

## Original Article

# Classification and surgical treatment for 180 cases of adrenocortical hyperplastic disease

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**Abstract:** Objective: To review and discuss the diagnostic and surgical therapeutic methods of adrenocortical hyperplastic disease. Methods: A retrospective analysis was done to 180 adrenocortical hyperplasia patients (74 males, 109 females, aged 6~76 (average 40.1)). Studies were done to the relationship between patients' clinical characteristics, biochemical, endocrinological and imaging examination results, the therapeutic effects. Results: Among all 180 cases, there are 107 Cushing disease (CD), 19 ectopic adrenocorticotropin adrenal hyperplasia (EAAH), 28 adrenocorticotropin independent macronodular adrenal hyperplasia (AIMAH), 4 primary pigmented nodular adrenocortical hyperplasia (PPNAH), and 28 Idiopathic Hyperaldosteronism (IHA). Twenty-four-hour urinary free cortisol (24 h UFC) excretion of CD, EAAH, AIMAH and PPNAH patients were 95.2~535.7  $\mu\text{g}$  (average 287.6  $\mu\text{g}$ ), 24.8~808.2  $\mu\text{g}$  (average 307.9  $\mu\text{g}$ ), 102.5~3127.0  $\mu\text{g}$  (average 852.5  $\mu\text{g}$ ), and 243.8~1124.6  $\mu\text{g}$  (average 564.3  $\mu\text{g}$ ). Both low and high-dose dexamethasone suppression tests (DDST) were not suppressed in AIMAH, PPNAH and EAAH groups, but HDDST was suppressed in CD group. CT thin scanning results of 180 patients all showed enlargements in the affected side adrenal gland. Unilateral adrenalectomies were performed in 102 hypercortisolism cases. Local lesion excisions were done to 21 IHA patients. 57 patients had surgeries in both sides of the adrenal glands (39 bilateral total adrenalectomies, 16 total adrenalectomy in one side and subtotal adrenalectomy in the other, 2 bilateral subtotal adrenalectomies). 106 (59%) patients were followed up for 4~158 (average 32) months. Conclusion: Unilateral adrenalectomy was the first choice for operable adrenocortical hyperplasia patients. The operation mode for the other adrenal gland should be based on the type of hyperplasia and clinical observation.

**Keywords:** Adrenocortical hyperplasia, diagnosis, surgical treatment, cushing disease, hyperaldosteronism, adrenalectomy

## Introduction

The adrenal glands produce multiple hormones that are vital in various metabolic procedures of the human body. When hyperplastic disease occurs, changes in some hormones' levels often happen, which will secondarily lead to metabolic and physiological disorder [1]. The morphology of such adrenal disease can be showed a variety type, such as completely normal, and can also show thickening and enlargement of the gland. Sometimes also can be showed as nodular hyperplasia, macronodular or micronodular [2, 3].

At the same time, the adrenal lesions are Bilateral or Unilateral. Clinical manifestations of this type disease expressed in a variety form [4, 5]. Clinical treatment of such diseases is very

difficult and have not a uniform standard at Current time. It is a problem when bilateral adrenal gland total excision with hormone supplements after the surgery [6]. And it is difficult to measure how much gland was saved after partial adrenalectomy. So based on clear diagnoses, effective and targeted treatments must be given [7, 8]. We admitted 1323 adrenal cortical hyperplasia patients from 1990 to 2012. Among them, 180 (13.6%) received surgical treatments at urology surgery department. Following is a report on the 180 cases, to discuss diagnostic and surgical therapeutic methods of adrenocortical hyperplastic disease.

## Patients and methods

The ages in the group ranged from 6~76 (average 40.1). There were 74 males (41%, average

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**Table 1.** Age and gender composition of the patients

Clinic grouping	Category	Number	Male	Female	Average age
Hypocortisolism	CD	107	38	69	39.5
	AIMAH	22	10	12	41.8
	EAAH	19	12	7	38.4
	PPNAH	4	2	2	27.2
Aldosteronism	IHA	28	12	16	44.0
Total		180	74	106	40.1

age 41.5) and 106 females (59%, average age 39.1). All patients postoperative pathology reports supported the diagnoses of adrenal cortical hyperplasia. Of all patients in the group, 152 had hypocortisolism with symptoms like central obesity, sanguine appearance and metabolic disorders, while 28 others had hyperaldosteronism with hypertension and hypokalemia. Examination and laboratory test as follows were performed for all of the patients.

