VI. Endocrine Hypertension

DIAGNOSIS AND ASSESSMENT

http://guidelines.hypertension.ca/diagnosis-assessment/endocrine-hypertension/

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Recommendations

A. Hyperaldosteronism: screening and diagnosis
   1. Screening for hyperaldosteronism should be considered for the following patients (Grade D):
      i. Hypertensive patients with spontaneous hypokalemia (K+ < 3.5 mmol/L);
      ii. Hypertensive patients with marked diuretic- induced hypokalemia (K+ < 3.0 mmol/L);
      iii. Patients with hypertension refractory to treatment with ≥ 3 drugs;
      iv. Hypertensive patients found to have an incidental adrenal adenoma.
   2. Screening for hyperaldosteronism should include assessment of plasma aldosterone and plasma renin activity or plasma renin (Supplemental Table S7).
   3. For patients with suspected hyperaldosteronism (on the basis of the screening test; Supplemental Table S7, item iii.), a diagnosis of primary aldosteronism should be established by demonstrating inappropriate autonomous hypersecretion of aldosterone using at least 1 of the manoeuvres listed in Supplemental Table S7, item iv. Manoeuvres to demonstrate Autonomous Hypersecretion of Aldosterone. When the diagnosis is established, the abnormality should be localized using any of the tests described in Supplemental Table S7, item v.
   4. In patients with primary hyperaldosteronism and a definite adrenal mass who are eligible for surgery, adrenal venous sampling is recommended to assess for lateralization of aldosterone hypersecretion. AVS should be performed exclusively

by experienced teams working in specialized centres (Grade C) (**new recommendation**).

B. Pheochromocytoma: screening and diagnosis

1. If pheochromocytoma is strongly suspected, the patient should be referred to a specialized hypertension centre, particularly if biochemical screening tests (Supplemental Table S8) have already been found to be positive (Grade D).

2. The following patients should be considered for screening for pheochromocytoma (Grade D):

   i. Patients with paroxysmal and/or severe (BP ≥ 180/ 110 mm Hg) sustained hypertension refractory to usual antihypertensive therapy;

   ii. Patients with hypertension and multiple symptoms suggestive of catecholamine excess (eg, headaches, palpitations, sweating, panic attacks, and pallor);

   iii. Patients with hypertension triggered by b-blockers, monoamine oxidase inhibitors, micturition, or changes in abdominal pressure;

   iv. Patients with incidentally discovered adrenal mass and patients with hypertension and multiple endocrine neoplasia 2A or 2B, von Recklinghausen neurofibromatosis, or von Hippel-Lindau disease;

   v. For patients with positive biochemical screening tests, localization of pheochromocytomas should involve the use of magnetic resonance imaging (preferable), computed tomography (if magnetic resonance imaging is unavailable), and/or iodine I-131 metaiodobenzylguanidine scintigraphy (Grade C for each modality).

Background

A. Hyperaldosteronism: screening and diagnosis

An excess of aldosterone as a cause for hypertension (primary aldosteronism) has traditionally been considered relatively rare (approximately 1% of hypertensive patients). However, recent studies using improved diagnostic methods have suggested that forms of hyperaldosteronism are much more prevalent, perhaps occurring in up to 15.5% of hypertensive patients and even 1.5% of normotensive subjects (1-6). Primary aldosteronism, is often caused by an aldosterone-producing adrenal adenoma, idiopathic hyperaldosteronism/bilateral adrenal hyperplasia, unilateral hyperplasia, and less commonly adrenal carcinoma and familial hyperaldosteronism (glucocorticoid remediable or non-remediable).

Hyperaldosteronism may be associated with the full spectrum of the hypertension severity, from mild to severe. Often, primary hyperaldosteronism is asymptomatic. Symptoms attributed to primary aldosteronism are nonspecific and have classically included weakness, cramps, and nocturia. While hypokalemia is suggestive of primary aldosteronism when present, its absence should not be relied on to exclude the diagnosis. In some reports, hypokalemia has been found in

less than 50% of confirmed cases of primary aldosteronism (4,7). Although plasma and urinary aldosterone concentrations are elevated, and the plasma renin activity concentration is very low, individual values of these parameters have low sensitivity and specificity.

The ratio of plasma aldosterone concentration to plasma renin activity may be determined as a screening test (8-11). We express plasma aldosterone in pmol/L (conversion factor from ng/dL: multiply by 27.74) and plasma renin activity in ng/mL/h (conversion factor from direct renin/renin mass assay in ng/mL: multiply by 0.206; this conversion factor varies among laboratories). Standardization of units is further complicated because some laboratories now measure renin mass/direct renin rather than plasma renin activity. There is no easy conversion, because the percentage of active renin varies considerably. When analyzing the ratios, it is extremely important be familiar with locally used units so there is no confusion/errors in interpretation.

