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The Role of Unilateral Adrenalectomy in Corticotropin-Independent Bilateral Adrenocortical Hyperplasias

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Abstract

Background The objective of the present study was twofold: to demonstrate our experience with unilateral adrenalectomy in the treatment of adrenocorticotropic hormone (ACTH)-independent Cushing syndrome (CS) caused by bilateral adrenocortical hyperplasias, and to evaluate the long-term results as evidenced by the main laboratory and clinical findings.

Methods From February 2000 to August 2009, unilateral adrenalectomy was performed on 27 patients with ACTH-independent CS and bilateral adrenocortical hyperplasias, including 14 patients with ACTH-independent macronodular adrenal hyperplasia (AIMAH) and 13 patients with primary pigmented nodular adrenocortical disease (PPNAD). Signs and symptoms of CS, endocrine examinations, and radiographic imaging were evaluated preoperatively and postoperatively.

Results At a median follow-up of 69 months (range: 23–120 months) for AIMAH and 47 months (range: 16–113 months) for PPNAD, 25 patients were cured by unilateral adrenalectomy. Serum cortisol level, daily urinary free cortisol (UFC), and plasma ACTH regained the normal range in both AIMAH and PPNAD patients at monthly follow-up visits; the circadian serum cortisol rhythm returned to normal, and a normal responsiveness to overnight low-dose dexamethasone administration (LDDST) became obvious. Both systolic and diastolic blood pressure (BP) levels were significantly reduced: 85 % of patients recovered normal BP levels, and the remaining patients need antihypertensive drugs, but at a reduced dose. No surgery-related morbidity occurred, and there was no sign of further enlargement of the residual adrenal gland after successful unilateral adrenalectomy. One patient with PPNAD and another patient with AIMAH with similar weights and sizes of the bilateral adrenals needed contralateral adrenalectomy.

Conclusions Unilateral adrenalectomy may be the suitable treatment for selected patients with AIMAH and PPNAD. It can achieve long-term remission of CS and improve glycemic control and BP values.

Introduction

Cushing syndrome (CS) is caused by chronic exposure to excessive glucocorticoid, and it can be divided into two types: adrenocorticotropic hormone (ACTH)-independent CS and ACTH-dependent CS. The most common cause of all ACTH-dependent disorders is Cushing disease. Some 15–20 % of endogenous CS is due to ACTH-independent cortisol-producing adrenal disease, usually by unilateral autonomous adrenocortical tumors, which can be diagnosed relatively easily by hormone assays associated with adrenal imaging examination [1].

Bilateral adrenal lesions include bilateral adrenocortical hyperplasias (BAH) and bilateral adrenocortical adenomas or carcinomas, and they represent 10–15 % of all ACTH-independent CS of adrenocortical origin. In most instances,

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primitive bilateral adrenal pathology is due to the two main subtypes of BAH: ACTH-independent macronodular adrenal hyperplasia (AIMAH) and primary pigmented nodular adrenocortical disease (PPNAD), both of which are unusual and rarely reported. The AIMAH form represents a rare benign adrenal tumor characterized by massive enlargement of bilateral adrenal glands [2], whereas PPNAD is characterized by several small pigmented nodules in the cortex of normal-sized adrenal glands [3]. Because few series of patients with ACTH-independent CS caused by AIMAH or PPNAD have been described, the diagnosis and management of such patients have been problematic up until now.

The universally acknowledged treatment for AIMAH and PPNAD is total bilateral adrenalectomy, but after such treatment patients will require a life-long steroid replacement therapy and are prone to adrenal crisis. For these reasons, unilateral adrenalectomy of the larger gland for patients with AIMAH has been advocated to reduce glucocorticoid levels and improve clinical symptoms [2, 4]; however, there is no relevant literature demonstrating whether unilateral adrenalectomy can be used as a safe and effective alternative in the treatment of PPNAD. In the present study, we summarized our experience with unilateral adrenalectomy in the treatment of CS arising from AIMAH or PPNAD. Moreover, we evaluated the long-term laboratory results and clinical manifestations of these rare disorders after unilateral adrenalectomy.

