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ORIGINAL ARTICLE

Analysis of various etiologies of hypertension in patients hospitalized in the endocrinology division

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Abstract This research aimed to analyze the clinical data of various etiologies of hypertension in patients hospitalized in the Endocrinology Division. The differences between essential and secondary hypertension were examined to provide a basis for clinical differential diagnosis. The data from all the inpatients with hypertension of unknown origin admitted in the Endocrinology Division of the First Affiliated Hospital of the Zhejiang University School of Medicine from January 2001 to May 2011 were reviewed. The patients were classified into either essential or secondary hypertensive groups. The differentiating parameters of these forms of hypertension were analyzed using the one-factor and multi-factor logistic regression analysis. A total of 1,001 cases were selected in which 346 cases (34.6%) were essential hypertensive and 655 cases (65.4%) were secondary hypertensive. Adrenal hypertension was the primary cause of secondary hypertension, followed by renal artery, central, psychogenic, and renal hypertension as well as others that have not been classified systematically. Using one-factor analysis, significant differences were found among duration of hypertension, age, the onset age, family history of hypertension, diastolic pressure on admission, Cushing syndrome, body mass index (BMI), urine protein, serum creatinine, orthostatic aldosterone, ratio of orthostatic aldosterone to renin activity, incidence of fatty liver displayed by type-B ultrasound, and computed tomography adrenal masses incidence ($P < 0.05$). Multi-factor regression analysis showed that family history of hypertension (OR = 7.196) and BMI above the normal range (OR = 15.124) were the independent factors that predicted essential hypertension, but failed to determine any other valid predictors of secondary causes except adrenal masses (OR = 10.114), orthostatic aldosterone value >200 pg/ml (OR = 9.742), and a ratio of orthostatic aldosterone and renin activity >40 (OR = 4.723).

Keywords Essential hypertension · Secondary hypertension · Endocrinology · Cause analysis

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Introduction

The continuously changing living standards and dietary patterns have led to the gradual increase in the prevalence rate of hypertension. It has been estimated that up to 1.5 billion people worldwide could be hypertensive by 2025 [1]. Secondary hypertension is a type of hypertension with underlying potentially correctable causes. Approximately, 5–10% of all cases of hypertension in adults have secondary causes. Similarly, Omura et al. [2] found that 9.1% of all the subjects they studied had hypertension with diagnosable causes. Additionally, with the development of endocrine diagnosis techniques and the deeper understanding of adrenal disease, the prevalence rate of secondary hypertension, mainly adrenal hypertension, has remarkably increased [3]. If secondary hypertension can be examined clinically with the necessary laboratory tests and its causes can be diagnosed as early as possible, the efficacy of treatment can be increased and medical costs can be reduced. Thus, a high index of detection and appropriate investigation are required for diagnosis. This research aimed to analyze the clinical data of patients with hypertension of unknown origin (i.e., patients who had been

suspected of having some disease and whose elevated blood pressures indicated that disease) hospitalized in the Endocrinology Division of the First Affiliated Hospital of the Zhejiang University School of Medicine from January 2001 to May 2011 in an attempt to explore the differences between essential and secondary hypertension and provide a basis for clinical differential diagnosis.

Patients and methods

Subjects

Regression analysis was conducted on patients with hypertension of unknown origin (i.e., those suspected of having secondary hypertension) who were hospitalized in the Endocrinology Division. The diagnostic criteria for adult hypertension were recommended by the European Society of Hypertension and the European Society of Cardiology.

Admission into the Endocrinology Unit for hypertension was limited to patients with: (1) new or sudden onset before the age of 40; or (2) nausea or vomiting, dizziness, palpitation, and flushing; or (3) physical signs or a specific body habitus (e.g., central obesity, purple striae, *Acanthosis nigricans*, abdominal bruits, etc.); or marked changes in body weight; or (4) resistant or refractory hypertension by three or more kinds of antihypertensive drugs; or (5) BP $>$ 180/100 mmHg on first examination; or (6) hypokalaemia; or (7) worsening renal function or severe end organ disease; or (8) presence of adrenal masses. Excluded from the unit were patients with (1) established primary hypertension, (2) suspected highly of essential hypertension in clinic, and (3) known diagnostic causes.

