoperatively.

The important issue, however, is how to predict preoperatively what can be anticipated postoperatively. If an important intermediary step in this is the recognition of multinodular disease, then we need to have some information to predict which patients would be expected to have such gross findings. The authors clearly have information that is alluded to, but not provided, in this article. First, what is the response in aldosterone secretion, and plasma renin activity to posture? The authors suggest that some of the patients had venous sampling

to localize their disease. What were those values? Could they discriminate the response to unilateral operation? The authors talk of putting some patients on spironolactone. Did the response to that drug predict which patients would subsequently respond? It is very clear that the authors have information which would provide answers to these questions for the patient and the surgeon.

The argument to leave micronodules behind because they do not contribute to outcome is, I think, a brave one. A unilateral adrenalectomy as opposed to a partial adrenalectomy has minimal additional morbidity. The other unanswered question concerns why there is a delay in the normalization of blood pressure in patients in group II and group III, i.e., those with multinodular disease. Is there any reason to suspect or predict why this delay should take place? Is it just a reflector of better pharmacological control of hypertension? Overall, while the authors have provided us with some clues as to possible outcome based on macroscopic findings at the time of operation or in the pathology department, they clearly have more information which would allow us to discriminate whether this intraoperative finding could be predicted preoperatively, and unnecessary operation avoided. Conversely, they make the intriguing observation that despite the return of plasma renin activity and plasma aldosterone concentration to normal, this does not parallel return to normal blood pressure.

The authors have a great deal of valuable information not provided in this article, and we will look forward to the next article which may provide the answer to the difficult question of which patient with primary aldosteronism should undergo unilateral adrenalectomy with a high probability of prolonged control of antecedent hypertension.