Materials and methods

A total of 27 patients (10 male; 17 female) with clinical ACTH-independent CS, including 14 cases of AIMAH and 13 cases of PPNAD, were recruited from the Department of Urology, Ruijin Hospital, which is affiliated with Shanghai Jiaotong University of Medicine, between February 2000 and August 2009. Patients with bilateral adrenocortical adenomas or carcinomas were not included in this study. With approval from the Ethics Committee of Shanghai, we reviewed the complete medical records of these patients from our database.

The diagnostic evaluation was confirmed on the basis of clinical and laboratory information, including presenting signs and symptoms, results of endocrine evaluations, preoperative radiographic imaging studies, and histopathological examinations after surgery [5]. The enlargement of bilateral adrenal glands and multinodular adrenal glands were visualized by computed tomography (CT) or magnetic resonance imaging (MRI), and the largest diameter of the adrenal gland on CT or MRI could be regarded as the adrenal size. Serum cortisol circadian rhythm (08:00, 16:00, 00:00 h), ACTH levels (normal values, 10–50 ng/L), urinary free cortisol levels (UFC; normal values, 30–300 nmol/day), 1 mg overnight or high-dose dexamethasone suppression test (DST), arterial blood pressure (BP), serum sodium and potassium, plasma renin activity, plasma aldosterone concentration, plasma epinephrine and norepinephrine, fasting plasma glucose, and plasma glucose after the 75 g oral glucose tolerance test (OGTT), HbA1c levels, and body mass index (BMI) were investigated and recorded preoperatively and again postoperatively, at the time of the most recent follow-up visit.

The curative criteria of CS included clinical remission without relapse and normalized postoperative serum cortisol level. Normotensive patients were defined on the basis of systolic BP <140 mmHg and diastolic BP <90 mmHg without the use of antihypertensive medications. The BMI was calculated as body weight in kilograms divided by the square of height in meters (normal values: 20–24.9). Diabetes mellitus or impaired glucose tolerance (IGT) was diagnosed when fasting plasma glucose was >6.1 mmol/L or the plasma glucose at 2 h after OGTT was >7.8 mmol/L. At 3, 6, and 12 months of the first year and annually thereafter, the follow-up evaluation was performed using biochemical tests to exclude recurrence, and recurrence was identified as the presence of elevated urinary or plasma cortisol levels and/or an abnormal DST (1 mg overnight) during the follow-up period.

Statistical analyses were performed with SPSS statistical package v. 16.0. Patient characteristics were expressed as average ± standard deviation (SD), and Student's *t* test was performed for group differences. All tests were 2-tailed, and *P* values <0.05 were considered statistically significant.

Results

Tumor characteristics and clinical features of patients with AIMAH and PPNAD are shown in Table 1. Among the 14 AIMAH patients, 9 were women, and 5 were men. The mean age of patients at presentation was 47.57 ± 9.36 years (range: 26–58 years). The 13 patients with PPNAD included 8 females and 5 males, ranging in age from 12 to 53 years of age (mean age: of 25.00 ± 10.30 years). Clinical symptoms of CS developed in all patients: fragile and thin skin; purplish-pink stretch marks on the body; and upper-body obesity, among others. Preoperatively, 26 (96.30 %) of the 27 patients had hypertension, and BP was 140–240/90–165 mmHg (mean BP: 181 ± 28/117 ± 21 mmHg). Altogether, weight gain was obvious in 10 (37.04 %) of 27 cases, and obesity (BMI ≥ 30 kg/m^2) was noted in 8 patients (29.63 %) preoperatively. Thirteen patients, 4 with AIMAH and 9 with PPAND, had hyperglycemia and fasting plasma glucose levels of 6.9–9.7 mmol/L; the prevalence of diabetes mellitus was 18.52 % (5/27). Five patients (2 with AIMAH and 3 with PPAND) had hypokalemia, and their plasma

Table 1 Tumor characteristics and clinical features of patients with ACTH-independent macronodular adrenal hyperplasia (AIMAH) and primary pigmented nodular adrenocortical disease (PPNAD)

Clinical characteristic	AIMAH	PPNAD
Total number of patients	14	13
Gender		
Male	5	5
Female	9	8
Age at presentation (year); mean (range)	47.57 ± 9.36 (26–58)	25.00 ± 10.30 (12–53) ($P < 0.001$)
Clinical symptoms of CS	14	13
Hypertension	14	12
Weight gain	4	6
Obesity	3	5
Hyperglycemia	4	9
Diabetes mellitus	3	2
Hypokalemia	2	3
Operation		
Right adrenalectomy	3	5
Left adrenalectomy	10	7
Bilateral adrenalectomy	1	1
Weight of excised gland (g), mean (range)	59.6 ± 24.7 (17–102)	13.0 ± 3.9 (8.3–20) ($P < 0.001$)
Follow-up (months), mean (range)	69(23–120)	47(16–113)

potassium levels ranged from 2.9 to 3.2 mmol/L. Primary aldosteronism and pheochromocytoma diagnosed by biochemical testing in all cases were not included in this study.

