Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jicc

Approach to the true resistant hypertensive and treatment approaches

Matthew Weir

Division of Nephrology, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, United States

ARTICLE INFO

Article history:
Received 19 January 2015
Accepted 11 February 2015

1. Introduction

The definition of resistant hypertension (HTN) based on JNC-7 is a failure to reach an appropriate blood pressure (BP) goal with at least a three-drug regimen in fully approved doses one of which is a diuretic and that the patient is actually taking. That is a critical issue. 90% of HTN is essential in nature; remaining 10% is obviously secondary HTN.

1.1. *Identifiable causes of HTN*

Kidney disorders are an important cause of secondary HTN but endocrine disorders important in part that is related particularly to the adrenal gland. Both hypo- and hyperthyroidism can be associated with high blood pressure (BP). Several other causes are as described in Table 1.

1.1.1. *Subclinical hypercortisolism*

Subclinical hypercortisolism is important. A study involved more than 400 people who were appropriately tested and ultimately confirmed (8% had confirmed hypercortisolism), representing adrenal gland at work. Correlates of confirmed subclinical hypercortisolism were older age ($p = 0.02$), DM ($p = 0.06$) and non-dipping pattern of ambulatory BP Monitoring ($p = 0.04$). Interestingly, this type of disease might also be responsive to a drug like spironolactone.

1.1.2. *Thyroid disease*

Hypothyroidism interestingly is associated more with diastolic rather than the systolic BP and is often related to reduced cardiac output, reduction in heart rate. In hyperthyroidism, somewhat different pathophysiology exists. Rise in systolic BP is much more common than diastolic BP.

1.1.3. *Pheochromocytoma*

One needs to remember it is an exceedingly rare and really the most important syndrome. There might be pseudo-pheochromocytoma simply because that is more commonly seen in people who are excitable, anxious but also one needs to consider. There are simple and straightforward strategies to rule it out.

1.1.4. *Hyperparathyroidism*

There are linkages with early evidence of vascular disease. What is most fascinating about this disease is that even if one corrects the parathyroid elevation surgically, it does not always go away suggesting that there are lingering structural effects.

1.1.5. *Primary hyperaldosteronism*

The prevalence of primary Hyperaldosteronism is substantial. In an Anglo-Scandanavian Cardiovascular Outcome Trial (ASCOT), more than 20000 people randomized to either get a beta-blocker and a thiazide or an ACE and a CCB. Nearly more than 1400 of the patients needed more medication and simply adding a whiff of spironolactone dropped the systolic BP about 20 mmHg which is impressive reduction.

E-mail address: Mweir@medicine.umaryland.edu.
http://dx.doi.org/10.1016/j.jicc.2015.03.020

Table 1 – Identifiable cause of hypertension.

Renal disorders	**Other causes**
- Parenchymal disease	- Sleep apnea
- Renovascular disease	- Coarctation of the aorta
Endocrine disease	- CNS tumors
- Thyroid disease	- Autonomic dysreflexia with spinal cord lesions
- Mineralocorticoid excess	- Porphyria
- Glucocorticoid excess	- Carcinoid
- Pheochromocytoma	- Exogenous substances
- Hypercalcemia	
- Acromegaly	

1.2. *Molecular mechanisms of aldosterone vascular toxicity*

There are lots of hypothetical mechanisms for the high aldosterone/low renin in hypertensives (Table 2).

Perhaps, the most important of interest is evidence that there may be visceral adipose tissue production of aldosterone which may explain why it is very common in overweight people, particularly those with obstructive sleep apnea. Overweight people tend to retain sodium and water by day. When they recline at night, the rostral shift of fluid shifts up to the neck and can facilitate more obstructive symptoms. Thus using a mineralocorticoid receptor antagonist in people with obstructive sleep apnea can actually be very helpful for the BP and very helpful for facilitating breathing at night. People with metabolic syndrome, have lower PRA and higher aldosterone levels compared to those without metabolic syndrome. Obese hypertensives have higher plasma aldosterone levels compared to overweight and normal weight hypertensive probably related to visceral adiposity (Fig. 1).

