

Conn's Syndrome

Background

1. Definition:

- Increased aldosterone secretion due to adrenal adenoma, adrenal hyperplasia, or carcinoma

2. General info:

- Jerome Conn, in 1955, described a syndrome of hypokalemia and hypertension associated with adrenal adenoma and increased aldosterone

Pathophysiology

1. Pathology of disease

- Increased aldosterone leads to sodium retention, potassium and hydrogen ion loss in the distal tubules causing hypertension, hypokalemia, and metabolic alkalosis
- Causes:
 - Adrenal adenoma, usually unilateral (30-60%)
 - Bilateral adrenal hyperplasia (10-40%)
 - Glucocorticoid remediable hyperaldosteronism (GRA) (Familial type I)
 - Familial occurrence of aldosterone producing adenoma or bilateral hyperplasia (Familial type II)
 - Carcinomas

2. Incidence, prevalence:

- 4.8-5.9% in hypertensive population^{10,11}
- 14% prevalence in patients with diabetes and resistant hypertension⁹
- 11.3% incidence in patients with resistant hypertension⁷

3. Morbidity / mortality

- 1° aldosteronism
 - Higher prevalence of cardiovascular events than essential hypertension, no further increased risk after tx
 - Renal dysfunction, reversible with tx³

Diagnostics

1. Suspect dx in pts with:

- Hypokalemia and hypertension
- Resistant hypertension
- Incidental finding of adrenal adenoma
- Family hx of early onset hypertension
- CVA <40 yo and HTN
- Family hx of 1° hyperaldosteronism
- (Consensus panel recommendation from The Endocrine Society)¹³

2. History

- Can be asymptomatic
- Headache, muscle weakness, fatigue, cramping, polyuria (hypokalemic nephropathy), nocturia, polydipsia, paresthesias, tetany, attacks of recurrent weakness

3. Physical exam

- Diastolic hypertension
- Severe hypertension

- Drug resistant hypertension
- 4. Diagnostic testing
 - Laboratory evaluation:
 - Hypokalemia (25-60%)
 - Metabolic alkalosis
 - Screening plasma aldosterone concentration/plasma renin activity ratio (PAC/PRA):
 - PRA decreased and PAC increased:
 - Suspect hyperaldosteronism
 - PRA increased and PAC increased:
 - Suspect secondary hyperaldosteronism
 - PAC and PRA decreased:
 - Suspect hypercortisolism or licorice ingestion
 - Additional PAC/PRA notes:
 - Aldosterone receptor antagonists (spironolactone) should be discontinued 6 weeks prior to testing
 - ACEIs and ARBs may falsely elevate PRA
 - If PRA very low in presence of ACEI or ARB
 - Highly predictive of 1° hyperaldosteronism
 - Liberalize sodium intake prior to testing
 - Testing done mid morning with pt sitting 5-15 min and either standing or sitting previous 2 hr
- 5. Diagnostic imaging:
 - CT or MRI to detect adenomas if PAC/PRA increased
 - Absence of mass does not exclude adenoma (lesion <1 cm)
 - Bilateral lesions are not always diagnostic of hyperplasia (1 side with nonfunctioning adrenal nodule)
 - Adrenal vein sampling (AVS) as directed by endocrinologist, may help to distinguish between adenoma and hyperplasia
 - Diagnosis confirmation: (recommend endocrinologist referral)
 - PAC/PRA >23.6 (when patients are sitting) had 97% sensitivity and 94% specificity, PAC/PRA >66.9 had 100% specificity
 - In another study the cut-off value of a PAC/PRA of 69 corresponded to the best compromise value between sensitivity (96%) and specificity (85%), the mean values for the PAC/PRA in patients with essential hypertension are 4-10
 - PAC/PRA not diagnostic alone
 - Further information on confirming diagnosis may be complex
 - See Funder et. al.¹³ for details

Differential Diagnosis

1. Essential hypertension
2. Renovascular hypertension
3. Pheochromocytoma

Therapeutics

1. Surgical tx:

- If imaging is positive for unilateral mass and age <40 consider adrenalectomy
- Unilateral:
 - 4-fold increase in PAC with AVS, consider adrenalectomy for adenoma or hyperplasia
- No lateralization of AVS results
 - Medical tx for hyperaldosteronism
 - Consider screening for GRA

2. Medical tx: aldosterone antagonist

- Spironolactone most effective, dosing from 50-400 mg div BID
- Eplerenone has less antiandrogen activity
- Amiloride and triamterene are alternatives to spironolactone
- Long-term issues with aldosterone antagonists include:
 - Men: possible gynecomastia and impotence
 - Women: dysmenorrhea and intermenstrual bleeding
 - May need alternative drug

Follow-Up

1. Refer to specialist

- Endocrinology consult
 - Direct confirmatory testing
 - Differentiate between hyperplasia and adenoma
 - Determine surgical vs. medical tx

References

1. Milliez P, Girerd X, et al. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol* 2005 Apr 19;45(8):1243-8.
2. Catena, Cristiana, MD, PhD, Colussi, GianLuca, et al. Cardiovascular Outcomes in Patients With Primary Aldosteronism After Treatment. *Arch Intern Med* 2008 Jan 14;168(1):80
3. Sechi, Leonardo, Novello, Marileda, et al. Long-term Renal Outcomes in Patients With Primary Aldosteronism. *JAMA* 2006 Jun 14;295(22):2638
4. Mulatero, Paolo, Stowasser, et al. Increased Diagnosis of Primary Aldosteronism, Including Surgically Correctable Forms, in Centers from Five Continents. *J Clin Endocrinol Metab* 2004 Mar;89(3):1045-50.
5. Tiu, Sau-Cheung, Choi, et al. The Use of Aldosterone-Renin Ratio as a Diagnostic Test for Primary Hyperaldosteronism and Its Test Characteristics under Different Conditions of Blood Sampling. *J Clin Endocrinol Metab* 2005 Jan;90(1):72
6. Boscaro, Marco; Ronconi, et al. Diagnosis and management of primary aldosteronism. *Current Opinion in Endocrinology, Diabetes & Obesity*. 15(4):332-338, August 2008.
7. Douma S, Petidis K, Douma M, et al. Prevalence of primary hyperaldosteronism in resistant hypertension: a retrospective observational study. *Lancet*. 2008 Jun 7;371(9628):1921-6

8. Bernini G, Moretti A, Orlandini C, et al. Plasma and urine aldosterone to plasma renin activity ratio in the diagnosis of primary aldosteronism. *J Hypertens*. 2008 May;26(5):981-8.
9. Umpierrez GE, Cantey P, Smiley D, et al. Primary aldosteronism in diabetic subjects with resistant hypertension. *Diabetes Care*. 2007 Jul;30(7):1699-703. Epub 2007 Apr 11
10. Fogari R, Preti P, Zoppi A, et al. Prevalence of primary aldosteronism among unselected hypertensive patients: a prospective study based on the use of an aldosterone/renin ratio above 25 as a screening test. *Hypertens Res*. 2007 Feb;30(2):111-7.
11. Rossi GP, Bernini G, Caliumi C, A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol*. 2006 Dec 5;48(11):2293-300.
12. Young WF Jr. Primary aldosteronism: A common and curable form of hypertension. *Cardiol Rev*. 1999 Jul-Aug;7(4):207-14.
13. John W. Funder, Robert M. Carey, Carlos Fardella, et al. Case Detection, Diagnosis, and Treatment of Patients with Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, September 2008, 93(9):3266–3281.

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