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Application of Metabolomics-Based Screening for AVS Indications in the Diagnosis and Treatment of Primary Aldosteronism

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Abstract: Objective: To investigate the application value of metabolomics technology in the screening of indications for bilateral adrenal venous sampling (AVS) and the diagnosis and treatment of primary aldosteronism (PA), and to provide clinical evidence for the precise diagnosis and treatment plan selection of PA. Methods: A total of 25 patients with suspected PA after preliminary clinical screening admitted to our hospital from October 2024 to June 2025 were selected as the experimental group. Additionally, 15 patients with essential hypertension and 10 healthy individuals during the same period, totaling 25 cases, were selected as the control group. General clinical data and laboratory test indicators of the two groups were collected. Ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) was used to detect serum metabolomic indicators. Differential metabolites were screened, and their correlations with AVS test results and the diagnosis and treatment of PA were analyzed. Results: There were no statistically significant differences in general data such as gender, age, BMI, systolic blood pressure, and diastolic blood pressure between the experimental group and the control group ($P > 0.05$). Serum aldosterone (ALD) and aldosterone-to-renin ratio (ARR) in the experimental group were significantly higher than those in the control group, while serum potassium levels were significantly lower ($P < 0.001$). There were no statistically significant differences in serum sodium, creatinine, urea nitrogen, and cortisol (COR) levels between the two groups (all $P > 0.05$). A total of 128 serum metabolites were identified by UPLC-MS/MS. After OPLS-DA analysis and screening (VIP > 1 and $P < 0.05$), 32 differential metabolites were obtained, of which 19 were significantly upregulated and 13 were significantly downregulated in the experimental group. Among the 25 suspected PA patients in the experimental group, 20 were diagnosed with PA (PA group) after AVS. No cases of PA were found in the 25 control subjects after examination. The sensitivity and specificity of the combination of metabolomic differential indicators and ARR detection were significantly higher than those of single ARR detection. Conclusion: Metabolomics technology can screen for differential metabolites associated with PA. These differential metabolites can serve as potential biomarkers for screening AVS indications. Combined with traditional laboratory indicators, they can improve the diagnostic accuracy of PA, providing important support for the rational application of AVS and the precise diagnosis and treatment of PA.

Keywords: Metabolomics; Bilateral adrenal venous sampling; Primary aldosteronism; Biomarkers

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1. Introduction

Primary aldosteronism (PA) is a clinical syndrome characterized by excessive aldosterone secretion due to adrenal cortical lesions, leading to water and sodium retention and inhibition of the renin-angiotensin system, resulting in hypertension and hypokalemia. It is one of the most common causes of secondary hypertension, with a prevalence rate of approximately 5%–10% in the hypertensive population and over 20% in patients with refractory hypertension[1,2]. Early and accurate diagnosis and targeted treatment can significantly reduce the risk of cardiovascular and cerebrovascular complications and improve patient prognosis[3]. Bilateral adrenal venous sampling (AVS) is the "gold standard" for the diagnosis of PA and the identification of the affected side. It can distinguish between unilateral aldosterone-secreting adenoma and bilateral adrenal hyperplasia, providing crucial evidence for surgical or medical treatment[4]. However, AVS is an invasive procedure with high operational difficulty, risks of complications, and high costs, making it unsuitable as a routine screening method for suspected PA patients. Therefore, accurately screening AVS indications and avoiding unnecessary invasive procedures are key to the diagnosis and treatment of PA. Metabolomics studies the changes in endogenous metabolites in organisms and can reflect the pathophysiological state of the body by detecting differences in metabolites in samples such as serum and urine. It has been widely used in the diagnosis and treatment of endocrine diseases. Abnormal aldosterone metabolism can affect metabolite levels in the body, suggesting that metabolomics may provide new ideas for the diagnosis of PA and the screening of AVS indications.

2. Materials and Methods

2.1. Study Subjects

A total of 25 patients with suspected PA after preliminary clinical screening admitted to the Endocrinology Department of our hospital from October 2024 to June 2025 were selected as the experimental group. Ten healthy individuals from the Physical Examination Center of our hospital and 15 patients with essential hypertension admitted to the Cardiology Department during the same period, totaling 25 cases, were selected as the control group. Screening criteria for suspected PA: ① Persistent hypertension (systolic blood pressure > 150 mmHg, diastolic blood pressure > 100 mmHg), or uncontrolled blood pressure despite the use of three or more conventional antihypertensive drugs, or blood pressure control requiring the use of four or more antihypertensive drugs; ② Hypertension complicated by spontaneous or diuretic-induced hypokalemia; ③ Hypertension complicated by adrenal incidentaloma; ④ Hypertensive patients with a family history of early-onset hypertension or early-onset (<40 years old) cerebrovascular accidents; ⑤ Serum aldosterone-to-renin ratio (ARR) > 30. Exclusion criteria: ① Other types of secondary hypertension; ② Severe liver and kidney dysfunction, heart failure, malignant tumors, etc.; ③ Recent use of drugs that affect aldosterone and renin secretion and inability to discontinue them for more than 3 weeks; ④ Pregnant or lactating women.