Patients who conformed to these standards and who had complete medical records, including general information, laboratory tests, and accessory and complication examinations referred to in this research method, were chosen to be subjects of the study. After extensive examinations, the patients were divided into essential and secondary hypertensive groups based on the cause of hypertension.

Research method

A computerized search of the medical records of inpatient subjects was performed, and data were initially screened to obtain all cases with hypertension of unknown origin in the admitting diagnosis. The following parameters were regression-analyzed.

General information

Gender, age, age of onset, duration of hypertension, family history of hypertension, blood pressure, body mass index (BMI), Cushing syndrome (obesity or weight gain, facial plethora, rounded face, decreased libido, thin skin, and menstrual irregularity), *Acanthosis nigricans*, purple striae, and drug history.

Laboratory tests

Routine blood test, routine urine test, triglyceride, cholesterol, low-density lipoprotein, very low-density lipoprotein, high-density lipoprotein, aspartate aminotransferase, alanine aminotransferase, urea nitrogen, serum creatinine, blood uric acid, blood electrolytes, blood sugar–blood insulin (fasting, 2-h postprandial), blood renin–angiotensin–aldosterone (lying and orthostatic positions), blood adrenocorticotropic hormone (ACTH)–blood corticosteroid (8 am, 4 pm, 0 am) thyronine–triiodothyronine, blood growth hormone, blood and urine adrenalin–norepinephrine, antinuclear antibody, anti-neutrophil cytoplasmic antibodies, and 24-h urine albumin, saline load test, fludrocortisone suppression test, 1-mg overnight dexamethasone suppression test, and 8-mg overnight dexamethasone suppression test.

Examination

Ambulatory blood pressure monitoring, electrocardiogram, ultrasound diagnosis of heart disease, adrenal gland or abdomen or chest computed tomography (CT), renal artery computed tomographic angiography (CTA), hypophysis magnetic resonance imaging, aorta-abdominal aorta type-B ultrasound, or CTA.

Complications

Fatty liver (liver ultrasonic diagnosis), diabetics, cerebrovascular accidents, myocardial infarct, and left ventricular hypertrophy (heart ultrasound diagnosis).

The diagnostic criteria for primary aldosteronism included high plasma aldosterone concentration (PAC), low plasma renin activity (PRA), a PAC/PRA ratio higher than 40 (PAC in ng/dl and PRA in ng/ml per hour), a positive saline load test, accompanied or not with hypertension, unexplained hypokalaemia, adrenal unilateral adenoma, or bilateral hyperplasia [4–6]. The diagnosis for pheochromocytoma included high levels (mostly four times higher than the normal limit) of plasma and/or urine metanephrines (metanephrines and normetanephrines), and/or the presence of masses in anatomic imaging (abdomen, chest) [7, 8]. The diagnostic criteria for Cushing's disease were increased total and free-serum cortisol levels, high levels of ACTH, high cortisol levels even after 1-mg dexamethasone overnight suppression test, and the presence of pituitary microadenoma [9, 10]. The diagnostic

criteria for hypercortisolism were cortisol levels that remained high even after 1- and 8-mg dexamethasone overnight suppression tests, inhibited plasma ACTH, and the presence of adrenal adenoma or carcinoma or hyperplasia [9, 10]. The diagnostic criteria for renal artery stenosis included hypertension and/or ischemic nephropathy and/or proteinuria, and activation of the renin–angiotensin–aldosterone system. Patients were screened by renal artery CTA and cases were confirmed by digital subtraction angiography [11]. Congenital adrenal hyperplasia was confirmed by genetic testing. Diagnoses of stress or neurosis were made by a psychiatrist after ruling out secondary causes, and psychological counseling was performed. Diagnoses of anxiety neurosis were made by two psychiatrists, and prescriptions from the psychiatric department were obtained when necessary.