The baseline serum ACTH levels were measured in all patients more than once, and undetectable or low serum ACTH unresponsive to plasma corticotropin releasing hormone (CRH) was observed in all patients. All patients had daily elevated levels of UFC and lacked the normal circadian variation of serum cortisol; the serum cortisol concentration at 8:00 a.m. and 4:00 p.m. was 273–1,061 nmol/L (normal reference range: 138–690 nmol/L) and 223–800 nmol/L (normal reference range: 69–345 nmol/L), respectively. The midnight serum cortisol concentration ranged from 336 to 698 nmol/L (normal reference range: 69–345 nmol/L). There were no significant differences between patients with AIMAH and patients with PPNAD in the 8:00 a.m., 4:00 p.m., and 0:00 a.m. serum cortisol concentrations (672.0 ±203.7 vs. 599.9 ± 160.9 nmol/L, 631.4 ± 163.9 vs. 567.0 ± 117.1 nmol/L, and 548.6 ± 125.8 vs. 486.5 ±114.8 nmol/L; $P > 0.05$). The daily levels of UFC were slightly higher in patients with PPNAD than in those with AIMAH, but the differences were not statistically significant (1,332.6 ± 877.0 vs. 1065.8 ± 752.3 nmol/day; $P > 0.05$). Moreover, the serum cortisol level of all patients was >600 nmol/L after overnight DST and, paradoxically, 7 patients had an increased UFC excretion after high-dose DST.

Fourteen patients with ACTH-independent CS satisfied the diagnostic criteria of AIMAH, with massive bilateral adrenal enlargement (markedly asymmetric in 13 cases) and multiple macronodules interspersed with multiple micronodules on CT scan. The attenuation was 13.4–83.2 Hounsfield units (HU) on unenhanced CT and 36.2–88.0 HU on enhanced CT (Fig. 1). Histopathological examination revealed that the adrenal cortex was thickened and contained multiple nodules 5 mm–4.5 cm in diameter (Fig. 2). The nodules are seen microscopically to be composed of large, clear, and lipid-rich vacuolated cells and compact eosinophilic cells. Normal or minimally hyperplastic adrenal glands in another 13 patients were revealed by CT or MRI. Bilaterally, small nodules can be seen in the adrenal glands of 10 of the patients, but a unilateral adrenal nodule appeared in 3 of 13 patients. Histologically, the size and weight of the adrenal glands

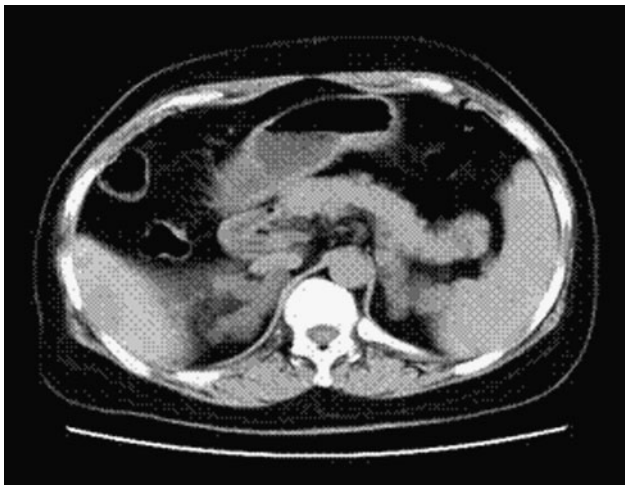

Fig. 1 Bilateral multinodular adrenal enlargement in ACTH-independent macronodular adrenal hyperplasia (AIMAH)

