

Amplified Screening and Workup Protocol for Primary Aldosteronism: A Strategy to Improve New Zealand's Woefully Low Diagnostic Rates? / Original Article

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Summary

Primary aldosteronism (PA) is diagnosed uncommonly in New Zealand despite reportedly affecting at least 2% of the general hypertensive population and up to 22% of patients referred to specialist clinics for hypertension. Using an amplified screening and workup protocol, the diagnostic rate for PA was increased four-fold at the Waitemata DHB hypertension clinic, compared with an earlier series. The details and implications of this are discussed.

Abstract

Aim

To increase diagnostic rate of primary aldosteronism at the Waitemata DHB hypertension clinic

Method

An amplified screening and diagnostic protocol for PA was implemented from the beginning of 2013 and results audited after 18 months

Results

Diagnostic rate for PA was 5.2% (33 of 631 new hypertensive patients), compared with 1.25% in an earlier series.

Conclusion

The amplified screening and diagnostic protocol is suggested as a strategy to increase generally low diagnostic rates of PA in New Zealand.

Introduction

Primary aldosteronism (PA), also known as Conn's syndrome, is the collective term for a group of disorders characterised by autonomous aldosterone excess. Hypertension is the commonest manifestation,

with perhaps 50% also showing provoked or unprovoked hypokalaemia. Approximately 1/3 are due to a unilateral aldosterone-producing adenoma (APA), and unilateral adrenalectomy offers a potential cure in these individuals. The remainder have bilateral aldosterone production. These individuals are grouped under the loose term "bilateral adrenal hyperplasia" although the adrenals often show no abnormality on imaging. These patients are not amenable to surgical cure and treatment is with aldosterone receptor blockade, usually spironolactone. In a very small subgroup of PA is familial (FH Types 1, 2, and 3) ¹.

The Waitemata DHB Hypertension Clinic, based at North Shore Hospital was established in March 2009 and accepts referrals from general practitioners and hospital specialists of patients with difficult or resistant hypertension². From the outset, a policy of liberal screening for PA was established, with the majority of patients having renin and aldosterone checked at the first visit, generally without adjustment of medication. Where these results were suggestive of PA (renin < 10mu/l, aldosterone > 400pmol/l and ratio > 55) patients were subjected to a Saline Suppression Test⁵ (SST), which was (and remains) the favoured confirmatory test for PA in New Zealand. Where the SST demonstrated aldosterone non-suppressibility patients were referred for adrenal imaging, and a small number also went on to adrenal

vein sampling (AVS). The first 635 patients through the clinic (March 2009 – December 2011) were audited for prevalence of PA³. Despite 71% of patients having renin and aldosterone checked on at least one occasion only 8 cases of PA were identified, giving a (clinic) prevalence of 1.25%. Furthermore, all 8 patients had a history of both resistant hypertension and hypokalaemia.

8 cases and 1.25% of referred hypertensive patients diagnosed with PA seemed an unusually low number, given that the prevalence of PA is thought to be 2-5% of the general hypertensive population and 17-22% of the specialist hypertension clinic population^{1,4}. On the basis that we had probably been missing substantial numbers of cases we reviewed our practice and instituted a much more rigorous screening and workup protocol for PA. With small differences this was based on the work of Stowasser's group in Brisbane who are world-leaders in this area and whose unit diagnoses more than 50 cases of PA annually^{1,5}. This protocol was implemented from the beginning of 2013.

Method

All new patients attending the Waitemata Hypertension Clinic were screened for PA and (as appropriate) worked up with the new protocol from early January 2013, with a view to re-auditing diagnostic rate for PA at the end of 18 calendar months when approximately the same number of new patients as the earlier series would have been seen at the clinic.

