



Endocrine Hypertension- Strategy for Screening and Workup

Dr. Wing-bun Chan MBCHB, FRCP(Glas), FHKAM, FHKCP

Specialist in Endocrinology



Dr. Wing-bun Chan

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 October 2006.

Hypertension is one of the common chronic diseases affecting one fourth of the population worldwide.¹ Recent epidemiology studies showed that worldwide hypertension contribute around 20% of the risk in myocardial infarction.² Traditionally, less than 5% of hypertension was thought to be due to secondary causes and there has been much controversy in whether it is worthwhile to screen for secondary causes of hypertension.^{3,4} However, recent studies showed a much higher prevalence of secondary causes, although different studies yielded different results due to different target populations, different settings and different methodologies in detection of secondary causes.^{5,6} The importance of diagnosing secondary hypertension lies in the fact that it may convert an incurable disease into a potentially curable disease. Even if the underlying disease may not be curable, being able to offer disease specific treatments will often make blood pressure control much easier. Furthermore, the underlying diseases often confer damages beyond effect of high blood pressure alone and hence need specific treatment by itself. This article will discuss endocrine causes of hypertension and the strategy for screening.

Common causes of endocrine hypertension are listed in Table 1. Running through the list of causes, it is not difficult to notice that most of the causes either affect the adrenal or the pituitary gland. The most common causes of secondary hypertension is primary hyperaldosteronism.^{5,7} The renin-angiotensin-aldosterone(RAS) system is an important system in the regulation of intravascular volume as well as the blood pressure. RAS system will be activated in the case of intravascular volume depletion such as dehydration and acute blood loss. The activated system will cause vasoconstriction and resorption of Na. There will be urinary loss of potassium due to exchange with Na during the resorption process. However, in patients with primary hyperaldosteronism, there is partial/complete autonomous secretion of excess aldosterone. This will cause hypertension, hypokalaemia and alkalosis. The signs and symptoms of primary hyperaldosteronism are mostly non-specific, although some patients may present with symptoms of severe hypokalaemia such as paralysis or muscle ache.⁸ Quite often, the only clue to the diagnosis is unprovoked hypokalaemia in the presence of hypertension. Spot renin or aldosterone has limited

value due to their diurnal variation in level, change in respond to posture and interference by concomitant antihypertensive drugs.⁹⁻¹¹ With recent advances in the screening method using renin-aldosterone ratio, which is less affected by concomitant anti-hypertensive medications, we gain much deeper understanding of primary hyperaldosteronism. There has been a number of studies trying to address the prevalence of primary hyperaldosteronism using renin-aldosterone ratio alone or in combination with aldosterone concentration as a screening tool. However, it should be noted that these studies were conducted in quite different settings, using different methodologies and using different cut-off points in the ratio. Some studies were done at primary care settings,^{15,18,19} while more were done in referral centres.^{12,14,16,17} Some studies standardised the anti-hypertensive medications,¹³ while others have the renin-aldosterone ratio checked without any change in anti-hypertensive medications.^{12,17} Different cutoff points have been adopted in different studies, mostly ranging from 20-30(ng/dl)/(ng/ml/hour).^{13,17} Lastly, different methods have been adopted to confirm the diagnosis. Due to large differences in methodology, we would expect a large variation in the prevalence of hyper-aldosteronism. However, taking a glance at the studies, it is not difficult to realize that the prevalence of primary hyperaldosteronism is around 5-13%, which is much higher than previous reported.

Take the study by Loh et al as an example,¹⁷ using renin aldosterone ratio of 20 (ng/dl)/(ng/ml/hour) with aldosterone concentration greater than 15 ng/dl as cutoff points, it detected a prevalence of primary hyperaldosteronism as 4.6%. Similar cutoff points have also been adopted by the Mayo Clinic. It should be noted that anti-hypertensive medications were not changed at the time of screening and that the initial screening yielded a high rate of 18% suspected primary hyperaldosteronism although only 4.6% were confirmed eventually, a relatively low positive predictive rate. Using similar methodology but with adjustment of antihypertensive drugs to minimise possible interference with screening, study by Stowasser M et al at referral settings found a high prevalence of confirmed primary hyperaldosteronism up to 18%. One interesting point is that the initial screening rate is 19.6%, therefore a much high positive predictive rate.¹³ The differences in these two studies



can be due to difference in prevalence in primary hyperaldosteronism in the respective population, or more likely, due to lower specificity in the absence of adjustment in concomitant medications. Furthermore, it should be noted that around half of the confirmed primary hyperaldosteronism patients have normal potassium level and therefore serum potassium level is not a sensitive enough tool for detecting hyperaldosteronism.^{13,17}