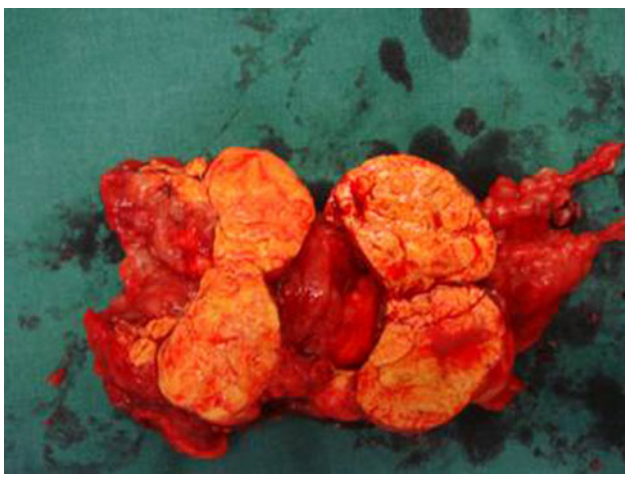

Fig. 2 Macroscopic view of a resected adrenal with AIMAH

were normal in 7 patients. Histopathological examination of surgical specimens of all 13 patients showed multiple brown or black nodules (0.5–1.5 cm) composed of large cells with eosinophilic cytoplasm and hyperchromatic nuclei, consistent with the diagnosis of PPNAD (Figs. 3, 4). Three patients had serum prolactin concentrations measured, and one of the reported boys had prolactinoma; in addition, a 27-year-old woman had lentigines, spotty pigmentation of the buccal mucosa and lips, and congenital absence of a vagina with an infantile uterus. In view of these findings, these two patients fulfill the criteria for Carney complex (CNC). Another male patient had bilateral cryptorchidism. To exclude coexisting atrial myxoma, echocardiograms were performed in these 13 patients after operation, and all were negative.

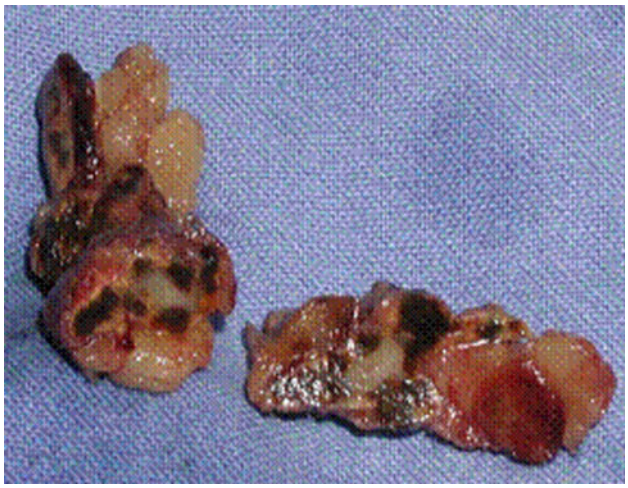

Fig. 3 Macroscopic view of a resected adrenal with primary pigmented nodular adrenocortical disease (PPNAD)

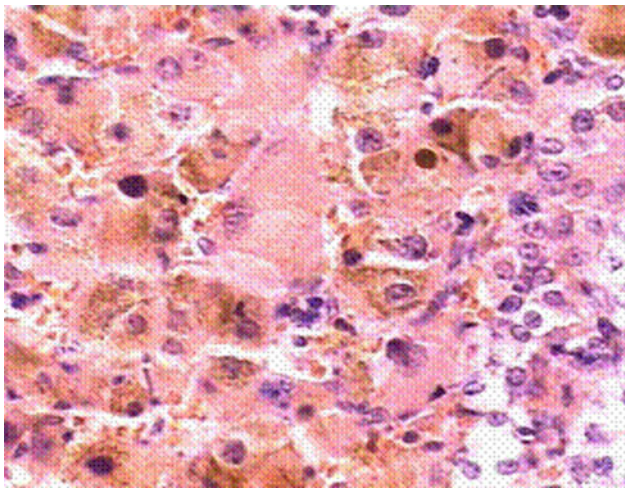

Fig. 4 Histological view of a resected adrenal gland from a patient with PPNAD. (hematoxylin and eosin staining; original magnification, ×40)

Open total adrenalectomy was performed in 12 patients, and retroperitoneal laparoscopic adrenalectomy was performed in another 15 patients. Thirteen patients with AIMAH and 3 patients with PPNAD underwent unilateral adrenalectomy of the largest adrenal gland as determined by image examinations before operation. In the 11 patients with normal-sized or symmetrically hyperplastic adrenal glands, right adrenalectomy was performed in 5 cases and left adrenalectomy in the other 6 cases. The mean weight of the resected glands in cases of AIMAH and PPNAD was 59.6 ± 24.7 g (range: 17–102 g) and 13.0 ± 3.9 g (range: 8.3–20 g), respectively. After unilateral adrenalectomy, the regular dosage of hydrocortisone or cortisone acetate was recommended routinely. Two AIMAH patients with a relatively small-sized contralateral gland and one PPAND patient had transient post-surgical adrenal insufficiency, and hydrocortisone was injected intraoperatively by intravenous drip.