2.2. Research Methods

2.2.1. Collection of General

Data and Laboratory Indicators General data of the two groups, including gender, age, height, weight, blood pressure (systolic and diastolic blood pressure), and disease duration, were collected. All subjects fasted for more than 12 hours, and 5 mL of peripheral venous blood was collected in the morning. The blood was centrifuged (3000 r/min, 10 min) to separate the serum, which was then stored in a -80°C refrigerator for later use.

An automatic biochemical analyzer was used to detect serum potassium, sodium, creatinine, and urea nitrogen levels. Radioimmunoassay was used to detect serum aldosterone (ALD) and renin (PRA) levels, and the aldosterone-to-renin ratio (ARR) was calculated. Electrochemiluminescence was used to detect serum cortisol (COR) levels.

2.2.2. AVS Examination

All subjects in the experimental group underwent AVS examination, which was performed by experienced interventional radiologists. Medications that affect aldosterone and renin secretion were discontinued for more than 3 weeks before the

examination. During the examination, the patient was placed in a supine position. A catheter was inserted through the femoral vein and advanced to the bilateral adrenal veins. Blood samples were collected from the bilateral adrenal veins and peripheral veins to detect blood aldosterone and cortisol levels. The success criteria for AVS were: adrenal vein cortisol/peripheral vein cortisol > 2. According to the AVS results, the experimental group was divided into a PA group and a non-PA group. The diagnostic criteria for PA were: unilateral adrenal vein aldosterone/contralateral adrenal vein aldosterone > 2 (unilateral dominance) or elevated aldosterone levels in both adrenal veins without significant unilateral dominance (bilateral hyperplasia).

2.2.3. Metabolomic Detection

(1) Instruments and reagents: An ultra-performance liquid chromatography-high-resolution mass spectrometry system equipped with a HILIC column (2.1 × 100 mm, 1.8 μm) and a mass spectrometry resolution of ≥70,000 was used. Reagents included chromatographically pure methanol, acetonitrile, and formic acid. The internal standards were sodium hexanesulfonate and deuterated phenylalanine, all purchased from Sigma Company. The experimental water was ultrapure water with a resistivity of ≥18.2 MΩ·cm. (2) Chromatographic conditions: Mobile phase A was acetonitrile-water (95:5, v/v) containing 0.1% formic acid, and mobile phase B was water containing 0.1% formic acid. Gradient elution was performed according to a preset program. The flow rate was 0.3 mL/min, the column temperature was 35°C, the injection volume was 5 μL, and the interval was 2 min. (3) Mass spectrometry conditions: An electrospray ionization source was used, with positive and negative ion mode scanning. The resolution was 70,000, and the m/z range was 50–1000. The ion source temperature was 350°C, the spray voltages were 3.5 kV in positive mode and 3.0 kV in negative mode, the sheath gas and auxiliary gas were 35 arb and 10 arb, respectively, the collision energy was 10–40 eV, and data-dependent scanning was used to collect signals. (4) Metabolite extraction and detection: 100 μL of serum was taken, and 400 μL of methanol was added. The mixture was vortexed for 30 s and then left to stand at 4°C for 30 min. After centrifugation, the supernatant was filtered through a 0.22 μm filter membrane and then injected for analysis. Internal standards were added to correct for differences in extraction and ionization efficiency.

2.3. Statistical Methods

SPSS 26.0 statistical software was used for data analysis. Measurement data were expressed as mean ± standard deviation (±s). For measurement data that conformed to a normal distribution and had homogeneous variance, independent sample t-tests were used for comparison between two groups. Count data were expressed as the number of cases (rate), and chi-square tests were used for comparison between two groups. A P-value < 0.05 was considered statistically significant.

3. Results

3.1. Comparison of General Data between the Two Groups

There were no statistically significant differences in general data such as gender, age, BMI, systolic blood pressure, and diastolic blood pressure between the experimental group and the control group (P > 0.05), indicating comparability. See Table 1.

