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New Insight on Primary Aldosteronism Vagenete

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Abstract

Primary Hyperaldosteronism is not an uncommon cause of secondary hypertension and labeled before as difficult to treat hypertension, especially in the absence of hypokalaemia which leads to sustained uncontrolled hypertension on polypharmacy and development of many vascular complications leading to early death. Identification of aldosterone secreting adenoma leads to permanent cure with surgical intervention. Diagnosing glucocorticoid remediable hypertension leads to permanent cure with glucocorticoid. Timely diagnosis of familial genetic hyperaldosteronism could prevent haemorrhagic stroke in males and preeclampsia in females.

Introduction

17-year-old young gentleman has been referred to your clinic because of uncontrolled hypertension since the age of 14. He is on three antihypertensive medications -amlodipine 10mg daily, ramipril 5mg daily and indapamide 1.25 mg daily - with no optimum control. His 24 hours systolic blood pressure monitoring ranges between 190-220 and diastolic between 100 and 130. He has no early morning dipping.

The biochemistry showed urea 6 mmol/L (1.2-3mmol/L), uric acid 0.2 mmol/L (0.18-0.48), Na 134, K 3.8 mm, creatinine 50umol/L (61-110 umol/L). Echocardiogram showed concentric hypertrophy of the left ventricle. Cardiac MRI did not show evidence of infiltration or cardio myopathy.

The family history confirmed that his brother died at the age of 22 with haemorrhagic stroke due to uncontrolled hypertension, and his sister died at the age of 23 because of severe hypertension and pre-eclampsia. No family history of polycystic kidney disease.

How can you approach this patient?

Discussion

This article will address the difficulty of early diagnosis of primary hyperaldosteronism (PA), because of its similarity to essential hypertension. Timely diagnosis of PA followed by the subtyping is of paramount importance as it enables the patient to have an almost permanent cure either by surgery or pharmacotherapy and avoids the serious cardiovascular complications including death at a young age. [1], the incidence of Screening of PA in newly diagnosed hypertension is very low as most clinicians only screen patients with hypokalaemia. While the normokalaemia PA is very common but rarely diagnosed in a timely manner. An Italian study analyzed total number of 980 patients with newly diagnosed hypertension (PAPY study) and found that 7.3% of them have PA, and the prevalence was 11.2% in consecutive referred hypertensive patients [2].

Most common cause of secondary hypertension is primary hyperaldosteronism. The three most common subtypes of PA are bilateral idiopathic hyperaldosteronism, Conn's syndrome (aldosterone producing adenoma) and familial hyperaldosteronism. Familial hyperaldosteronism is a genetic disease affecting families at a young age that can cause early death because of haemorrhagic stroke in males and severe pre-eclampsia in females.

The adverse effect of hyperaldosteronism on the cardiovascular system extends beyond the effect of hypertension on the kidney, heart, brain, and peripheral vessels. Aldosterone had a direct effect on the heart causing direct stimulation and proliferation of cardiac myocytes, and fibroblast which causes inflammation. Programmed aldosterone increases free intracellular calcium which induces cardiac cell death and fibrosis. Post-mortem examination of heart for patients with PA showed severe coronary inflammatory lesions, monocyte and macrophages infiltration resulting in extensive focal coronary

ischemic lesions.

Aldosterone causes greater left ventricular hypertrophy than in other non-PA patients with essential hypertension of same severity. Aldosterone has a direct effect on cardio myocytes. Aldosterone increases free intracellular calcium in vascular smooth muscle cells. Aldosterone affects the electrophysiology of the myocardium causing decrease of Na-K pump current. The adverse effect of aldosterone on the heart is independent from its salt retaining effect on the kidney. In animal studies, aldosterone has an auto and paracrine effect of perivascular inflammation which is independent of the myocardium. Most animal studies confirmed the pathological effects of aldosterone on cardio myocytes, myofibroblasts, and vascular smooth muscles.