The median postsurgery follow-up for patients with AIMAH was 69 months (range: 23–120 months) and that for PPNAD was 47 months (range: 16–113 months). No surgery-related morbidity occurred, and to date there has been no sign of further enlargement of the residual adrenal glands on CT scanning after successful unilateral adrenalectomy. During the follow-up period, 25 patients were cured by unilateral adrenalectomy. A significant decrease in daily UFC (1,210 ± 841.2 vs. 83.8 ± 45.0 nmol/day; $P < 0.001$) and serum cortisol levels (645.6 ± 174 vs. 291.6 ± 84.4 nmol/L; $P < 0.001$) was observed. The levels of plasma ACTH were significantly increased (3.67 ± 2.23 vs. 27.32 ± 36.04 ng/L; $P = 0.003$). Subsequently, the levels of daily UFC, serum cortisol, and plasma ACTH regained the normal range in both AIMAH and PPNAD patients at monthly check. In addition, the circadian serum cortisol rhythm returned to normal, and a normal responsiveness to LDDST became obvious. Improvement in the clinical symptoms and signs of CS were also noted in these 25 patients.

One PPNAD patient who underwent a right laparoscopic adrenalectomy had recurrence of hypercortisolism and the manifestations of CS after 2 months, and the contralateral adrenalectomy was performed. An AIMAH patient with bilateral adrenal enlargement also underwent the contralateral adrenalectomy to reduce the persistent symptom of severe hypercortisolism after right adrenalectomy, because the size and weight of the gland excised at the primary operation was similar to the contralateral adrenal. After the second surgery, hypocortisolism developed, and the manifestations of CS were completely relieved. To maintain the improvement, life-long treatment with glucocorticoid was begun (7.5–10 mg prednisone per day).

Hypertension resolved in all 26 patients carrying that diagnosis at baseline, both systolic BP (181 ± 28 vs.

134 ± 11 mmHg; $P < 0.001$) and diastolic BP levels (117 ± 21 vs. 87 ± 8 mmHg; $P < 0.001$); 22 of 26 patients who recovered to normal BP levels were subsequently withdrawn from the hypertension medications, and another 4 patients needed antihypertensive drugs at a reduced dose. Eleven of 13 patients who had diabetes or glucose intolerance regained normal glycometabolic control, and in two others a reduction of need for hypoglycemizing medications was achieved. A significant improvement was observed in fasting plasma glucose levels (7.35 ± 0.99 vs. 4.60 ± 1.11 mmol/L; $P < 0.001$), serum glucose levels after OGTT (10.79 ± 2.57 vs. 7.10 ± 1.72 mmol/L; $P = 0.002$), and HbA1c levels (6.95 ± 1.09 vs. 5.25 ± 0.97 %; $P < 0.001$). The serum potassium level returned to normal in the 5 patients with hypokalemia, and the BMI decreased significantly (28.14 ± 3.65 vs. 22.93 ± 1.32 kg/m^2; $P < 0.001$).

Discussion

Cushing syndrome may result from various sources [6]. With the exception of iatrogenic causes, endogenous CS is divided into two types: ACTH-independent CS and ACTH-dependent CS. The ACTH-dependent form, which mainly caused by Cushing disease and ectopic ACTH syndrome, accounts for ~80–85 % of CS cases [7]. As a result of autonomous primary adrenal pathology producing cortisol, ACTH-independent CS accounts for 15–20 % of endogenous CS, and most cases result from unilateral adrenal adenoma or carcinoma [8]. Bilateral adrenal masses are rare causes of adrenal CS, including bilateral adrenal adenomas or carcinomas, AIMAH, and PPNAD. Approximately 10 % of primary adrenal CS involves AIMAH and PPNAD, and this represents diagnostic and therapeutic challenges [9].