Statistical method

Data were processed using the SPSS 11.5 software package. Measurement data in normal distribution were expressed by mean ± standard deviation ($x \pm s$), and the two groups were compared using independent sample t test. Enumeration data were shown by case number or proportion, whereas χ^2 test was employed to compare the two groups. One-factor ANOVA was adopted in the mean test of three groups or more. The median was obtained to show the mean for non-normal distribution. The value in parentheses was the interquartile range. If the measurement data were not consistent with normal distribution and (or) variance was not homogeneous, the rank sum test was adopted. The risk factors of primary hypertension were screened with the χ^2 test, and then the risk factors were judged by logistic regression analysis. During the regression calculation, the exclusion criteria were limited to data that were more than 0.1 with $P < 0.05$ and statistically significant differences.

Results

General information

A total of 1,001 cases were included in the research. There were 346 cases of essential hypertension (34.6%) with 247 male and 99 female, with the male to female ratio of 2.49:1 and an age range between 27 and 57 years old (44.3 ± 3.9). There were 655 cases of secondary hypertension (65.4%) with 395 male and 260 female, with the male to female ratio of 1.52:1 and an age range between 17 and 54 years old (37.8 ± 8.6). The ages between the two groups differed statistically ($P < 0.001$).

The proportions of patients' ages were 3.2, 26.4, 37.1, 24.4, and 8.9%, corresponding to 10–20, 21–30, 31–40, 41–50, and 51–60 years old, respectively.

Cause of secondary hypertension

In the 655 secondary hypertensive cases, adrenal hypertension was the primary cause of secondary hypertension (Figs. 1, 2, 3, and 4), followed by renal artery, then central, psychogenic, and renal hypertension, among other causes without systematic classification. The specific causes are shown in Table 1.

Characteristics of essential and secondary hypertensive patients

Blood pressure upon admission

The systolic pressures of the two groups on admission were 158 ± 21 versus 154 ± 18 mmHg, with a statistically nonsignificant difference ($t = 0.423$, $P = 0.724$). The diastolic pressure of the secondary hypertensive group (100 ± 21 mmHg) was significantly higher than that of the essential hypertensive group (95 ± 17 mmHg) ($t = 3.762$, $P = 0.001$).

Comparison of general information of essential and secondary hypertensive patients

Using the one-factor analysis, a significant difference among the duration of hypertension, age, age of illness onset, family history of hypertension, diastolic pressure in admission, Cushing syndrome, BMI, urine protein, serum creatinine, orthostatic aldosterone, the ratio of orthostatic aldosterone and renin activity, the incidence of fatty liver displayed by type-B ultrasound, and CT adrenal masses incidence was determined ($P < 0.05$). The details are shown in Table 2.

Multi-factor regression analysis showed that family history of hypertension (OR = 7.196) and BMI above the normal range (OR = 15.124) were the independent factors that predicted essential hypertension, whereas adrenal masses (OR = 10.114) indicated secondary hypertension. Orthostatic aldosterone values of >200 pg/ml and a ratio of orthostatic aldosterone to renin activity of >40 appear to be useful predictors of secondary hypertension caused by primary aldosteronism (Table 3).

Discussion

Hypertension is mainly divided into essential and secondary hypertension, markedly different according to pathogenesis,