Diagnosis

Diagnosis usually starts with the case detection, followed by confirmatory tests and then subtype evaluation. Although most antihypertensive medications affect renin and aldosterone measurement and can cause false positive results, dihydropyridine calcium channel blockers and alpha blockers do not affect aldosterone and renin level. Setting a high cut off aldosterone can avoid ceasing medication during testing. Initial testing will be plasma aldosterone, plasma renin activity, and plasma aldosterone renin ratio. High plasma aldosterone and low plasma renin activity is not diagnostic by itself and needs demonstration of autonomous inappropriate aldosterone secretion [2].

Oral sodium loading test

Patient should have normal plasma sodium, potassium before testing and controlled blood pressure. Patient should consume 5000mg sodium over three days either in the form of high sodium diet or sodium chloride tablets, then sampling from day 3 at 0800 until day 4 at 0800 for a 24-hour urine testing for aldosterone, sodium and creatinine. In normal circumstances, renin and aldosterone should be normal if the urine sodium exceeds 200mEq. Urinary aldosterone more than 33.2nmol over 24 hours in the setting of low plasma renin activity is confirmative of primary hyperaldosteronism.

Saline infusion test

Two liters of intravenous saline over 4 hours in the seated position with close monitoring of the heart rate and blood pressure. The failure of plasma aldosterone concentration to decrease below 139pmol/L almost confirms the diagnosis of autonomous secretion of aldosterone [3,4].

Further testings for subtyping

Computed tomography (CT)

CT can detect adrenal producing adenoma; however, this is confounded by increased incidence of non-function nodule which increases with age. CT cannot differentiate with high accuracy between adrenal producing adenoma and bilateral aldosterone secretion or familial hyperaldosteronism.

Adrenal venous sampling

Adrenal venous sampling is the standard of care to differentiate between unilateral and bilateral adrenal disease. The right adrenal vein is small, and this impose difficulty to locate and calculate. Expertise and

volume load of the procedure are essential to keep the skills of interventional radiologist. Essential factors for the success of the procedure are appropriate patient selection, protocol consistent with the international guidelines, accurate and agreed date interpretation, high technical skill and expertise, organization with high volume of the procedure each year. Protocol should be centre-specific agreed by specialized group of endocrinologists, hypertension specialists, interventional radiologists and laboratory specialists. Mayo clinic used ACTH infusion 30 minutes before sampling to reduce fluctuation in aldosterone during sampling as a result of stress and maximize secretion of aldosterone from adrenal producing adenoma. Cortisol from adrenal veins and inferior vena cava is used to confirm successful cannulation (minimum adrenal veins to inferior vena cava cortisol gradient is more than 5:1). Aldosterone producing adenoma can co excrete cortisol if adenoma is more than 1.5 cm, primary aldosteronism and Cushing syndrome may co-exist [3-5].

Treatment

Primary aldosteronism

Unilateral adrenalectomy is an optimum treatment for aldosterone producing adenoma. It is vital for clinical practitioners to understand that treating hypertension only is not an optimum treatment due to adverse effect of aldosterone on heart and blood vessels. Achieving normal aldosterone level in the presence of controlled blood pressure is vital, [4-7]. Patients with bilateral adrenal hyperplasia do better with indefinite mineralocorticoid blockers versus bilateral adrenalectomy as they need lifelong glucocorticoid and mineralocorticoid. Patients with PA has intact hypothalamic -pituitary adrenal axis and they are do not develop adrenal crisis in surgically treated patients.

Pharmacotherapy for PA includes spironolactone with the starting dose of 12.5 mg and the dose can increase up to 400mg daily. Achieving normal sodium and potassium is important to obtain optimum control of aldosterone. The side effects of spironolactone when dose exceeding 50mg include painful gynecomastia, erectile dysfunction, decreased libido in males, and menstrual irregularity in females because of its agonistic activity at the progesterone receptors.