Methods for confirming the diagnosis of primary hyperaldosteronism also vary with different centres. The more commonly adopted methods include the saline suppression test, oral salt loading test, and fludrocortisone suppression test.²⁰⁻²² Recent studies showed that the saline suppression test may be as reliable as fludrocortisone suppression test and is more convenient to be conducted at out-patient setting.²² After biochemical confirmation of the diagnosis, we need to find out the exact aetiology of primary hyperaldosteronism. The main issue is to differentiate adrenal adenoma from bilateral adrenal hyperplasia. The exact aetiology will be further differentiated using CT scan, MRI scan and iodocholesterol scan. Postural response of aldosterone also gives hint to the underlying aetiology.²³⁻²⁷ CT scan is the most often arranged investigation because of its wide availability and reasonable accuracy,²³ although some studies showed a rather low sensitivity.²⁶ The main problem in imaging is that there is significant proportion of adrenal incidentaloma, and therefore, the presence of adrenal mass even in the presence of hypertension does not necessarily point to primary hyperaldosteronism.²⁷ On the other hand, normal adrenal imaging does not exclude primary hyperaldosteronism since bilateral adrenal hyperplasia may not be well shown on imaging and small adenoma may not be detected by CT alone.^{24,28} In difficult cases with high suspicion of adrenal adenoma but normal CT, we may have to resort to adrenal venous sampling.^{13, 24, 28} Some authorities even suggested that venous sampling should be done in all cases with confirmed hyperaldosteronism.²⁸ For confirmed cases of aldosterone producing adenoma, the best treatment is adrenalectomy.²⁹ With recent advances in the technology of laparoscopic adrenalectomy, the operation has been made much less invasive and hospital stay has been much shortened.³⁰ For patients with bilateral adrenal hyperplasia or who refuse surgery, they should be treated medically with aldosterone receptor antagonist, aldosterone.^{31,32} However, aldosterone may be limited by its side effects, namely gynaecomastia, decreased libido and menstrual problems.³³ With surgical excision of adrenal adenoma, there is around 60% chance that the patient can be taken off antihypertensive medications. Other patients can usually have the number or dose of anti-hypertensive medications decreased. Hypokalaemia is often cured. The blood pressure control is usually improved in those receiving medical treatment.^{13,34}

With the wide spread use of renin-aldosterone ratio as a screening tool, there is increased prevalence of primary hyperaldosteronism over the last few decades. The pattern of disease seems to change as well. Before 90s, the predominant lesion of primary hyperaldosteronism was aldosterone-producing adenoma. However, after 90s, bilateral adrenal hyperplasia accounted for a much higher proportion.³⁵ Furthermore, we now realize that only around 50% of patients with primary hyperaldosteronism

have hypokalaemia.^{35, 13, 17} All these raise the possibility that we are now detecting milder cases which do not need specific intervention and raise the question of cost-effectiveness in screening. Looking at the previous series, non-selective screening only yielded about 2-5% of potentially curable adenoma among all subjected screened.^{13, 17} However, the screening strategy led to an improvement in blood pressure control in 16% of the subjects with the disease specific treatment, a much lower and more acceptable number needed to be treated from a screening perspective.¹³ Furthermore, aldosterone receptors present not only in the kidney, but also in the heart, brain and blood vessels. Presence of excess aldosterone leads to myocardial fibrosis. Therefore, hyperaldosteronism may have deleterious effects beyond hypertension and hypokalaemia.³⁶ All these speak for more aggressive screening for primary hyperaldosteronism. However, large scale randomised trials are needed to answer the question of cost-effectiveness in the screening strategy of primary hyperaldosteronism more definitively.