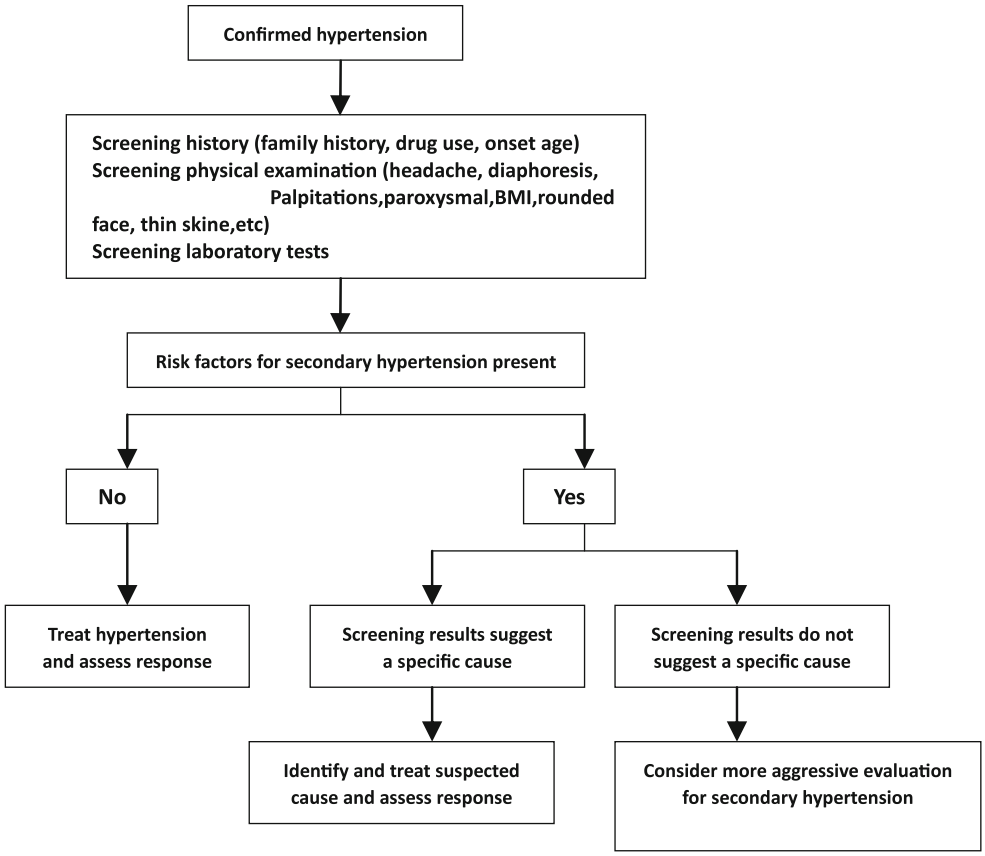

Fig. 1 General strategy for diagnosing a secondary cause of hypertension

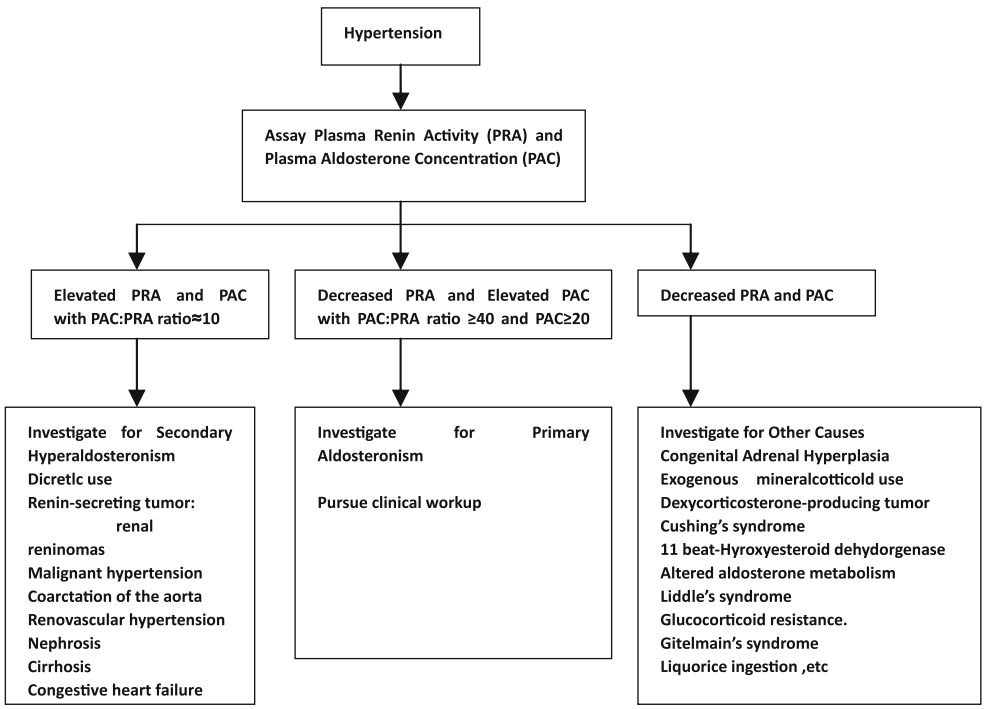

Fig. 2 Laboratory algorithm demonstrating use of plasma renin and aldosterone levels to ascertain cause of hyperaldosteronism. Note that suppressed renin levels in conjunction with elevated aldosterone levels suggest primary hyperaldosteronism