Eplerenone is a competitive and selective mineral corticoid antagonist. It has only 0.1% binding capacity to androgen receptors and less than 1% binding affinity to progesterone receptors. The efficacy of eplerenone is less than spironolactone in controlling of blood pressure but it has less side effects, eplerenone has a shorter half-life and need to be given twice daily.

Familial hyperaldosteronism

Familial hyperaldosteronism (FH) should be seriously considered in any patient who has been diagnosed with hypertension before the age of 20 years or when more than one family member had been diagnosed with hypertension, haemorrhagic stroke or pre-eclampsia. The most common subtypes FH type 1, which is named as Glucocorticoid-remediable aldosteronism (GRA). GRA was discovered in 1966 and the pathogenesis was discovered 25 years later. Patients with GRA have a non homologous unequal crossing over on chromosome 8Q24.3 between CYP11B1gene (which encodes 11- beta-Hydroxylase) and CYP11B2 gene (which encodes aldosterone synthesis) which results in the CYP11B1/CYP11B2 chimeric

gene where mineral corticoid production being regulated by ACTH(Corticotrophin) instead of angiotensin 11. CYP11B1/CYP11B2 chimeric gene is characterised by causing early onset hypertension which could be severe enough and can cause haemorrhagic stroke in male, and pre-eclampsia in females, the diurnal fluctuation of aldosterone explains the infrequency of hypokalemia. The chimeric gene is expressed throughout the adrenal cortex. Cortisol in the adrenal fasciculata is subject to C18 hydroxylation and C8 oxidation, which results in overproduction of 18-hydroxycortisol and 18-oxycortisol. Genetic testing for gene CYP11B1/CYP11B2 should be considered for patients who are diagnosed with hypertension at a young age or have a family history of stroke or pre-eclampsia at a young age. Lifelong treatment with small dose of corticosteroids is curative and can prevent early death and comorbidities [8,9].

Three other types of familial primary hyper aldosteronism were discovered: Type II Familial hyperaldosteronism which encodes germline CLCN2 chloride channel, Type III Familial Hyperaldosteronism which encodes germline KCNJ5 mutation, and Type IV Familial Hyper aldosteronism which encodes germline CACNA1DH mutation and germline CACNA1D mutation. Type IV disease is characterised by seizures in addition to hypertension. Patient in the vignette has early onset resistant hypertension, not controlled by three antihypertensive medications and has strong family history of hypertension and stroke. Patient may continue treatment during testing with dihydropyridine calcium channel blockers and alpha-blocker, potassium should be optimised to 4 mmol/L. Plasma aldosterone and plasma renin activity need to be measured, followed by saline infusion test and recheck of 24-hour plasma aldosterone and plasma renin activity. CT adrenal is a complementary test to exclude any coexistence adrenal disease like Cushing syndrome. Patient should be counselled and tested for CYP11B1/CYP11B2 chimeric gene, which confirms the diagnosis of Familial Hyperaldosteronism type 1. Treating with lifelong small dose of corticosteroid will ameliorate all symptoms, cures hypertension and prevent adverse effect of aldosterone. Early death, stroke and pre-eclampsia [9,10].

Conclusion

Primary hyperaldosteronism is the most common cause for secondary hypertension. It is rarely diagnosed in a timely manner because of the infrequency of hypokalaemia which only occurs in 20% of patients. Failure of early diagnosis and treatment results in hypertensive organ damage in the heart, kidney, brain in addition to the deleterious effect of aldosterone on the heart and blood vessels. Familial hyperaldosteronism account for 1% of primary hyperaldosteronism which affect patients at a young age and runs in family in an autosomal dominant pattern, diagnosis can be confirmed by genetic testing for CYP11B1/CYP11B2 chimeric gene. Primary hyperaldosteronisms due to adrenal adenoma is curative by surgery. Primary hyperaldosteronisms due to bilateral adrenal hyperplasia is curative with mineral corticoid antagonist. Familial hyperaldosteronism type 1 (Glucocorticoid remediable hyperaldosteronisms) is cured by small dose of glucocorticoids.

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