Review

New advances in the diagnosis of primary aldosteronism

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Abstract

Primary aldosteronism (PA) is a common form of endocrine hypertension. The diagnostic process of PA includes a screening test, confirmatory test, and subtype classification. In this review, we have summarized the latest advances in the diagnosis of PA with regard to screening and confirmatory tests and provided some recommendations to improve clinical practice.

Keywords: Primary aldosteronism; Screening test; Confirmatory test

Introduction

Primary aldosteronism (PA) is a lesion of the zona glomerulosa of the adrenal cortex; this leads to the spontaneous secretion of aldosterone. PA is characterized by increased plasma aldosterone and suppressed renin. The main causes of PA include aldosterone-producing adenoma (APA), idiopathic hyperaldosteronism (IHA), unilateral adrenocortical hyperplasia, and familial hyperaldosteronism (FH). The process for diagnosing PA include screening test, confirmatory test, and subtype classification. PA was first reported by Conn in 1954 and was considered a rare disease, accounting for about 1% of patients with hypertension. However, further epidemiological investigations have confirmed that PA is one of the most common forms of secondary hypertension. In the past few years, tremendous advances had been made in the field of PA globally. However, some questions remain to be explored. In this paper, we have summarized the latest advances in the diagnosis of PA with regard to screening and confirmatory tests and provided some recommendations to guide clinical practice better.

Prevalence

Some studies have shown that PA accounts for 5%—10% of patients with hypertension. Although China still lacks a large-scale epidemiological survey of PA, a study in Singapore showed that PA accounts for at least 5% of Asian patients with hypertension. Therefore, it is speculated that among 266 million hypertensive patients in China, there are at least 13.3 million patients with PA; this indicates that PA is not a rare
disease. The prevalence of PA is as high as 20% in people with refractory hypertension. However, a study conducted by the Ruijin Hospital in Shanghai showed that the prevalence of PA was 7.1% in people with refractory hypertension.

An elevated plasma aldosterone concentration (PAC) in patients with PA has a detrimental effect, despite good blood pressure control. Consequently, the incidence of target-organ damage (e.g. cerebrovascular, cardiovascular, or kidney damage) is increased in patients with PA than in those with essential hypertension.

**Screening**

**Significance**

Despite the high prevalence of PA and its detrimental effects, the majority of high-risk populations with PA (e.g. those with refractory hypertension) have not been screened. The frequent misdiagnosis is due to unawareness or lack of screening for PA. Therefore, in the past, a large number of PA patients had been misdiagnosed as having essential hypertension. Many doctors still diagnose PA according to the criteria of hypertension with hypokalemia. In fact, serum potassium was normal in more than half of PA patients; the incidence of hypokalemia in IHA was only 17%. Conversely, if the screening test is completed, it would have to be followed by a confirmatory test, image examination, adrenal venous sampling (AVS), or surgery. This process can be complicated and costly. As such, some primary care physicians do not actively screen for PA. Even in some developed countries, the rate of diagnosing PA is only 1%—2% of patients with hypertension.

In addition, the low screening rate is also related to a variety of diagnostic criteria, including aldosterone-to-renin ratio (ARR) cutoffs. Therefore, it is necessary to improve the rate of screening in the high-risk population of PA. The Endocrine Society's practice guidelines emphasized that it is obligatory to screen all high-risk populations of PA, and that the huge burden on society caused by PA should not be ignored. Recently, it was postulated that the diagnostic algorithm should be simplified. The screening test should be performed at least once for every patient with hypertension.

**Screening method**

Since screening for PA was proposed by Hiramatsu et al in 1981, the ARR has been widely accepted globally. Currently, the Endocrine Society's practice guidelines and the Chinese consensus of PA recommend that ARR should be used to screen for PA after the patient has been in the upright position for 2 hours (not recumbent). For patients who were tested positive on a screening test, a further confirmatory test is needed. The plasma renin activity (PRA) was determined by radioimmunoassay, a method to detect the conversion rate of angiotensin I from angiotensinogen and to measure the biological activity of renin. However, this method is affected by the concentration of angiotensinogen. Further, the measurement process is manual and can be affected by sample pretreatment, incubation time, pH, or other factors. It is also difficult to standardize. In addition, separate samples are needed for the detection of PAC and PRA which is time consuming. Therefore, based on the determination of PAC and PRA, using ARR as an indicator for PA, screening in clinical practice is greatly limited.

Recently, many hospitals had carried out automated chemiluminescence immunoassays for the direct determination of PAC and plasma renin concentration (PRC). This has many advantages, including not being affected by the concentration of angiotensinogen, simple sample processing and rapid detection, good stability and repeatability, and easy standardization. It is possible to gradually replace the use of the radioimmunoassay in the near future. In addition, the simultaneous determination of PAC and PRC in one blood sample is also beneficial for the rapid screening of outpatients. There have been many studies that have compared the diagnostic value of the two methods, showing that there is a good correlation between them. Therefore, the chemiluminescence method is recommended for the rapid determination of PAC and PRC, and the calculation of the ARR value is recommended for PA screening.