We selected a ratio (greater than 750 pmol/L/ng/ml/h (1)) for screening to be consistent with other organizations; therefore, we recommend confirmatory testing for those with higher ratios. The most appropriate method of measuring renin remains a contentious issue (12). It is increasingly common to measure direct renin/renin mass (or renin concentration) in place of plasma renin activity. While direct renin/renin mass measurements are considerably easier to perform, renin activity may be more precise, particularly when active renin concentrations are low. The test results and the units in which these results are expressed will depend on local laboratory services. The various units in which the results may be expressed may bewilder the clinician and as such, a table with estimated conversion rates is appended (Table 5). Because of possible laboratory-to-laboratory variation in technique and reference ranges, clinicians who use these conversion factors should confirm these conversion values with their local laboratories.

Uncorrected hypokalemia (K+ <3.3mmol/L), severe sodium restriction, and administration of renin-angiotensin inhibitors, diuretics and DHP-calcium channel antagonists may cause false-negative ratios and beta-blockers can cause a false positive (13). Other factors that can interfere with interpretation include renal dysfunction, oral contraceptives, NSAIDs, and in particular mineralocorticoid receptor antagonists. If possible, alpha blockers, hydralazine, and/or verapamil should be used for blood pressure control while testing since they have minimal interference with biochemical testing (but this may not be possible depending on the risk and clinical situation). The ratio should be measured in patients that have been ambulatory for at least 2 hours using morning specimens drawn after sitting for at least 15 min (1,4,14). The value of these ratios appears to be primarily in defining a subpopulation with a high rate of confirmed primary aldosteronism (29% to 93%). Aldosterone levels below 330 pmol/L are rarely associated with hyperaldosteronism, even if the ratio is elevated.

Options for confirmation of autonomy of aldosterone secretion include one or more of those cited in the recommendations above (4,15-17). This includes oral sodium loading, intravenous sodium loading, or captopril suppression testing. In all cases, aldosterone supressibility, ascertained through plasma or 24hr urine aldosterone, is a normal finding. Few studies have assessed the

comparative utility among this repertoire of testing options (17). In the presence of familial hyperaldosteronism, glucocorticoid-suppressible hyperaldosteronism should be ruled out with genetic testing.

When the diagnosis of primary aldosteronism is confirmed, differentiation among possible causes should be attempted using functional assays and/or adrenal imaging (18-20). The presence of adenomas is suggested by postural testing when the plasma aldosterone level decreases or fails to increase following 2 to 4 h of upright posture (but this test is not widely performed). A small retrospective study has shown that in patients with proven Primary Aldosteronism, high levels of plasma 18-Oxocortisol (6.1ng/dL) correlates more with a unilateral aldosterone producing adenoma and levels < 1.2ng/dL with bilateral adrenal hyperplasia. In these situations, adrenal vein sampling may be avoided along with unnecessary surgery for nonfunctioning nodules. However, prospective, multicentric studies need to confirm these results (21). CT scanning is the first imaging test of choice due to sensitivity; specificity is reduced because of incidentalomas (22,23). Adenomas greater than 1 cm in diameter are more readily detected, but those smaller than 1 cm in diameter are difficult to detect. Localization with 131iodine-labelled iodocholesterol under dexamethasone suppression can be performed, but is not widely available and may yield false negative results if the lesion is < 1.5cm (23).

Adrenal venous sampling may be the only method that can assess lateralization reliably (24-27); however, the test is invasive and requires expertise that is not widely available.

It may be possible to avoid AVS (adrenal vein sampling) before adrenalectomy when the diagnosis of primary hyperaldosteronism is confirmed if there is a high probability of the cause being an aldosterone producing adenoma with the following features (14,28,29):

- Young age < 40yo
- Severe HTN
- Moderate-severe hypokalemia
- If ARR (aldosterone-renin ratio) is positive (> 27 ng/dL/ng/ml/h or 750 pmol/L/ng/ml/h) & basal plasma aldosterone is greater than 40 ng/dL (approx. 1,100 pmol/L)
- and plasma aldosterone very high after infusion of 2L of 0.9% NaCl in 4h OR very high 24hr urine aldosterone after 3 day po sodium load
- imaging shows definite adrenal mass > 1cm

Aldosterone-producing adenonas can usually be removed by unilateral adrenalectomy, usually laparoscopically, with good surgical and hypertension outcomes along with normalization of potassium levels (30-32). However, a significant proportion of such patients remain hypertensive and, therefore, warrant close follow-up especially if strong family history of HTN, multiple medications required pre-op or BP control, older age, and longer duration of HTN (30,32-34). Aldosterone antagonists, particularly spironolactone in low to moderate doses, are quite effectivein idiopathic/bilateral hyperplasia hyperaldosteronism and moderately effective even in those who are

not surgical candidates or refuse surgery for aldosterone producing adenomas (35), reducing both blood pressure, normalizing potassium, and the need for multiple drug therapy (12,35). Blood pressure lowering responses to other potassium-sparing diuretics, ACEIs, ARBs and calcium channel blockers are modest-to-moderate (36).