The detailed protocol is in Table 1, but the most important considerations are:

- Universal screening for PA in patients attending the hypertension clinic, with a renin and aldosterone level checked at the first clinic visit, with the patient on their existing medication.
- Careful adjustment of drug therapy, if required, prior to rechecking renin and aldosterone levels.
- An understanding that hypokalaemia has a profound effect on aldosterone levels, and that “non-elevated” aldosterone levels in the presence of hypokalaemia are uninterpretable and do not exclude a PA diagnosis. This is also a situation where aldosterone-renin ratio < 55 is common and does not exclude PA. (In fact, aldosterone-renin ratio is not mentioned in the protocol).
- Replacement of SST Test by Fludrocortisone Suppression Test (FST- described Table 1.)

- Adrenal imaging includes computerised tomographic venography (CTV) to assist interventional radiologist with adrenal vein sampling.
- Adrenal vein sampling (AVS)⁵ in most patients with biochemically confirmed PA who are potentially fit for laparoscopic adrenalectomy, irrespective of radiological findings

Results

631 new patients with difficult or resistant hypertension were seen at the Waitemata Hypertension Clinic between January 2013 and June 2014.. Average blood pressure at the first clinic visit was 155/87 and average age was 57 years. 85% of patients were on medication (mean 2.6 drugs).

33 of the 631 patients (5.2%) were diagnosed with definite (29) or probable (4) PA. Demographics and clinical details are in Table 1. In summary:

- 12 unilateral APA treated with laparoscopic adrenalectomy
- 17 bilateral adrenal hyperplasia (confirmed with AVS) treated with spironolactone

- 2 with resistant hypertension (1 of whom hypokalaemic) and suggestive aldosterone-renin ratios lost to follow-up
- 2 with resistant hypertension (1 of whom had a radiological adenoma) and suggestive renin-aldosterone ratios, probable PA, and treated empirically with spironolactone, but not fully investigated because of advanced chronic kidney disease in both, and age (65 and 73).

11 of the 33 cases did not meet the JNC-7 criteria for the diagnosis of resistant hypertension (blood pressure not at target despite a combination of optimal doses of a minimum of 3 complementary antihypertensive drugs, one of which is a diuretic)⁶, and 18/33 had no history of provoked or unprovoked hypokalaemia.

29 patients had biochemical diagnosis of PA confirmed with and aldosterone-suppression test. In 2 this was SST, and in 27 FST. Importantly, among the 27 with positive FST were 5 who had previously had negative SST and had had the diagnosis of PA excluded, sometimes for a number of years. These 5 were among 15 patients who had been seen earlier at specialist clinics, specifically for difficult hypertension,

and had the diagnosis of PA missed (6 at endocrine clinics, 3 at renal clinics, 4 at internal medicine clinics and 2 at a cardiology clinics). Reasons for earlier mis-diagnosis included:

- Normal SST
- Failure to screen for PA
- Misinterpretation of available renin and aldosterone levels.
- Failure to retest patients after cessation or replacement of interfering medications.
- Failure to ascertain a specific cause for persisting unprovoked hypokalaemia

21 cases had adrenal vein sampling, which, although a technically challenging procedure, provided useful diagnostic information in all cases. The importance of AVS is illustrated by:

- Patients case 2 and 22, who had no radiological adenoma, but AVS showed clear lateralisation and both went on to laparoscopic adrenalectomy which was curative.
- Patient 28, who had what appeared to be a good-sized unilateral adrenal adenoma, but AVS revealed bilateral aldosterone secretion, proving that the lesion was an incidentaloma, and laparoscopic adrenalectomy would have been ineffective.

It is acknowledged that 8/12 patients who had laparoscopic adrenalectomy (all of whom experienced clinical and biochemical cure of PA) were not subjected to AVS. This was in part a hang-over from the previous era where individuals "clinically obvious" PA and with a typical APA > 1.5cm diameter were referred direct for adrenalectomy. This practice carries inherent risk, and by the end of the period of this audit, all patients with biochemically conformed PA were being referred for AVS, regardless of radiological findings.

Discussion

33 cases of confirmed or probable PA were diagnosed among 631 patients attending a specialist hypertension clinic from January 2013 – June 2014: – 5.2% of the total. Although this number is still relatively low, it represents a four-fold increase in our earlier diagnostic rate of 1.25%, and this was entirely due to the implementation of a much more rigorous screening and workup protocol.