Table 2 – Hypothetical mechanisms for relatively high aldosterone, despite low renin, in hypertensives.

- Aldosterone stimulating factor in visceral adipose tissue
- Other aldosterone stimulating factors
- Secretion of aldosterone by adipocytes
- Decreased NO bioavailability
- "Autonomous" aldosterone production
- Variation in aldosterone synthetase (*CYP11B2*)

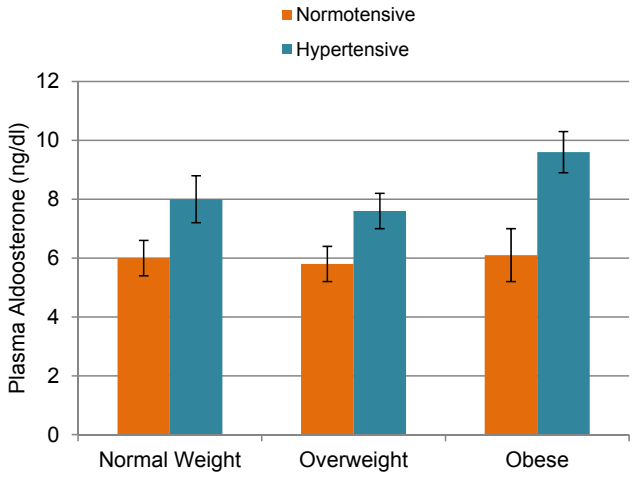

Fig. 1 – Plasma aldosterone levels by body weight and BP status.

Table 3 – Prevalence of primary aldosteronism around the world.

- 1994 – Australia – 8.5% (n = 199)
- 1994 – India – 8.7% (n = 103)
- 1999 – Slovakia – 13.0% (n = 115)
- 1999 – UK – 14.4% (n = 135)
- 1999 – S. Africa – 6.4% (n = 303)
- 2000 – Singapore – 4.6% (n = 350)
- 2000 – Chile – 5.2% (n = 305)
- 2002 – Italy – 6.3% (n = 1043)
- 2002 – Olmsted County, USA – 12.0% (n = 117)
- 2004 – Japan – 5.9% (n = 1020)

Interestingly, increasing left ventricular mass (LVM) and higher proteinuria have positive correlation with higher plasma aldosterone concentration. These raise greater concern for vascular disease and resistant HTN. Thus in a society where we tend to eat too much salt, it is the combination of being overweight, having obstructive sleep apnea, and having too much aldosterone which appears to predispose to greater problems with the blood pressure.

Aldosterone excess is fairly common around the world (Table 3). Probably it is even more common if discerning techniques for screening people who are overweight and particularly those with obstructive sleep apnea are applied.

2. Obstructive sleep apnea and resistant HTN

There is high prevalence of unrecognized sleep apnea in drug-resistant hypertension, in large part related to excess aldosterone. In people with resistant hypertension, obstructive sleep apnea is frequent (Fig. 2).

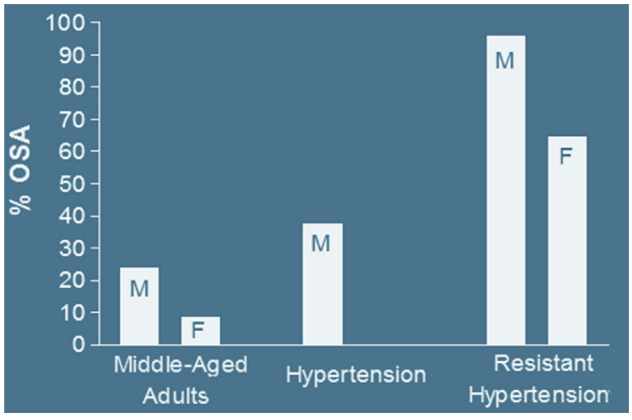

Fig. 2 – Prevalence of obstructive sleep apnea. Source: Logan AG, et al. J Hypertens. 2001 Dec;19:2271–2277