The presence of excess glucocorticoid is known as Cushing's Syndrome. The clinical features of Cushing's Syndrome almost involve all parts of the body; the more commonly found clinical features include central obesity, facial plethora, hypertension, easy bruising, glucose intolerance, etc.³⁷ Although hypertension is a known feature of Cushing's Syndrome, the prevalence of Cushing's Syndrome in hypertension is only 1%.^{5,6} Furthermore, unlike primary hyperaldosteronism, patients with Cushing's Syndrome are often symptomatic, therefore mass screening for hypertension subjects are often not needed. The difficulty in diagnosing Cushing's Syndrome lies in that most of the clinical features are commonly found in subjects without the disease, such as people with obesity, as well. Previous studies showed that bruising, plethora, and myopathy have highest differential value among all the clinical features.³⁸ Furthermore, we should never forget that the one of the common causes of Cushing's Syndrome is exogenous Cushing's.³⁹ Therefore, a careful medical history is mandatory, especially for those with skin and joint problems. Over the counter drugs is another possible source of steroid apart from doctor's prescriptions. If exogenous Cushing's is suspected, short synacthen test should be performed to assess adrenal cortisol reserve and proper physiological glucocorticoid replacement is important⁴⁰. For endogenous Cushing's Syndrome, the commonly employed screening tests are overnight dexamethasone suppression test and 24 hour urinary cortisol excretion.^{41, 42} A morning cortisol level greater than 54 nmol/l after taking 1 mg dexamethasone at midnight or urinary cortisol excretion greater than normal range raises the suspicion of Cushing's Syndrome. In our experience, overnight dexamethasone suppression is much more convenient as the patient does not need to comply with complete collection of urine sample over 24 hours, which can be quite cumbersome. However, one should be aware of concomitant medications such as anti-epileptic or anti-tuberculosis drugs which will affect the validity of tests.^{43,44} Endogenous Cushing's Syndrome can be confirmed with low-dose dexamethasone suppression test with CRH stimulation.^{45,46} A base line ACTH is often done at the same time of low dose dexamethasone suppression. A suppressed ACTH points to the underlying cause as adrenal in origin while a normal or raised ACTH points to ACTH dependent Cushing's



Syndrome, which is usually pituitary in origin or due to ectopic ACTH. The underlying disease is usually further localised with imaging of the respective site, namely CT adrenal or MRI pituitary.⁴⁷ It should be noticed that MRI pituitary can only pick up less than 70% of pituitary Cushing's,⁴⁸ and therefore a normal MRI pituitary does not rule out the disease. On the other hand, pituitary incidentaloma can confuse the clinical picture.⁴⁹ The treatment of Cushing's Syndrome usually aims at cure by resection of the tumour. However, the details of treatment are beyond scope of this article.

Phaeochromocytoma is a rare cause of hypertension. It is estimated to occur in less than 0.2% of hypertensive population.⁵⁰ It originates from the chromaffin tissues of sympathetic nervous system. It is a disease which is very difficult to diagnose. Post-mortem series showed that around one third of patients who die from phaeochromocytoma have their disease unsuspected during lifetime.⁵¹ Although it is a very rare disease, proper diagnosis and management is very important. With correct diagnosis and proper management, phaeochromocytoma is potentially curable. However, misdiagnosis and improper management can be potentially fatal.⁵² Most of phaeochromocytoma are sporadic cases. However, a small proportion are associated with genetic diseases such as MEN IIa and IIB, von-Hippel Lindau Syndrome and neurofibromatosis.^{53,54} Around 90% of phaeochromocytomas are unilateral and found within adrenal gland. However, around 10% of phaeochromocytomas are extra-adrenal and bilateral. The most typical clinical features of phaeochromocytomas are hypertension, headache, palpitation and paroxysms.^{51, 55} However, none of these features are specific and can mimic anxiety. Therefore, the correct diagnosis often relies on a high index of suspicion. Methods of screening for phaeochromocytoma differ between different centres. The often-employed methods include urinary catecholamine, plasma catecholamine, urinary metanephrine and plasma fractionated metanephrine. So far, plasma fractionated metanephrine seems to be the most promising method, but is limited by local availability.^{56, 57} It should be realised that some drugs such as methyldopa and labetalol, acute sepsis or obstructive sleep apnoea may either interfere with the assay or cause acute rise in sympathetic activity and affect the accuracy of the biochemical diagnosis. Phaeochromocytomas are often localized by CT and MRI examination. Both CT and MRI have very high sensitivity, but the specificity is limited by incidentaloma as previously discussed. In this regard, MRI is more specific tool but is limited by its cost. MIBG scan is especially useful in detecting extra-adrenal involvement of phaeochromocytoma.⁵⁸ The definitive treatment for phaeochromocytoma is surgical excision. The mortality of operation was very high in the old days, up to 24-50% in some old series. With introduction of alpha and beta blockade before operation, the survival of the operation has rise up to 97-100%. Agents used for alpha and beta blockade include phenoxybenzamine, prazosin, propranolol, metoprolol, labetalol.⁵⁹ It should be remembered that unopposed beta-blocker in the case of phaeochromocytoma is very dangerous and can be fatal.⁵²