Although the liquid chromatography-tandem mass spectrometry (LC-MS) method has higher sensitivity and specificity, it is expected that it will not be commonly used in the future due to the expensive equipment and its cumbersome operation.

**Interpretation of results**

Currently, the optimal cutoff for the PA screening test has not been completely unanimously. The screening cutoff for the upright ARR recommended by the Endocrine Society's practices guidelines is 20—40 (ng/dl)/(ng/ml/h) when PRA is used or 2.4—4.9 (ng/dl)/(uIU/ml) when PRC is used. Our previous data showed that an upright PAC/PRC ratio of 4.3 (ng/dl)/(uIU/ml) as the best cutoff for PA...
screening; this was consistent with the cutoffs recom-
mended by the Endocrine Society's practice guide-
lines.\textsuperscript{14} Later, after increasing the sample size, it was 
found that if the cutoff decreased to $1.0\textendash 2.0$ (ng/dl)/ 
(uIU/ml), a higher sensitivity could be achieved.\textsuperscript{15} 
Recently, Young from the Mayo Clinic reported that a 
PAC $>10$ ng/dl and a PRA $<1.0$ ng/ml/h or a PRC 
below detection levels is a better cutoff.\textsuperscript{7} Based on data 
from the Chongqing Primary Aldosteronism Study 
(CONPASS), we found that a PAC/PRC ratio $>1.0$ (ng/ 
dl)/(uIU/ml) combined with a PAC $>10$ ng/dl, can 
achieve a diagnostic sensitivity of $>90\%$ (in press).

The measurement of PAC and PRC is also affected 
by factors such as antihypertensive drugs, serum po-
tassium concentration, posture, sodium intake, and the 
menstrual cycle. Medications used to treat hyperten-
sion can potentially cause false-negative testing results 
in patients with mild PA. However, there is almost no 
medication that can cause false-positive results. 
Therefore, if an ARR ratio is positive, antihypertensive 
drugs that may cause false-negative results (e.g. spi-
ronolactone and eplerenone) do not need to be dis-
continued for the confirmatory test or subtype 
classification with AVS.\textsuperscript{7}

In particular, the screening and confirmatory tests for 
PA depend largely on the accurate measurement of PAC 
and PRC or PRA; the measurement accuracy is crucial 
for clinical decision making. Each laboratory needs to 
establish a quality control system, including standard-
ized specimen pretreatment and units, inter-laboratory 
quality control, and external quality assessment.

**Confirmatory test**

**Significance**

A positive ARR result should always be followed by 
a suppression test to definitively confirm the diagnosis; 
however, there is one exception. If a patient with hy-
pertension has spontaneous hypokalemia with a PAC 
$>20$ ng/dl and a PRA $<1.0$ ng/ml/h (or a PRC below 
the detection level), the diagnosis of PA can be 
established; no confirmatory test is needed. Four 
confirmatory tests are recommended by the Endocrine 
Society's practice guidelines: the saline infusion test 
(SIT), captopril challenge test (CCT), fludrocortisone 
suppression test (FST), and oral sodium loading test.\textsuperscript{1} 
Some researchers believe that FST is more reliable 
and stable and is even regarded as the “golden stan-
dard” for diagnosing PA.\textsuperscript{16} However, fludrocortisone 
is not commercially available in some countries and re-
gions, and FST is cumbersome, time-consuming, and 
expensive; therefore, it is not routinely conducted in 
clinical practice. Currently, SIT and CCT are 
commonly used for the diagnosis of PA, but their 
sensitivity and specificity is debated.\textsuperscript{17\textendash 19} Due to the 
inconsistent results of previous studies, the Endocrine 
Society's practice guidelines and the Chinese 
consensus conclude that there is insufficient evidence 
to suggest one optimal confirmatory test.

**Results**

The optimal cutoff of post-SIT PAC values, re-
commended by the Endocrine Society's practice 
guidelines, was $5\textendash 10$ ng/dl. Early studies in China 
have suggested that the optimal cutoff is $5$ ng/dl.\textsuperscript{20} 
However, recent studies found that in some Chinese 
patients with essential hypertension and healthy vol-
unteers, the post-SIT PAC value was still $>5$ ng/dl, 
suggesting that this cutoff has a high false-positive 
rate.\textsuperscript{21} Recently, in a prospective study using FST, 
we observed that the optimal cutoff of recumbent 
saline suppression testing (RSST) in the Chinese 
population was a post-SIT PAC of $\geq8$ ng/dl; this 
was consistent with the international guidelines. This 
optimal cutoff has a sensitivity of $85\%$ and a speci-
ficity of $92\%$. In the recent years, some studies have 
shown that seated saline suppression testing (SSST) is 
better than RSST; many centers have switched to 
using SSST.\textsuperscript{18} Based on automated chem-
iluminescence immunoassay and using FST as a 
reference standard, we found that the diagnostic ef-
cicacy of SSST was equal to that of CCT in Chinese 
population. We also found that sodium intake might 
affect the diagnostic efficacy of SSST, but it had little 
effect on CCT (data to be published). Our data indi-
cated that when sodium intake was insufficient, the 
diagnostic efficacy of SSST would decrease; this, 
suggests that it is necessary to adequately supplement 
sodium while performing SSST.

