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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.[1] 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.[1] 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.[2] 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

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disease. The prevalence of PA is as high as 20% in people with refractory hypertension.[1] However, a study conducted by the Ruijin Hospital in Shanghai showed that the prevalence of PA was 7.1% in people with refractory hypertension.[3]

An elevated plasma aldosterone concentration (PAC) in patients with PA has a detrimental effect, despite good blood pressure control. Consequentially, 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.[4]

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%.[5] 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.[6]

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.[7]

Screening method

Since screening for PA was proposed by Hiramatsu et al[8] 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.[9] 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.[10] 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.[11−13] 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.[1] 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 recommended by the Endocrine Society's practice guidelines.[14] Later, after increasing the sample size, it was found that if the cutoff decreased to 1.0−2.0 (ng/dl)/(uIU/ml), a higher sensitivity could be achieved.[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.[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 potassium concentration, posture, sodium intake, and the menstrual cycle. Medications used to treat hypertension 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. spironolactone and eplerenone) do not need to be discontinued for the confirmatory test or subtype classification with AVS.[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 standardized 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 hypertension 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.[1] Some researchers believe that FST is more reliable and stable and is even regarded as the "golden standard" for diagnosing PA.[16] However, fludrocortisone is not commercially available in some countries and regions, 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.[17−19] 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, recommended by the Endocrine Society's practice guidelines, was 5−10 ng/dl. Early studies in China have suggested that the optimal cutoff is 5 ng/dl.[20] However, recent studies found that in some Chinese patients with essential hypertension and healthy volunteers, the post-SIT PAC value was still >5 ng/dl, suggesting that this cutoff has a high false-positive rate.[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 ≥8 ng/dl; this was consistent with the international guidelines. This optimal cutoff has a sensitivity of 85% and a specificity 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.[18] Based on automated chemiluminescence immunoassay and using FST as a reference standard, we found that the diagnostic efficacy 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 indicated 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 inhibition 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 Japanese 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).[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.[22] 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.[17] 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.[23] 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).[24] 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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