Table 1. Comparison of General Data between the Two Groups

Indicator	Experimental Group (n=25)	Control Group (n=25)	t/χ^2	*P*
Gender (Male/Female, cases)	13/12	14/11	0.081	0.777
Age (years)	51.24 ± 8.76	50.86 ± 9.13	0.004	0.997
BMI (kg/m²)	24.35 ± 3.12	23.98 ± 3.25	0.401	0.691
Systolic pressure (mmHg)	158.64 ± 12.35	156.87 ± 13.12	0.489	0.627
Diastolic pressure (mmHg)	98.76 ± 8.45	97.54 ± 9.12	0.491	0.626

3.2. Comparison of Laboratory Indicators between the Two Groups

The serum aldosterone (ALD) and aldosterone-to-renin ratio (ARR) in the experimental group were significantly higher than those in the control group, while the serum potassium level was significantly lower ($P < 0.001$). There were no statistically significant differences in serum sodium, creatinine, urea nitrogen, and cortisol (COR) levels between the two groups (all $P > 0.05$). See Table 2 for details.

Table 2. Comparison of Laboratory Indicators between the Two Groups

Indicator	Experimental Group (n=25)	Control Group (n=25)	*t*	*P*
Serum Potassium (mmol/L)	3.28±0.45	4.12±0.38	7.216	<0.001
Serum Sodium (mmol/L)	142.35±3.21	141.87±3.45	0.509	0.613
Serum Creatinine (μmol/L)	78.65±12.34	76.89±13.12	0.486	0.629
Urea Nitrogen (mmol/L)	5.23±1.12	5.08±1.25	0.445	0.658
Renin (mmol/L)	5.49±1.67	9.26±2.15	6.924	<0.001
Aldosterone (pg/mL)	189.65±42.38	112.34±28.57	7.563	<0.001
ARR (pg/mL·h^{-1})	34.52±8.76	12.15±4.32	11.439	<0.001
Cortisol (μg/dL)	18.65±4.32	17.89±4.56	0.605	0.548

3.3. Analysis of Serum Metabolomic Differences between the Two Groups

A total of 128 serum metabolites were identified through UPLC-MS/MS detection. After OPLS-DA analysis and screening (VIP > 1 and $P < 0.05$), 32 differential metabolites were obtained. Among them, 19 metabolites were significantly upregulated in the experimental group, while 13 metabolites were significantly downregulated.

The upregulated differential metabolites mainly included steroid hormones (such as aldosterone, corticosterone, and 11-deoxycortisol), purine metabolites (such as hypoxanthine and xanthine), and fatty acids (such as arachidonic acid and palmitic acid). The downregulated differential metabolites mainly included amino acids (such as L-carnitine, taurine, and L-arginine) and lipid metabolites (such as lysophosphatidylcholine and sphingosine). The specific expression levels of some differential metabolites are shown in Table 3.

Table 3. Analysis of Serum Metabolomic Differences between the Two Groups

Differential Metabolite	Experimental Group ($\bar{x} \pm s$)	Control Group ($\bar{x} \pm s$)	t	P	Trend
Aldosterone (ng/mL)	0.19 ± 0.04	0.11 ± 0.03	8.398	<0.001	Upregulated
Corticosterone (ng/mL)	12.35 ± 2.14	8.67 ± 1.89	6.447	<0.001	Upregulated
Hypoxanthine (μg/mL)	2.89 ± 0.56	1.76 ± 0.42	8.017	<0.001	Upregulated
L-Carnitine (μg/mL)	3.21 ± 0.67	5.89 ± 0.89	12.020	<0.001	Downregulated
Taurine (μg/mL)	4.56 ± 0.78	7.23 ± 0.95	10.772	<0.001	Downregulated
L-Arginine (μg/mL)	2.13 ± 0.45	3.89 ± 0.67	10.835	<0.001	Downregulated
Arachidonic Acid (μg/mL)	5.67 ± 0.89	3.45 ± 0.76	9.495	<0.001	Upregulated
Lysophosphatidylcholine (μg/mL)	1.89 ± 0.34	3.21 ± 0.56	9.988	<0.001	Downregulated

3.4. Diagnostic Value of AVS Results and Metabolomic Indicators

Among the 25 suspected PA patients in the experimental group, after AVS examination, 20 were diagnosed with

primary aldosteronism (PA group), including 12 cases of aldosterone-producing adenoma and 8 cases of idiopathic hyperaldosteronism. Five patients were excluded from having PA (non-PA group). After examination, none of the 25 subjects in the control group had PA.

Using AVS results as the gold standard, the diagnostic value for PA was evaluated by using single ARR detection and a combination of metabolomic differential indicators (selecting the three most representative differential metabolites: aldosterone, L-carnitine, and hypoxanthine) along with ARR detection. The results showed that the sensitivity and specificity of the combination of metabolomic differential indicators and ARR detection were significantly higher than those of single ARR detection. See Table 4 for details.