### General examination

Blood routine, blood biochemistry (electrolyte, blood sugar, renal and liver function, etc.), glucose tolerance (hypocortisolism patients only) and 24 h urine potassium (hyperaldosteronism patients only).

### Blood cortisol circadian rhythm

The patient had 2 blood tests (8:00 and 24:00) for blood cortisol levels in the same day. If the level at 24:00 was less than a half of that at 8:00, then the rhythm still exists; if more, the rhythm had disappeared.

### Twenty-four-hour urine free cortisol (24 h UFC)

The normal range 12.3~103.5 µg; blood adrenocorticotrophic hormone (ACTH): normal range 0~46 pg/ml. Low-dose dexamethasone suppression test (LDDST) and High-dose dexamethasone suppression test (HDDST).

### Standing and lying aldosterone test

Lying overnight with full diet in previous day, the patient had his blood drawn in bed at 8:00 in the morning before breakfast followed by 40 mg intramuscular Furosemide injection. Then the patient was asked to move around for 2 h and received another blood draw at 10:00 in standing position. Radioimmunoassay was

used to analyze the two samples of blood aldosterone (Ald), plasma renin activity (PRA), and angiotensin-II (AT-II) levels. The reference values are: lying position: Ald 8.6±3.75 ng/dL, PRA 0.42±0.37 ng/ml·h, AT-II 40.2±12.0 pg/ml; standing position: Ald 15.1±8.8 ng/dL, PRA 2.97±1.02 ng/ml·h, AT-II 85.3±30.0 pg/ml.

### Imaging examination

All patients were given plain and contrasted CT (slice thickness 3.75 mm) to both sides of adrenal glands.

### Surgical methods

The unilateral or bilateral adrenalectomy, including local excision of the lesions, subtotal excision and total excision.

## Results

### General condition

Of all 180 cortical hyperplasia patients, 152 had hypocortisolism (including 107 Cushing disease, 59%; 22 ectopic adrenocorticotropin adrenal hyperplasia [EAAH], 12%; 19 adrenocorticotropin independent macronodular adrenal hyperplasia [AIMAH], 11%; 4 primary pigmented nodular adrenocortical hyperplasia [PPNAH], 2%), and 28 had hyperaldosteronism (all shown as idiopathic hyperaldosteronism, 16%). patients' sex and age distribution was showed in **Table 1**.

Patients with CD, EAAH, PPNAH all had different levels of Cushing appearance. 59% (13/22) AIMAH patients had Cushing appearance, and 41% (9/22) had no apparent signs of central obesity and sanguine appearance. Hypertension rates in four groups are: CD 90% (96/107), AIMAH 82% (18/22), EAAH 100% (19/19), PPNAH 100% (4/4). Diabetes or glucose tolerance decrease rate are: CD 40% (43/107), AIMAH 41% (9/22), EAAH 63% (12/19), PPNAH 75% (3/4). All 28 IHA patients had hypertension, and 61% (17/28) had hypokalemia related hypodynamia and nocturia, etc.

### Laboratory examination

24 h UFC of four groups were: CD 95.2~535.7 µg (average 287.6 µg), AIMAH 24.8~808.2 µg

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**Table 2.** The incretionary laboratory examination result for all kinds of hypercortisolism patients

Category	24 h UFC >103.5 µg	ACTH		Circadian rhythm disappearance	Responded negative to LDDST	Responded negative to HDDST
		<5 pg/ml	>15 pg/ml			
CD	94% (101/107)	0% (0/107)	88% (94/107)	99% (102/103)	99% (101/102)	4% (4/102)
AIMAH	67% (14/21)	70% (14/20)	0% (0/20)	92% (11/12)	95% (19/20)	89% (16/18)
EAAH	95% (18/19)	0% (0/19)	100% (19/19)	100% (17/17)	100% (18/18)	94% (16/17)
PPNAH	100% (4/4)	0% (0/4)	0% (0/4)	100% (4/4)	100% (4/4)	100% (3/3)

Annotate: the number in bracket (positive/total).

**Table 3.** The laparoscopy management for the different adrenal hyperplasia

Category	Unilateral adrenal operation (123)		Bilateral adrenal operation (57)			Total
	Unilateral adrenalectomy	Lesions resection	Bilateral adrenalectomy	Total + subtotal	Bilateral subtotal	
CD	76	0	19	12	0	107
AIMAH	14	0	4	2	2	22
EAAH	4	0	15	0	0	19
PPNAH	3	0	1	0	0	4
IHA	5	21	0	2	0	28
Total	102	21	39	16	2	180

Note: Annotate: total + subtotal = adrenalectomy of one side and subtotal resection adrenal of the other side.