ACTH-independent macronodular adrenal hyperplasia is a bilateral adrenal hyperplastic disease first described in 1964 by Kirschner et al. [10]. It was reported to have a relatively uneven gender distribution, more frequent in males [11] or in women with GIP-dependent AIMAH [12], whereas there is a slight female preponderance in PPNAD. The majority of AIMAH patients develop clinical manifestations of CS between the ages of 50 and 60, but the diagnosis in most cases of PPNAD is commonly made in childhood, late adolescence, or early adulthood [13]. In our series, the mean age at presentation in cases of AIMAH and cases of PPNAD was 47.57 ± 9.36 years (range: 26–58 years) and 25.00 ± 10.30 years (range: 12–53 years), respectively, similar to previous series. A small proportion of AIMAH may develop in conjunction with McCune-Albright syndrome (MAS) during the first year of life. This consists of polyostotic fibrous dysplasia, café-au-lait skin pigmentation, and endocrine dysfunction. Nearly half of PPNAD can be associated with CNC, a form of multiple endocrine neoplasia (MEN) represented by schwannomas, myxoma, cutaneous lentigines, and endocrinopathy [14].

Although CS is the most common clinical presentation of AIMAH, overproduction of mineralocorticoid, cortisol-estrone, or androgen has also been discovered in some patients [15, 16]. The associated manifestation of CS in patients with PPNAD could be clinically classic, subclinical, cyclical, or atypical [1]. Consequently, it is difficult to make the biochemical diagnosis of AIMAH and PPNAD with subclinical or atypical hypercortisolemia, and both can be misdiagnosed as other more common adrenal disorders. It is important to differentiate AIMAH and PPNAD from other types of ACTH-independent CS, and to carefully distinguish the two conditions from each other.

All of our patients had a "classical" primary adrenal CS presentation. Hypertension and hyperglycemia were also commonly associated with both AIMAH and PPNAD in our study.

Patients with AIMAH have bilaterally enlarged adrenal glands with numerous nodules up to 5.5 cm in size and low attenuation on CT; on T1-weighted MRI, the signal intensity is equal to muscle, whereas in T2-weighted images, the intensity can be higher than liver [17, 18]. Diffuse enlargement of the adrenal without any distinct nodules and asymmetric hyperplasia of adrenal macronodules have also been reported in some cases [8, 19]. Although PPNAD is also a bilateral adrenal hyperplastic disease, adrenal glands with several small pigmented cortical nodules are usually of normal size or minimally hyperplastic. The size of the nodules typically does not exceed 5 mm, but in some older patients, one or several larger nodules 1–2 cm in diameter may appear, mimicking unilateral tumors [20]. Compared to surrounding atrophic cortical tissue, the adrenal nodules demonstrate lower T1 and T2 signal intensity on MRI [21]. Our radiological findings are consistent with the literature, in that CT scanning revealed massive bilateral adrenal gland enlargement and multiple macronodules interspersed with multiple micronodules in 14 cases of AIMAH and normal or minimally increased size of the adrenals, which contained discrete nodules between 5 and 15 mm in diameter in 13 cases of PPNAD. Bilaterally, small nodules were identified in 10 cases of PPNAD, but a single unilateral adrenal nodule was noted in the other 3 patients. The adrenal glands of these 13 patients had the typical histological features of PPNAD: pigmented micronodules <15 mm in diameter were visible, and there was atrophy of the intervening cortex.

Total bilateral adrenalectomy is considered the standard treatment for ACTH-independent CS diagnosed as AIMAH or PPNAD. This procedure can effectively ameliorate Cushingoid appearance and hypercortisolism; however, absence of the adrenal glands requires patients to rely on life-long steroid replacement therapy and susceptibility to

adrenal insufficiency [16, 22, 23]. Because of inefficient steroid hormone synthesis, hypercortisolism is usually slight or moderate in AIMAH, suggesting that unilateral adrenalectomy may be a therapeutic alternative. Recent reports show that unilateral adrenalectomy for AIMAH in adult patients successfully improves clinical symptoms and endocrinological status in CS, particularly in patients with asymmetric hyperplasia and mildly elevated hormone synthesis [2, 24, 25].