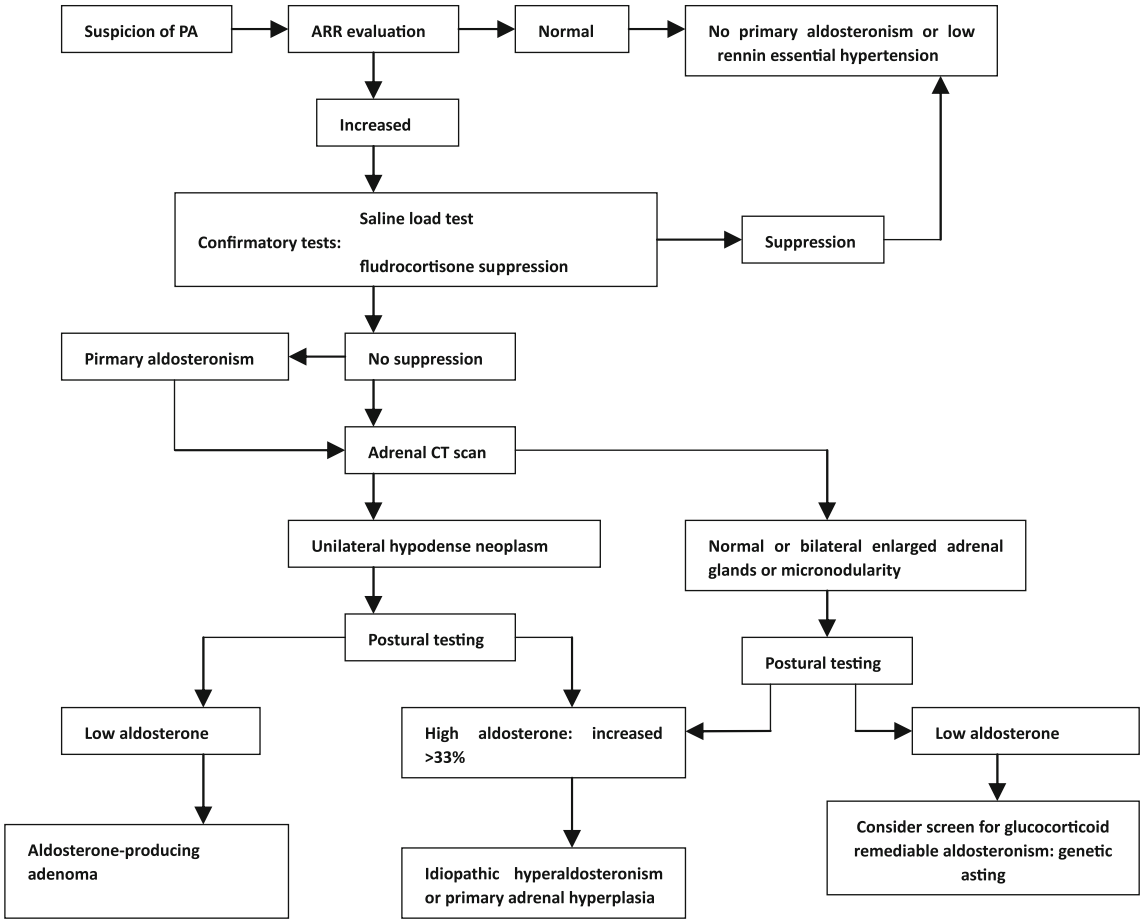

Fig. 3 Algorithm for differential diagnosis between primary hyperaldosteronism and bilateral adrenal hyperplasia. *PA* primary aldosteronism, *ARR* aldosterone/renin ratio