Furthermore, 33 cases of PA in the Waitemata DHB (population 550 000) over 18 months, in the New Zealand context, is a very large number. There is no registry or formal counting of PA cases in New

Zealand, but this is a diagnosis, which, in general, is made only sporadically, and uncommonly, usually by endocrinologists. The first author (WvdM) did an informal poll of all 19 individuals identifying as endocrinologists in the greater Auckland region (population 1 540 000) asking the question "how many new cases of primary aldosteronism did you diagnose in the calendar year 2013". Among the 13 respondents there were 6 cases. This suggests that the majority of PA diagnoses in greater Auckland are made at the Waitemata Hypertension Clinic which serves only 1/3 of the greater Auckland population. This in turn suggests, indeed confirms, that the majority of PA cases in greater Auckland must still be going undiagnosed. Informal discussions with colleagues in other centres suggests that this situation probably pertains throughout the country.

Confining PA screening to those with resistant hypertension and hypokalaemia would likely miss the majority of cases. In our series, 1/3 did not meet the criteria for resistant hypertension, and more than 1/2 had no history of provoked or unprovoked hypokalaemia.

In the authors' opinion and experience, FST is superior to SST as a confirmatory test for PA, and 5/33 patients cases were previously misdiagnosed on the basis of a negative SST. This remains unresolved in the literature however, and there are few direct comparisons of the tests. One head-to-head study though⁷, did suggest that SST was more likely to give a false-negative result. The recent study of Ahmed et al⁸ suggests that technical refinements to the SST may make it more reliable. From a purely logistic point of view the authors find FST more convenient as it is conducted on a purely outpatient basis, whereas SST requires half a day in a hospital or clinic with attendant nursing and other costs.

Does widespread non-diagnosis of PA matter, given that the majority of undiagnosed patients will likely be on antihypertensive treatment anyway? Current evidence suggests that it probably does, and that cardiovascular and renal outcomes may be worse in patients with undiagnosed PA treated with conventional antihypertensive therapy rather than adrenalectomy or aldosterone receptor blockade^{9,10}. In the authors' view it is also a great pity to deny patients access to one of the few truly curable forms of hypertension (laparoscopic adrenalectomy in APA).

Given that neither hypokalaemia nor resistant hypertension are reliable markers of PA, and that many, perhaps the majority, of affected individuals will never get to a specialist clinic, consideration should be given to universal screening of hypertensive patients for PA. This would involve a blood test for renin and aldosterone prior to commencing individuals on antihypertensive drugs in primary care. Specialist support would be required to review suspicious results and see patients as required.

Either way, substantial efforts need to be made to increase the diagnostic rate of PA in New Zealand, and, as a starting point our amplified screening and diagnostic protocol is commended to clinicians in New Zealand seeing patients for hypertension at specialist clinics.

Table 1. Waitemata DHB Hypertension Clinic amplified screening and workup protocol for PA in hypertensive patients

At first visit check plasma renin, aldosterone, and electrolytes on existing medication
(if on no medication, do not start any drugs until results available)
Renin is reported as $\mu\text{U/l}$ (divide by 8.4 to get ng/ml/hour)
Aldosterone is reported as pmol/l (divide by 27.7 to get ng/dl)

Interpretation of renin and aldosterone levels in hypertensive patients according to existing drug therapy at first clinic visit

No drugs

K < 3.5, renin < 8.2, aldo > 416 (very likely PA)
K < 3.5, renin < 8.2, aldo > 165 (likely PA)
K < 3.5, renin < 8.2, aldo < 165 (possible PA)

K > 3.5, renin < 8.2, aldo > 165 (possible PA)

K > 3.5, renin < 8.2, aldo < 165 (very unlikely PA)

K < 3.5, renin > 8.2, aldo (any) (very unlikely PA)