(average 307.9 µg), EAAH 102.5~3127.0 µg (average 852.5 µg), PPNAH 243.8~1124.6 µg (average 564.3 µg); the proportions of patients who had their 24 h UFC increased were 94%, 67%, 95% and 100% respectively; cortisol circadian rhythm disappearance rate were 99%, 92%, 100%, and 100%. AIMAH and PPNAH patients responded negative to both LDDST and HDDST. Patients with CD were all suppressible, and most patients with EAAH were insuppressible by HDDST (**Table 2**). Seventeen out of all 28 IHA patients had hypokalemia (<3.5 mmol/L), while the blood potassium level of the group ranged from 2.1~3.9 mmol/L (average 3.1 mmol/L). Eighteen patients had 24 h urine potassium tests. The results showed 83% (15/18) increases. All 28 patients had standing and lying aldosterone tests. The results were: lying PRA 0.1~0.5 ng/ml/h (average 0.2 ng/ml/h), standing PRA 0.1~1.3 ng/ml/h (average 0.5 ng/ml/h); lying Ald 10~34 ng/dL (average 19 ng/dL), standing Ald 24~46 ng/dL (average 33 ng/dL).

### CT imaging

All patients were given CT thin scanings to both adrenal glands. The results showed enlargements in the affected side. Among

which, hypercortisolism group included 98% (149/152) patients with both sides affected (shown as different levels of enlargements in the volume of the glands). CD and EAAH patients had similar manifestations which was relatively even thickening of both adrenal glands, while PPNAH group had no obvious thickening and AIMAHs showed unsymmetrical nodularization of various size. IHA patients were mostly unilateral (75%, 21/28). Their CT scans showed unilateral adenomatous nodularization.

### Therapy and follow-up

As shown in **Table 3**, all 180 patients received surgical treatments by laparoscopy (). Among them, 123 (68%) only had surgery in one of the adrenal glands. The 102 hypercortisolism patients' had unilateral adrenalectomy, and their 24 h UFC one week after the surgery were: CD 56.2~233.5 µg (average 157.4 µg), AIMAH 22.5~418.5 µg (average 117.9 µg), EAAH 116.5~1137.0 µg (average 756.7 µg), PPNAH 124.6~422.6 µg (average 164.3 µg). The 21 IHA patients had local lesion excision under the preoperative diagnoses of adenoma. Eight (38%) patients' postoperative blood pressure returned normal, while 13 (62%) others' though

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dropped to some extent (95~105/150~170 mmHg), but were still above normal threshold. Fifty-seven others had surgery in both adrenal glands. Among them, 39 had bilateral total excision with hormone supplements after the surgery; 16 had total excision in one side and subtotal excision in the other (14 hypercortisolism patients whose 24 h UFC were 12.8~98.5  $\mu\text{g}$  [average 77.6  $\mu\text{g}$ ] one week after surgery; 2 IHA patients regained normal blood pressure); 2 AIMAH patients had bilateral subtotal excision and their 24 h UFC returned normal after the surgery. All bilateral adrenalectomies were given at twice. When to have the second surgery depended on the kind of disease the patient had. EAAH patients were usually more severe, so surgery to the second adrenal gland were given 2 weeks later, while CD and AIMAH patients mostly had the second surgery 3 months after the first one.

Altogether, 106 (59%) received follow up studies lasting from 4~158 months (average 32 months). Among them there are 93 hypercortisolism patients. Their Cushing symptoms were relieved in various degree (bilateral total adrenalectomy group were given HRT). No Nelson syndrome was found in follow-up studies. Thirteen patients from IHA group who had local lesion excision were followed up. Two of them were able to maintain normal blood pressure, while 11 others though had their blood pressure dropped, but still needed to stick to p.o. antisterone or other antihypertensives.

### Discussion

A normal adrenal gland is flat in shape, with the dimensions of 4~6×2~3×0.3~0.6 (cm). Left adrenal glands are usually a little bigger than right ones. Adrenal hyperplasia is the enlargement of the adrenal gland caused by increased number of parenchymal cells. This enlargement could be either diffuse or nodular. Diffuse hyperplasia is commonly seen in congenital adrenal cortical hyperplasia, pituitary or ectopic ACTH hypersecretion [9, 10]. Nodular hyperplasia is mostly found with multiple outbreak, sometimes with sporadic as well. The distinguishable characteristics that tell a sporadic nodular hyperplasia from an adenoma is that, in a sporadic nodular hyperplasia, there is no envelope capsuling the node, and hyperplastic malformation could be found in either homo- or counter-lateral, or both adrenal glands.