treatment, and clinical prognosis [12]. In previous epidemiological surveys, secondary hypertension accounts for 5–10% of incidences of hypertension. With the development of diagnosis techniques, the prevalence rate of secondary hypertension increases gradually [13]. In this research, secondary hypertensive patients comprised majority of the inpatients with hypertension of unknown origin. Notably, adrenal hypertension accounted for 53.82% (543–1,009), probably related to the samples of the inpatients that were chosen (in the outpatient services, some essential hypertensive patients had been excluded). A slight difference between the clinical syndromes and laboratory tests of essential and secondary hypertension in the Endocrinology Division was determined using case analysis. Multi-factor regression analysis shows that a family history of hypertension and BMI above the normal range indicate an essential hypertension, whereas adrenal masses, as well as a ratio of orthostatic aldosterone and renin activity >40, suggest secondary hypertension. The research results aid in differentiating diagnosis of hypertension.

This research proves that positive family history of hypertension is a risk factor for essential hypertension. Essential hypertension is a disease caused by the mutual effects of environmental and genetic factors, in which genetic susceptibility plays an important role [14, 15]. In JAMA surveys, patients with one hypertensive parent had a prevalence rate 1.5 times higher than that of patients without a family history of hypertension, and patients with parents who were both hypertensive had a prevalence rate two to three times higher than those without [16]. Similar conclusions were found by Goldstein et al. [17]. In our study, essential hypertensive patients who had a family history of positive hypertension accounted for 87.0%. Shirakawa et al. [18] also discovered that essential hypertensive patients who were more than 50 years old and had a family history of hypertension accounted for 59%.

This research found that BMI greater than the normal range was an independent factor of essential hypertension, conforming to previous research results. Insulin resistance always exists [19] in patients with high BMI and is accompanied by fatty liver or combined with metabolic

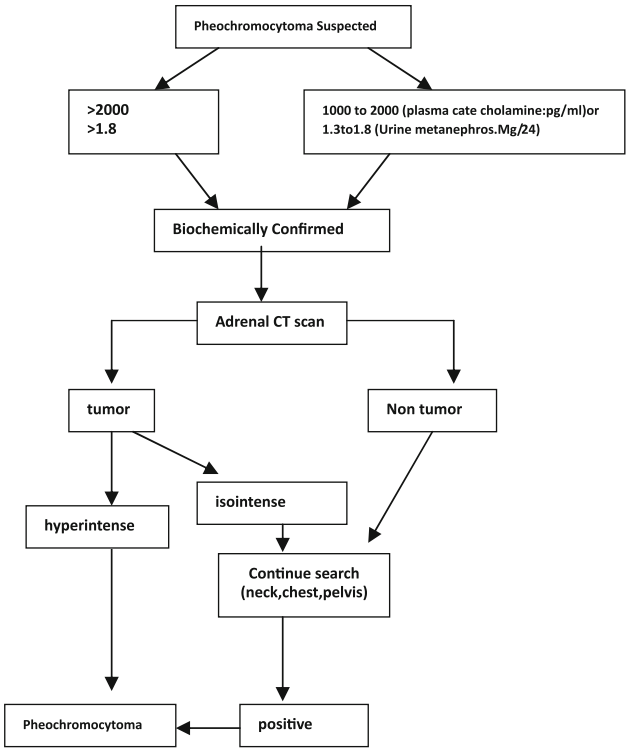

Fig. 4 Algorithm for the diagnosis and localization of pheochromocytoma

syndrome. This condition results in an increase in blood pressure probably because insulin resistance changes the cellular activity for the Na^+–K^+–ATP enzyme, increases the content of Na^+ in cells, stimulates sympathetic activity, raises kidney's reabsorption of water and Na, increases sensitivity to salt of blood pressure, stimulates growth factor (especially in vascular smooth muscle), and increases the secretion of endothelin [20, 21].