Table 4. Diagnostic Value of AVS Results and Metabolomic Indicators

Diagnostic Method	Sensitivity(%)	Specificity(%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Single ARR Test	75.00 (15/20)	72.00 (18/25)	68.18 (15/22)	78.26 (18/23)
Metabolomics Differential Index + ARR Test	90.00 (18/20)	88.00 (22/25)	85.71 (18/21)	91.67 (22/24)

4. Discussion

Primary aldosteronism (PA) is a leading cause of secondary hypertension, with its core pathological alteration being the abnormal secretion of aldosterone by the adrenal cortex, leading to water and sodium retention, renin suppression, and subsequent clinical manifestations such as hypertension and hypokalemia[5]. Early and accurate diagnosis, along with differentiation of lesion types, is crucial for selecting treatment options and improving patient prognosis. Adrenal vein sampling (AVS), considered the gold standard for the differential diagnosis of PA, can precisely determine the affected side. However, due to its invasive nature and high cost, clinical indications must be strictly screened to avoid unnecessary examinations.

In this study, patients clinically suspected of having PA served as the experimental group, while patients with essential hypertension and healthy individuals served as the control groups, with 25 cases in each group. The results showed that serum aldosterone levels and the aldosterone-to-renin ratio (ARR) were significantly higher in the experimental group than in the control groups, while serum potassium levels were significantly lower, consistent with the pathophysiological characteristics of PA. These findings align with previous studies, suggesting that aldosterone, ARR, and serum potassium remain important laboratory indicators for PA diagnosis[6]. However, the sensitivity and specificity of a single ARR test are limited, and some suspected PA patients may exhibit false-positive or false-negative results, making it difficult to accurately screen for AVS indications.

Metabolomics, as an emerging omics technology, can comprehensively reflect the body's metabolic state and capture early metabolic abnormalities in diseases, demonstrating promising applications in biomarker screening for PA[7]. In this study, through UPLC-MS/MS detection, 32 differential metabolites were identified between the two groups, primarily involving pathways such as steroid hormone metabolism, amino acid metabolism, lipid metabolism, and purine metabolism. Among these, the steroid hormone metabolism pathway showed the most significant differences, with steroids such as aldosterone and corticosterone significantly upregulated in the experimental group, closely related to the core pathological mechanism of excessive aldosterone secretion by the adrenal cortex in PA patients[8]. As a characteristic metabolite of PA, elevated aldosterone levels not only serve as an important diagnostic basis for PA but also participate in the development of hypertension and target organ damage by influencing water and sodium metabolism and vascular tone.

Hypoxanthine, an intermediate product of purine metabolism, was significantly upregulated in the experimental group, and its elevation may be related to increased oxidative stress levels in PA patients. Excessive aldosterone secretion in PA patients can lead to increased reactive oxygen species production, triggering oxidative stress reactions, which in

turn affect purine metabolism and result in hypoxanthine accumulation[9]. Amino acid metabolites such as L-carnitine, taurine, and L-arginine were significantly downregulated in the experimental group, all of which participate in processes such as energy metabolism and antioxidant stress in the body. L-carnitine promotes fatty acid oxidation and maintains energy metabolism balance, and its decreased levels may lead to fatty acid metabolism disorders, exacerbating metabolic abnormalities in PA patients; taurine has antioxidant and ion balance regulatory effects, and its reduced levels may increase the risk of oxidative stress damage in the body[10]; L-arginine, as a precursor of nitric oxide, regulates vascular dilation function, and its decreased levels may aggravate vascular constriction in PA patients, further elevating blood pressure.

In this study, using AVS results as the gold standard, the sensitivity and specificity of metabolomic differential indicators combined with ARR testing were significantly higher than those of a single ARR test, suggesting that metabolomic differential metabolites can serve as potential biomarkers for AVS indication screening. Combining them with traditional laboratory indicators can improve the diagnostic accuracy of PA, helping clinicians accurately screen patients suitable for AVS examination and avoid unnecessary invasive procedures. Additionally, aldosterone levels were significantly higher in patients with aldosterone-producing adenomas than in those with idiopathic hyperaldosteronism, indicating that this metabolite can also be used for the preliminary differentiation of PA subtypes, providing a reference for treatment option selection.

5. Conclusion

In summary, metabolomic technology can screen for differential metabolites related to PA, which primarily participate in pathways such as steroid hormone metabolism and amino acid metabolism and can serve as potential biomarkers for AVS indication screening. Metabolomic differential indicators combined with ARR testing can significantly improve the diagnostic sensitivity and specificity of PA, providing important support for the rational application of AVS examination and the precise diagnosis and treatment of PA, with high clinical application value.

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Disclosure statement

The author declares no conflict of interest.

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