B. Pheochromocytoma: screening and diagnosis

Pheochromocytomas and paragangliomas (PPGL) are an infrequent cause of hypertension (less than 0.3%) (37,38). The prevalence is greater among patients with adrenal incidentaloma (4%) (39,40). Because of the low incidence of pheochromocytoma/PPGL, the significant risk of severe adverse sequelae (stroke, myocardial infarction, arrhythmias, CHF, cardiomyopathy, and particularly abrupt onset of malignant hypertension), and specialized therapeutic interventions, we recommend referral of individuals suspected of having pheochromocytomas/PPGL to centres with experience in their management.

Pheochromocytoma/PPGL may present with a wide spectrum of clinical features, including those that are not generally attributed to excess catecholamines (41). Paroxysmal or severe sustained hypertension, labile hypertension, hypertensive crises triggered by beta-blockers or monoaminoxidase inhibitors, surgery, anesthesia, or symptoms such as severe headache, palpitations, sweating (a common triad of symptoms), pallor, tremulousness, syncope, weight loss, abdominal pain, paroxysmal hypertension with micturition, require investigation for pheochromocytoma/PPGL (38,41,42). Other suggestive signs include orthostatic hypotension, tachycardia, palpable flank mass, polycythemia, hypercalcemia, shock, port wine hemangiomas (von Hippel-Lindau disease), thyroid tumour, and mucosal neuromas, cafe au lait spots or the presence of several axillary freckles. It is important to note that persons with pheochromocytomas/PPGLs may also be normotensive and asymptomatic, particularly those with familial forms (about 10% of cases) (41). About 10% of Pheochromocytomas/PPGLs are extra-adrenal, bilateral, familial, malignant, recurrent, in children, and present with stroke (Rule of 10's).

The differential diagnosis of pheochromocytoma/PPGL does include panic attacks, migraines, carcinoid, thyrotoxicosis, sepis, MI, dysautonomia, CNS lesions, certain drugs, cocaine, and drug/toxin withdrawal and a newer entity called pseudopheochromocytoma. However, these are diagnoses to consider once Pheochromocytoma/PPGL is ruled out.

Currently, the most widely used screening approach is a 24 h urine collection for the assessment of urinary fractionated metanephrines (catechol-0-methyltransferase metabolites of catecholamines), which are reported to have a sensitivity over 90% (37) and urinary catacholamines (sensitivity over 80%). Because of lower sensitivity, we advise against using urinary or plasma VMA measurements as screening tests. Concurrent collection of urinary creatinine concentration permits a creatinine correction to adjust for completeness of the 24 h collection (43,44).

However, in other cohorts of patients with pheochromocytoma/PPGL, urinary metanephrine testing has been reported to be less sensitive (45). Assays of plasma metanephrines measurements have exhibited a high sensitivity (45-47). However, this assay is not widely available. A negative plasma fractionated metanephrine measurement can be used in a low-risk setting to rule out pheochromocytoma. This is based on a systematic review (48) that demonstrated a pooled negative likelihood ratio of 0.02 (95% CI 0.01 to 0.07) for a negative plasma fractionated metanephrine measurement in predicting pheochromocytoma/PPGL in patients with sporadic pheochromocytoma (low-risk group) (49). Given the low specificity a positive result in a low-risk setting (refractory hypertension) should be interpreted with caution.

When borderline results are observed (only one panel of tests is abnormal, no hard clinical findings are present, mild elevation in results, false positive concerns), the 1st step is to repeat the testing. The clonidine suppression test is an option for differentiating pheochromocytoma from other conditions if the above approach is still equivocal. In three separate assessments, it was associated with sensitivity estimates of 73% to 100% and specificity estimates of 74% to 100% (50-52). Concerns regarding the glucagon stimulation test have included low sensitivity, false positives and the triggering of hypertensive episodes, and thus is seldom used or required (52,53).