To date, there have been no studies to demonstrate whether unilateral adrenalectomy is a suitable treatment for PPNAD or not. In the present study, we performed unilateral adrenalectomy for treating patients with CS caused by AIMAH or PPNAD, and the curative effects and long-term follow-up were evaluated postoperatively in our patients with these rare disorders. Unilateral adrenalectomy of the largest gland was performed in 13 AIMAH patients and 3 PPNAD patients. The decision was based on imaging of a unilateral adrenal nodule in 3 patients with PPNAD and asymmetric bilateral adrenal enlargement in 13 patients with AIMAH. In another 11 patients, including 10 patients with PPNAD and normal-sized or minimally enlarged adrenals and 1 patient with AIMAH who had symmetrically hyperplastic adrenal glands, right adrenalectomy was performed in 5 cases and left adrenalectomy was carried out in the other 6 cases.

At first, we planned a subsequent contralateral adrenalectomy in a delayed surgery in two patients with PPNAD who were at serious surgical risk; however, both of these patients had long-term remission of CS after unilateral adrenalectomy. In view of the success of unilateral adrenalectomy, we proceeded with that approach in the other patients. In patients with normal-sized or minimally enlarged adrenals or symmetrically hyperplastic adrenal glands, two criteria were used to select the side for adrenalectomy: adrenal iodine 131-norcholesterol scintigraphy was performed, and the prevalent side of uptake was selected; when the iodine 131-norcholesterol uptake at scintigraphy was symmetric, a subsequent contralateral adrenalectomy was planned. To avoid inferior vena cava injury in a delayed surgery, right adrenalectomy should be performed at the primary operation.

At a median postsurgery follow-up of 69 months for AIMAH and 47 months for PPNAD, significant improvement in the clinical manifestations, laboratory findings, and metabolic abnormalities were observed clearly in most patients. Unilateral adrenalectomy resulted in clinical and laboratory cure of CS in 92.59 % (25/27) of the patients, because daily UFC levels and serum cortisol levels decreased significantly, and ACTH levels of both AIMAH and PPNAD patients subsequently decreased to the normal range. In addition, the circadian serum cortisol rhythm returned to normal, and a normal responsiveness to LDDST became obvious. The improvement of the clinical symptoms and signs of CS are also found in these 25 patients. At 3, 6, and 12 months of the first year and annually thereafter, routine examinations, including daily UFC, serum cortisol levels, and imaging examinations, were performed to follow patients and possibly identify recurrence.

Failure occurred in one patient with PPNAD who needed contralateral surgery because of the recurrence of hypercortisolism and the manifestations of CS 2 months later. Another patient, with AIMAH and similar adrenal volume as well as similar weight and size of bilateral adrenal involvement, also underwent completion contralateral adrenalectomy to reduce the persistent symptom of severe hypercortisolism after right adrenalectomy; in that case, AIMAH showed a significant positive correlation with the volume [25]. Transient post-surgical adrenal insufficiency occurred in 2 AIMAH patients with a relatively small-sized contralateral gland and in one PPAND patient in our series. The treatment of choice in those cases was injection of hydrocortisone intraoperatively by intravenous drip. Moreover, the residual adrenal glands keep from growing larger after successful unilateral adrenalectomy on CT scanning during follow-up.

Conclusions

The results of the current series confirm that unilateral adrenalectomy may be suited for selected patients with AIMAH and PPNAD, especially AIMAH with an asymmetric involvement and PPNAD with a unilateral adrenal nodule apparent on CT or MRI scanning. Unilateral adrenalectomy can achieve long-term remission of CS and improve glycemic control and BP values. Contralateral adrenalectomy should be performed if CS recurs during follow-up, and lifelong treatment with glucocorticoid should be given subsequently.

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References

1. Lacroix A, Bourdeau I (2005) Bilateral adrenal Cushing's syndrome: macronodular adrenal hyperplasia and primary pigmented nodular adrenocortical disease. Endocrinol Metab Clin North Am 34:441–458 x
2. Iacobone M, Albiger N, Scaroni C et al (2008) The role of unilateral adrenalectomy in ACTH-independent macronodular adrenal hyperplasia (AIMAH). World J Surg 32:882–889. doi: 10.1007/s00268-007-9408-5
3. Stratakis CA, Kirschner LS (1998) Clinical and genetic analysis of primary bilateral adrenal diseases (micro- and macronodular disease) leading to Cushing syndrome. Horm Metab Res 30: 456–463