Acromegaly, congenital adrenal hyperplasia, etc are rare causes of secondary hypertension and will not be

discussed in detail in this article. Acromegaly is characterised by coarse facial feature, spade like hand, protruded jaw, which can be recognised clinically. However, it has a slow disease course and hence the diagnosis is usually delayed. The diagnosis can be as late as 10 years after onset of symptoms.⁶⁰ Only the rare type of congenital adrenal hyperplasia including 11-OH and 17-OH congenital adrenal hyperplasia will cause hypertension due to excess activity of 11-deoxycorticosteroid. The hint is usually hypertension at very young age, hypokalaemia and is associated with problems of sexual characteristics.^{61, 62}

Table 1. Endocrine causes of hypertension

Primary hyperaldosteronism
Cushing's Syndrome
Phaeochromocytoma
Acromegaly

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Endocrine Hypertension-Strategy for Screening and Workup" by Dr Wing-bun Chan and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheet via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 October 2006. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please choose the best answer.

1. What is the estimated attributed risk of hypertension to myocardial infarction worldwide?
 - a. 5%
 - b. 10%
 - c. 20%
 - d. 30%
2. What is the prevalence of hypertension worldwide?
 - a. 5%
 - b. 15%
 - c. 25%
 - d. 35%



3. Which of the following is not an endocrine cause for hypertension?
 - a. Cushing's Syndrome
 - b. Renal artery stenosis
 - c. Hyperaldosteronism
 - d. Pheochromocytoma
4. Which of the following is the most common causes of endocrine hypertension?
 - a. Primary hyperaldosteronism
 - b. Cushing's Syndrome
 - c. Pheochromocytoma
 - d. Acromegaly
5. Which of the following is the clinical feature of hyperaldosteronism?
 - a. Hypertension
 - b. Hyperkalaemia
 - c. Alkalosis
 - d. All of the above
6. Which of the following is the best screening method for primary hyperaldosteronism?
 - a. Young onset hypertension
 - b. Hypokalaemia
 - c. PAC/PRA ratio
 - d. CT adrenal
7. After successful resection of adrenal adenoma in primary hyperaldosteronism, what proportion of hypertensive subjects can be taken off anti-hypertensive medication?
 - a. 10-20%
 - b. 20-30%
 - c. 50-70%
 - d. 90-100%
8. Which of the following is not a good differential clinical characteristics in the diagnosis of Cushing's Syndrome?
 - a. Menstrual disturbance
 - b. Easy bruising
 - c. Myopathy
 - d. Plethora
9. Which of the following drugs can interfere with overnight dexamethasone suppression test?
 - a. Rifampicin
 - b. Carbamazepine
 - c. Phenytoin
 - d. All of the above
10. Which of the following drugs cannot be used alone to control the blood pressure of patients with pheochromocytoma?
 - a. beta-blocker
 - b. calcium channel blocker
 - c. thiazide diuretic
 - d. ACEI

ANSWER SHEET FOR OCTOBER 2006

Please return the completed answer sheet to the Federation Secretariat on or before 31 October 2006 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

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Dr Wing-bun Chan MBCHB, FRCP(Glas), FHKAM, FHKCP

Specialist in Endocrinology

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Name (block letters): _____ HKMA No.: _____

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Answers to September 2006 issue

Comparison of Various Biological Agents in the Treatment of Psoriasis

1. A 2. D 3. D 4. D 5. E 6. A 7. D 8. C 9. D 10. C