Localization of pheochromocytomas/PPGLs should include CT +/- MRI imaging and if indicated, 123 or 131 iodine MIBG scintigraphy, octreotide scanning or PET scanning. MRI is associated with a sensitivity of 98% to 100% for adrenal pheochromocytomas and 88% for extra-adrenal lesions (54,55). While aggregate estimates for the sensitivity of CT and MIBG imaging are 89% and 81%, respectively, they are much lower for bilateral (66% and 62%) and extra-adrenal (64% and 64%) pheochromocytomas/PPGLs (54). A combination of anatomical (MRI or CT) and functional imaging (MIBG) may often be desired because of reported low specificity of MRI and CT (50%) and higher specificity of MIBG (88% to 100%) (56-58). MIBG/Octreotide/PET scanning may (59) be useful to detect metastatic disease for persons with malignant pheochromocytoma/PPGL (60-63).

The assessments of therapeutic interventions for managing pheochromocytomas/PPGLs are based on small case series, at times with comparisons with historical controls. While these reports are methodologically weak, it is important to note the historically high mortality rates associated with this diagnosis when untreated or unsuspected (64,65), particularly if resected before the use of perioperative alpha-blockade (mortality of 25% to 50%) or if surgery occurs in persons with unsuspected pheochromocytoma (66,67). This compares with the currently low perioperative complication rates and expectations of a cure when benign pheochromocytomas/PPGLs are laparoscopically resected (41,68-70). In addition to alpha blockade 10-14 days pre-operatively, it is vital to have adequate volume replacement and liberal sodium intake since volume contraction is common in this condition. Other anti-hypertensives can be added as necessary but diuretics should be avoided if possible. Oral beta-blockers, usually necessary, should only be started after a few days of adequate alpha blockade to control tachycardia and prevent arrhythmias during surgery.

Alpha-blockade with prazosin, doxazosin or phenoxybenzamine has been studied following diagnosis and as part of preparation during the preoperative period (71-74). While prasozin was associated with blood pressure reduction and diminished symptoms, it did not prevent blood pressure rises during surgery, and intravenous phentolamine was often required. Currently, phenoxybenzamine is the oral alpha blocker of choice pre-operatively (it is a non-selective, irreversible alpha blocker) but it has no DIN number and requires Health Canada special access (75-81). Three controlled case series have reported favourable effects on blood pressure control, need for intravenous phentolamine, blood loss and volume replacement of approximately one month of preoperative administration of the catecholamine synthesis blocker alpha-methyl-p-tyrosine (metyrosine) (82-84). Metyrosine can be considered if a inoperable/malignant Pheochromocytoma/PPGL is present and as an adjunct to alpha blockade pre-operatively in rare instances. Again, it has no DIN number.

Laparoscopic resections of pheochromocytomas/PPGLs, when compared with nonrandomized, conventional transabdominal adrenalectomy control subjects, have been associated with longer procedure times, comparable or less intraoperative cardiovascular instability, less blood loss and more rapid convalescence (69,70,85). Our recommendation to administer intravenous volume expansion in the perioperative period to avoid postoperative shock is supported by evidence from only small case series (86,87). However, it is also supported by pathophysiological rationale, including vasodilation after excision of the tumour, the residual effects of pre- and intraoperative alpha-blockers and intra- operative fluid loss.

Undetected pheochromocytoma during pregnancy carries a particularly high risk for both mother and fetus (88). Nuclear scanning and CT scanning is contraindicated so MRI is preferred for imaging/localization. Management depends on gestational age and should be individualized, but carried out in centres with experience in the management of both high-risk obstetrics and pheochromocytoma. In early pregnancy, if a decision is made to terminate the pregnancy, this should be carried out under alpha- and beta-blockade, followed immediately by tumour resection. In late pregnancy, alpha- and beta-blockade, followed by elective cesarean section and immediate tumour resection is recommended.

Patients with inoperable or metastatic malignant pheochromocytomas may be considered for treatment with combination chemotherapy and/or high doses of 131 iodine MIBG or Indium-111 labeled octreotide. The combination of cyclophosphamide, vincristine and dacarbazine has been associated with tumour and bio- chemical response rates of 57% and 79%, respectively, and improved performance status and blood pressure control (89,90). The possible but uncertain benefit of chemotherapy should be balanced against recognized chemotherapy-induced toxicity. High dose 131-Iodine MIBG has been associated with reduced symptoms, tumour size and possibly death (61). The methodology employed to assess the benefits of both of these approaches is not strong.

For patients with pheochromocytomas/PPGLs long-term follow-up studies measuring urinary or, where available, plasma metanephrines should be performed because recurrence after laparoscopic partial or unilateral adrenalectomy may occur and especially more frequent with the familial forms. Genetic testing of first degree family members for the familial forms should be considered for those with a family history of Pheochromocytoma/PPGL, <50 years in age, multiple lesions, malignant lesions, and bilateral Pheochromocytoma/PPGLs.

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