4. Lamas C, Alfaro JJ, Lucas T et al (2002) Is unilateral adrenalectomy an alternative treatment for ACTH-independent macronodular adrenal hyperplasia?: long-term follow-up of four cases. Eur J Endocrinol 146:237–240
5. Arnaldi G, Angeli A, Atkinson AB et al (2003) Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 88:5593–5602
6. Bertagna X, Guignat L, Groussin L et al (2009) Cushing's disease. Best Pract Res Clin Endocrinol Metab 23:607–623
7. Ilias I, Torpy DJ, Pacak K et al (2005) Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. J Clin Endocrinol Metab 90:4955–4962
8. Nieman LK, Biller BM, Findling JW et al (2008) The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 93:1526–1540
9. Gunther DF, Bourdeau I, Matyakhina L et al (2004) Cyclical Cushing syndrome presenting in infancy: an early form of primary pigmented nodular adrenocortical disease, or a new entity? J Clin Endocrinol Metab 89:3173–3182
10. Kirschner MA, Powell RD Jr, Lipsett MB (1964) Cushing's syndrome: nodular cortical hyperplasia of adrenal glands with clinical and pathological features suggesting adrenocortical tumor. J Clin Endocrinol Metab 24:947–955
11. Aiba M, Hirayama A, Iri H et al (1991) Adrenocorticotropic hormone-independent bilateral adrenocortical macronodular hyperplasia as a distinct subtype of Cushing's syndrome. Enzyme histochemical and ultrastructural study of four cases with a review of the literature. Am J Clin Pathol 96:334–340
12. Lacroix A, Ndiaye N, Tremblay J et al (2001) Ectopic and abnormal hormone receptors in adrenal Cushing's syndrome. Endocr Rev 22:75–110
13. Zeiger MA, Nieman LK, Cutler GB et al (1991) Primary bilateral adrenocortical causes of Cushing's syndrome. Surgery 110:1106–1115
14. Stratakis CA, Kirschner LS, Carney JA (2001) Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. J Clin Endocrinol Metab 86:4041–4046
15. Goodarzi MO, Dawson DW, Li X et al (2003) Virilization in bilateral macronodular adrenal hyperplasia controlled by luteinizing hormone. J Clin Endocrinol Metab 88:73–77
16. Lacroix A (2009) ACTH-independent macronodular adrenal hyperplasia. Best Pract Res Clin Endocrinol Metab 23:245–259
17. Doppman JL, Nieman LK, Travis WD et al (1991) CT and MR imaging of massive macronodular adrenocortical disease: a rare cause of autonomous primary adrenal hypercortisolism. J Comput Assist Tomogr 15:773–779
18. Doppman JL, Chrousos GP, Papanicolaou DA et al (2000) Adrenocorticotropin-independent macronodular adrenal hyperplasia: an uncommon cause of primary adrenal hypercortisolism. Radiology 216:797–802
19. Newell-Price J, Bertagna X, Grossman AB et al (2006) Cushing's syndrome. Lancet 367:1605–1617
20. Doppman JL, Travis WD, Nieman L et al (1989) Cushing syndrome due to primary pigmented nodular adrenocortical disease: findings at CT and MR imaging. Radiology 172:415–420
21. Sahdev A, Reznek RH, Evanson J et al (2007) Imaging in Cushing's syndrome. Arq Bras Endocrinol Metab 51:1319–1328
22. Shen WT, Lee J, Kebebew E et al (2006) Selective use of steroid replacement after adrenalectomy: lessons from 331 consecutive cases. Arch Surg 141:771–774 discussion 774–776
23. Storr HL, Mitchell H, Swords FM et al (2004) Clinical features, diagnosis, treatment and molecular studies in paediatric Cushing's syndrome due to primary nodular adrenocortical hyperplasia. Clin Endocrinol (Oxf) 61:553–559
24. Sato M, Soma M, Nakayama T et al (2006) A case of adrenocorticotropin-independent bilateral adrenal macronodular hyperplasia (AIMAH) with primary hyperparathyroidism (PHPT). Endocr J 53:111–117
25. Vezzosi D, Cartier D, Regnier C et al (2007) Familial adrenocorticotropin-independent macronodular adrenal hyperplasia with aberrant serotonin and vasopressin adrenal receptors. Eur J Endocrinol 156:21–31