The guidelines recommend that the cutoff for CCT 
is the suppression rate of PAC (less than $30\%$). A 
retrospective analysis with 424 PA patients (178 with 
APA and 246 with IHA) and 222 EH patients at Peking 
Union Medical College Hospital showed that the in-
hibition rate of PAC (measured when seated upright in 
most EH patients was less than $30\%$ after the oral 
administration of captopril [25 mg]). The 2009 Japa-
nese Endocrine Society’s Guidelines for Primary 
Aldosteronism recommended an ARR of $>20\%$ 
(ng/dl)/(ng/ml/h) or a PAC of $>12$ ng/dl at 60 min or 
90 min after captopril administration as the cutoffs for 
PA diagnosis (with radioimmunoassay).\textsuperscript{22}
Recently, our group has completed a prospective study (Comparison of confirmatory tests in primary aldosteronism) and the results have been published in Hypertension. In this study, the automated chemiluminescence immunoassay (Italian Sorin) was used to determine the PAC/PRC ratio in hypertensive patients who have a high risk of PA. Three confirmatory tests (FST, SIT, and CCT) were performed on patients who were tested positive or who were tested negative, but PA was strongly suspected. The diagnostic value of SIT and CCT were compared with the FST used as the reference standard. Then, we found that CCT and SIT had a similar diagnostic value for PA; both were found to be accurate alternatives to the more complex FST. Based on advantages in safety and convenience, it is suggested that CCT should be prioritized when conducting a confirmatory test for large numbers of hypertensive outpatients. We strongly recommended to use the post-CCT PAC value rather than its suppression rate as the diagnostic criterion for Chinese hypertensive patients. In this study, we recommended a post-CCT (2 hours after CCT) PAC of 11 ng/dl as the optimal cutoff. The previous incorrect perception of CCT in the diagnosis of PA, regarding poor reliability, might be related to inaccurate diagnostic criteria, namely the PAC suppression rate of CCT.

Special remarks

Currently, there is no traceable aldosterone standard; this leads to great variations in PAC determined by different methods and different products from various companies. Some studies have shown that the PAC measured by radioimmunoassay is about 30% higher than that by chemiluminescence immunoassay. Our recent data showed that the PAC determined by chemiluminescence immunoassay is 45%—75% higher than that by LC-MS (data to be published). Therefore, it is strongly suggested that each laboratory should establish their own reference intervals for PAC, PRA, PRC, and their corresponding cut-offs, according to the measurement methods and products used.

Perspectives

Objectively speaking, there has been no “gold standard” test for the diagnosis of PA. Further, each confirmatory test may produce false-positive and false-negative results. Therefore, a definitive diagnosis of PA still relies on the comprehensive evaluation of clinical, biochemical, imaging, and pathological examinations, in addition to long-term follow-up. Although the diagnosis of PA has been gradually refined, whether it can be replaced by a simplified and economic method in the future remains unclear. A study suggested that the use of 24-h urinary aldosterone for PA screening might be superior to a single measurement of ARR; this finding warrants further investigation. In addition, with the advancement of the understanding of the pathogenesis and genetic background of PA, the evaluation of the PA subtype can be more accurate. FH, for example, can be diagnosed through genetic testing (e.g., cytochrome P [CYP] 11B1/CYP11B2 chimeric gene of FH-type I). Somatic gene mutation can also be performed on surgically removed adrenal specimens to achieve an etiological diagnosis (e.g., KCNJ5 mutation). Some findings established somatic mutations as the cause of aldosterone hypersecretion in approximately 50% of APA cases. Some other methods for subtyping, including 6b-131I iodomethyl-19-norcholesterol (NP-59) scintigraphy, blood 18-hydroxycorticosterone level measurement, and (11) C-metomidate positron emission tomography-computed tomography, have been reported by some researchers; however, the accuracy of these methods need to be verified in future studies. In addition, the search for molecular markers and diagnostic techniques that are more sensitive and specific is promising.

In conclusion, at present, PA is still a neglected form of endocrine hypertension. It is necessary for clinicians all over the world to improve their understanding of PA in regard to its high prevalence and associated risks for cardiovascular, cerebrovascular, and renal complications. Patients with hypertension should be screened for PA (considering ARR) at least once. The standardization of the plasma aldosterone and renin measurements is also recommended. The diagnostic algorithm for PA needs to be simplified. We hope that the majority of PA patients would benefit from the continuous improvement of the diagnostic algorithm for PA.

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Conflicts of interest

None.
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