Adrenal masses are major risk factors of secondary hypertension, probably related to the samples selected. As shown in the results, 81.78% of the secondary hypertensive patients had adrenal hypertension, most of which were primary aldosteronism, pheochromocytoma, and cortisol adenoma. These diseases are commonly presented to be adrenal masses in imaging [22]. In addition, there were 372 patients with cases of secondary hypertension showing high blood pressure before the occurrence of adrenal masses and who had undergone once to thrice imaging procedures within a 24-month interval when suspected of having secondary hypertension. Thereafter, adrenal masses were found 0.33–10 years later. Then, 162 cases were initially found to be adrenal masses during medical inspection, then diagnosed as hypertension on follow-up (0.92–4 years), and then finally diagnosed to be adrenal hypertension. The adrenal glands are the most likely culprits of endocrine or secondary hypertension, because either of an excessive production of mineralocorticoids, catecholamines or glucocorticoids. Comlekci et al. [23] also reported that the prevalence of hypertension in patients with adrenal incidentaloma was 54.9%, most of the adrenal adenomas were non-functioning (73.5%), subclinical Cushing syndrome was detected in 12.5%, which were similar with our conclusions.

This study found that orthostatic aldosterone value >200 pg/ml, as well as a ratio of orthostatic blood aldosterone and renin activity >40, indicates secondary hypertension.

Table 1 Analysis of the causes of secondary hypertension

Cause	Mean age	Case no.	Percent
Adrenal	38.0	543	82.90
Primary hyperaldosteronism	38.5	341	52.06
Aldosterone-producing adenoma (APA)	38.7	270	41.22
Idiopathic hyperaldosteronism (IHA)	37.8	65	9.92
Glucocorticoid-remediable aldosteronism (GRA)[a]	35.2	6	0.92
Hypercortisolism	35.3	95	14.50
Cortical adenoma	35.5	72	10.99
Cortical carcinoma	34.1	20	3.05
ACTH-independent bilateral macronodular adrenal hyperplasia	38.7	3	0.46
Pheochromocytoma	40.1	94	14.35
Congenital adrenal hyperplasia (CAH)	30.1	10	1.53
21-Hydroxylase deficiency	31.2	5	0.76
11β-Hydroxylase deficiency	19.3	3	0.45
17α-Hydroxylase deficiency	43.5	2	0.30
Teratoma	24	1	0.15
Malignant accessory nerve tumor	50	1	0.15
Ganglion cell neurofibroma	31	1	0.15
Renal artery	32.3	44	6.72
Renal artery stenosis	32.9	39	5.95
Accessory renal artery stenosis	27.2	5	0.76
Central	38.4	28	4.27
Cushing disease	34.9	20	3.05
Somatotropinoma	47.1	8	1.22
Psychogenic	40.2	19	2.90
Stress	37.7	13	1.98
Neurosis	45.5	6	0.92
Renal	62.2	5	0.76
Chronic nephritis	58.7	3	0.45
Gouty nephropathy	67.5	2	0.30
Other unclassified types	35.4	16	2.44
Drugs (contraceptive, diet pills, and liquorice)	29.5	8	1.22
Anxiety neurosis	40.2	6	0.92
Schizophrenia	45	2	0.30
Total	37.8	655	100

[a] Two in six patients underwent genetic testing; others underwent fludrocortisone suppression tests

Table 2 Comparison of the clinical performance and laboratory parameters of essential and secondary hypertension

	Essential hypertension (346 cases)	Secondary hypertension (655 cases)	*T* value or χ^2 value	*P*
Age of onset (years)	42.1 ± 2.1	35.7 ± 8.3	10.123	<0.001
Age (years)	44. 3 ± 3.9	37.8 ± 8. 6	9.171	<0.001
Duration of hypertension (years)	3.5 (0.1–10.4)	2.5 (0.1–3.7)	7.528	<0.001
Family history	301 (87.0%)	257 (39.4%)	42.316	<0.001
Diastolic pressure (mmHg)	95 ± 17	100 ± 21	3.762	<0.05
Cushing syndrome	1 (0.3%)	69 (10.5%)	32.967[a]	<0.001
BMI (kg/m^2)	27.2 ± 3.4	24.7 ± 4.6	9.747	<0.001
Urinary albumin (mg/day)	21 ± 10	34 ± 14	3.154	0.001
Serum creatinine (μmol/l)	83.6 ± 12.0	97.8 ± 15.7	5.124	<0.05
Orthostatic blood aldosterone (pg/ml)	107.3 ± 22.0	273.1 ± 48.0	23.789	<0.001
Ratio of orthostatic aldosterone to renin activity >40	2(0.6%)	307 (46.9%)	55.429[a]	<0.001
Fatty liver	227 (65.6%)	182 (27.8%)	16.754[a]	<0.001
Adrenal masses	19 (5.5%)	562 (85.8%)	42.145[a]	<0.001
Diabetics	47 (13.6%)	76 (11.6%)	0.448[a]	0.092