According to the size of the node, nodular hyperplasia could be categorized into macronodular hyperplasia and micronodular hyperplasia. Other adrenal hyperplasias include pigmented adrenal hyperplasia and lipid adrenal hyperplasia, etc.

Anatomically, adrenal hyperplasia could be categorized into the following three pathological types: adrenal cortical hyperplasia (ACH), adrenal medullar hyperplasia (AMH), and adrenal cortical & medullar hyperplasia (ACMH). Among them, ACH is the most common seen one. Its main manifestations include increased secretion of cortisol, aldosterone, and sex hormone.

Adrenal cortex is regulated by the hypothalamic-pituitary-adrenal axis. Its hyperplasia could be either secondary to certain hypothalamic-pituitary disease, or primarily started in the adrenal gland. Thus ACH could be further categorized into secondary and primary hyperplasia. The former one mainly includes CD, EAAH of hypercortisolism, and IHA of primary hyperaldosteronism. Its main pathological manifestation is bilateral diffuse adrenal hyperplasia. Some may also lead to nodular hyperplasia at late stage. The latter one mainly includes AIMAH and PPNAH, whose main manifestation is nodular hyperplasia [11].

The accurate diagnosis of ACH includes qualitative diagnosis and locative diagnosis, and it's highly significant in instructing treatments. The mission of qualitative diagnosis is mainly to make sure if the patient has hypercortisolism or hyperaldosteronism based on clinical manifestations and endocrinological exams. Different hormones sometimes could result in same clinical manifestations, e.g., hypertension, abnormal glucose tolerance, hypokalemia, etc. Thus, endocrinological exams, especially the subgroups for hypercortisolism, become the most important evidence. Blood ACTH level could help the preliminary differentiation between CD & EAAH and AIMAH & PPNAH [12]. To further differentiate CD from EAAH is relatively easy. However the differential diagnosis between AIMAH and PPNAH is very difficult. PPNAH is a very rare congenital disease [13]. It starts early in life, produces little clinical symptoms, shows mainly as micronodular hyperplasia, develops in long course, and is hard to be clearly diagnosed before surgery. The 4 cases of PPNAH in this group are all diag-

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nosed based on postoperative pathology reports.

Locative diagnosis is to find out if the focus is in the pituitary gland, the adrenal gland, or ectopic endocrine tumor based on HDDST and imaging exams done to the pituitary gland, the adrenal gland, and other related positions. Nuclide scanning is also highly significant in both locative and qualitative diagnosis of some diseases. Among all exams, CT thin scanning of the adrenal gland is the most important one. It's the major basis in determining the level of hyperplasia, type of disease and possible surgical plans. Normally, adrenal hyperplasia is bilateral. But among all 28 IHA patients in this group, only 7 are bilateral. Twenty-one others are unilateral. An explanation to that could be the 21 cases were first diagnosed with aldosterone-producing adenoma, but proved to be nodular hyperplasia by postoperative pathology reports.

Hypersecretion of hormones caused by adrenal hyperplasia may give rise to metabolic disorder, which could secondarily lead to various diseases. For example: hyperaldosteronism may cause pathological obesity, insulin resistance and abnormal lipid metabolism; hypertension, hypercoagulable state may cause changes in morphology and function of ventricles, which will increase risks of cardiovascular diseases [14]. Besides, diseases such as osteoporosis, mental disorder, growth hormone deficiency, sexual dysfunction and hypothyroidism are all closely related to hormone disorders. The 5-year survival rate of patients with untreated Cushing Syndrome (mainly CD) is as low as 50% [15]. Causes of death mainly include infection and cardiovascular accidents. However, successful surgery can increase their 5-year survival rate to 70% [16].

The surgical purpose of adrenalectomy is to directly correct the over-secretion of adrenalin, thus cut off all succedent pathological process thereafter. But the problem is that, adrenal hyperplasia often happens to both sides, it's very unlikely that a cure could be achieved unless a bilateral adrenalectomy is administered. Also a bilateral adrenalectomy will force a patient into lifetime hormone replacement therapy (HRT) and disappearance of the negative feedback regulation of pituitary adrenal axis which may bring Addison Crisis to 20~32%

patients. Therefore, whether or not a patient should be given the surgery requires careful consideration.

Patients with CD and EAAH should first be treated of the primary disease. An adrenalectomy should be attempted only when, all treatments for the pituitary gland and ectopic tumor end up in failure. Our experience shows that unilateral adrenalectomy could be the first choice in treating CD patients. Most of them report relief of symptoms after the surgery. This way, patient could avoid HRT, and has no risk of having Nelson Syndrome. When the symptom deteriorates, another surgery could be performed to cut the other adrenal gland, totally or subtotally. Some patients who have both of their adrenal glands taken out had tried subcutaneous implantation or sub-epigastric transplantation of the adrenal gland. But none of these attempts turned out to be ideal. As for subtotal adrenalectomy, it's hard enough to predict how much of the gland should be reserved, let alone the possibility that the remained part proliferate again in the high concentration of ACTH. So, careful consideration must be made before the surgery is performed. For patients with EAAH, as they were general more severe than CD patients, and has no risk of Nelson Syndrome, we chose bilateral total adrenalectomy for most of them. To some patients with less severe symptoms, unilateral adrenalectomy was also performed first to alleviate hypercortisolemia, but still the another total adrenalectomy had to be done sooner or later after the first one. In addition, as EAAH patients are usually in very critical conditions, surgeries to the second adrenal gland given at least two weeks after the one. Subtotal adrenalectomy is proved to produce a high recurrence rate of adrenal hyperplasia, so it's not recommended on most occasions.

As AIMAH is relatively autonomous secretory [17], its treatment and operation plan should be highly personalized. For most patients, excision could be done first to the more hyperplastic side. Plan of surgery on the counter-lateral gland should be made based on the postoperative observation. Statistics in our hospital shows that, unilateral adrenalectomy could ease Cushing Syndrome and hypertension in most AIMAH patients. Diabetic patients with Cushing Syndrome also feel released after the same surgery. If normal adrenal tissues are

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found in nodular hyperplastic tissues, total adrenalectomy to one side followed by subtotal adrenalectomy to the other side, or subtotal adrenalectomy to both sides, could be considered. The advantages of these methods are that, only the hyperplastic nodes are taken out, thus Cushing Syndrome is relieved, and the function of the adrenal glands is preserved. Bilateral total adrenalectomy could be performed only when the patient is suffering from extremely severe symptoms caused by massive bilateral nodular hyperplasia and no well functional adrenal tissues is possible to be preserved.

PPNAH is a very rare Cushing Syndrome in clinical practice. It's very hard to give preoperative diagnosis. Accurate diagnoses usually come from postoperative pathology reports. All 4 cases in this group were preoperatively suspected bilateral nodular hyperplasia with tiny and irregular nodes. Unilateral adrenalectomies were performed to all of them. Three patients experienced significant relief from their symptoms. The unreleased patient later had total excision of the other adrenal gland. As our hospital has limited number of cases, we haven't got much experience in this field. According to the literatures we've reviewed, bilateral adrenalectomy is the best treatment for this disease [13].

IHA accounts for 60~70% of primary hyperaldosteronism (18). Normally, medication should be administered shortly after accurate diagnosis. Among all 28 cases in this group, 21 could be excluded of the possibility of unilateral aldosterone-producing adenoma through preoperative qualitative and locative diagnosis. Unilateral adrenalectomies were performed to the 21 patients as reported before [19, 20]. Postoperative pathology reported cortical hyperplasia. Seven cases with lesions on both sides were preoperatively diagnosed IHA. As the outcome of medication is not satisfactory, adrenalectomies were done to the more severe side. In spite of that, no optimistic change is seen in two of the patients. They were again given subtotal adrenalectomy on the left adrenal gland. We consider the following situations could be indications of surgery for IHA patients: IHA can't be differentiate from aldosterone-producing adenoma; patients has renal dysfunction; high dose of antisterone is not effective in controlling blood pressure and blood potassium level

or has caused severe side effects such as sex hormone unbalance [21, 22].

In general, this group contains 157 (87%) patients with adrenal hyperplasia. Unilateral adrenalectomy is considered the first choice in treatments. Among them, 55 of them was performed total or subtotal adrenalectomy to the counter-lateral adrenal gland. Therefore, we believe that unilateral total adrenalectomy is the primary surgical treatment for adrenal hyperplastic diseases. Whether the other adrenal gland is to be kept, partly, or even totally, excised, should be determined based on the actual type of disease and clinical observation to achieve satisfactory outcome.

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None.

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