[a] χ^2 test, the rest are results of *t* test or rank sum test

Table 3 Results of multi-factor logistic analysis of inpatient subjects with hypertension of unknown origin

Parameter	*B* value	Standard error	Wald χ^2	df	*P*	OR	95% Credibility interval
Family history	2.269	0.885	4.752	1	0.001	7.196	0.295–99.147
BMI	2.952	0.998	8.742	1	0.001	15.124	3.256–114.721
Adrenal masses	−3.012	1.002	9.876	1	0.029	10.114	1.065–89.156
Orthostatic blood aldosterone value	−4.150	1.520	5.291	1	0.001	9.742	1.002–75.452
Ratio of orthostatic aldosterone and renin activity >40	−3.145	0.968	3.241	1	0.001	4.723	1.456–106.823

In essential hypertension, the plasma renin activity and aldosterone value are largely within the normal range. However, 25% of patients exhibited a decrease in plasma renin activity, whereas 14% of the patients had blood aldosterone value >200 pg/ml. Two cases had orthostatic blood aldosterone/renin ratio >40, probably related to the antihypertensive drugs taken before examination. In secondary hypertensive patients, primary aldosteronism may present high plasma aldosterone, as well as a ratio of orthostatic blood aldosterone and renin activity >40, caused by independent secretion of aldosterone and inhibited renin activity [24–26]. Renal artery stenosis leads to significant inhibition of plasma renin activity and an increase in secondary aldosterone because of renal ischemia [27]. Considering that the two types of hypertension consist of approximately 60% of secondary hypertension and 51% of patients with primary aldosteronism, the increased orthostatic aldosterone, as well as a ratio of orthostatic blood aldosterone and renin activity >40, emerges as the independent factor in judging secondary hypertension in our study.

The urinary albumin and serum creatinine of essential hypertensive patients are lower than those of secondary hypertensive patients. Although the multi-factor regression analysis demonstrates that the urinary albumin was not an independent factor, the increase in the urinary albumin and serum creatinine are still factors that predict secondary hypertension. The UKPDS [28] study had shown that compared with the normal albuminuria group, microalbuminuria group had higher diastolic blood pressure after excluding the significant differences in blood glucose and blood fat. Furthermore, only the increase in diastolic pressure differed statistically, indicating that the increase in diastolic pressure is closely linked with microalbuminuria. In this research, the diastolic pressure of the secondary hypertensive group is remarkably higher than that of the essential hypertensive group. Another cause of increased urinary albumin is the high percentage of primary aldosteronism in secondary hypertension. Sechi et al. [29] reported that aldosterone could cause cardiovascular and renal tissue damage in the form of inappropriate salt status

by activating mineralocorticoid receptors, which may result from increased oxidative stress and changes in the intracellular redox potential. Therefore, the urinary albumin of the secondary hypertensive group would be further increased, leading to a more obvious renal damage such as an increase in serum creatinine.

The limitations of our study include its retrospective design and suffer from potential selection bias, in that many patients included in the study were referred for adrenal mass, which could explain the higher proportion of APA. The test of adrenal vein sampling was not been performed and measurements of aldosterone renin ratio might have been potentially confounded by other antihypertensive medications even though, aside from verapamil or α-blockers, no hypotensive drugs were allowed for a 4-week period before the assay.

In summary, for clinically diagnosed hypertensive patients, a family history of hypertension and BMI greater than the normal range indicate the possibility of essential hypertension, whereas adrenal masses and orthostatic aldosterone value >200 pg/ml, as well as a ratio of orthostatic aldosterone and renin activity >40, show secondary hypertension, and then further examination is needed to identify and treat the primary disease.

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