Thiazides

K < 3.5, renin < 8.2, aldo > 416 (likely PA)

K < 3.5, renin < 8.2, aldo > 165 (possible PA)

K > 3.5, renin < 8.2, aldo < 165 (very unlikely PA)

K < 3.5, renin > 8.2, aldo > 165 (possible PA)

K > 3.5, renin > 8.2, aldo > 416 (possible PA)

ACE-inhibitors and DHP calcium channel blockers

K < 3.5, renin < 8.2, aldo > 416 (very likely PA)

K < 3.5, renin < 8.2, aldo > 165 (likely PA)

K > 3.5, renin < 8.2, aldo > 165 (possible PA)

K > 3.5, renin > 8.2, aldo > 416 (possible PA)

Beta blockers

K < 3.5, renin < 8.2, aldo > 165 (likely PA)

K > 3.5, renin < 8.2, aldo > 416 (possible PA)

K > 3.5, renin < 8.2, aldo < 165 (unlikely PA)

K > 3.5, renin > 8.2, aldo (any) (very unlikely PA)

Patients highlighted in bold selected for further evaluation

↓
Discontinue spironolactone, beta blocker, thiazide, (and if possible ACE/ARB, and DHP-CCB)

↓
Temporarily replace (if necessary) with verapamil +/- doxazosin +/- hydralazine

↓
Supplement with KCl as necessary to maintain normal serum K⁺ and encourage liberal sodium intake

↓
Wait several weeks

↓
Mid-morning renin, aldosterone and electrolytes (seated 5 mins after at least 1 hour in upright position)

↓
Plasma renin < 8.4 mu/l warrants further evaluation for PA, providing aldosterone > 165pmol/l and serum K⁺ >= 3.5mmol/l
(if serum K⁺ < 3.5mmol/l and aldosterone < 165pmol/l the test is uninterpretable and needs to be repeated after correcting potassium)

↓
Confirmatory Testing

Outpatient Fludrocortisone Suppression Test (FST)

5 day test:- first doses of test medication with lunch on day 1, last doses with breakfast on day 6

NaCl tabs 10mmol 3TDS + increase dietary sodium

Slow K 2 TDS (or more)

Fludrocortisone 0.1mg QID

Day 3 morning check U+E, If K < 3.5mmol/l increase Slow K to 3 TDS or QID

Day 6 mid-morning, seated 10-15 mins after ambulation 1-2 hrs , collect blood for renin, aldosterone, and electrolytes

PA is confirmed if Aldosterone > 165pmol/l and renin < 8.2mu/l and serum K > 3.5mmol/l

4.	65	M	European	N	Y	N	FST pos / past SST neg	Y/bilat	Spiron-lactone	normotensive	endocrine
5.	65	M	Middle-East	Y	Y	Y	FST pos	N	Laparoscopic adrenalectomy	cured	endocrine
6.	38	F	European	N	Y	Y	FST pos	N	Laparoscopic adrenalectomy	cured	-
7.	37	F	Maori	Y	Y	Y	FST pos / past SST neg	N	Laparoscopic adrenalectomy	cured	endocrine
8.	47	F	Chinese	N	Y	Y	FST pos	N	Laparoscopic adrenalectomy	cured	internal medicine
9.	40	F	European	N	N	N	FSTpos	Y/bilat	Spironolactone	normotensive	internal medicine
10.	64	M	European	Y	N	Y	No (CKD 4)	N	Spironolactone	normotensive	-
11.	59	F	Indian	Y	N	N	FST pos	Y/bilat	Spironolactone	normotensive	cardiology
12.	36	F	European	N	N	Y	FST pos	Y/unilat	Laparoscopic adrenalectomy	cured	-
13.	56	F	Maori	Y	Y	Y	FSTpos	N	Laparoscopic adrenalectomy	cured	-
14.	33	M	Maori	Y	Y	No imaging	No	-	-	Lost to followup	-
15.	42	F	Pacific	Y	N	No imaging	No	-	-	Lost to followup	-
16.	73	M	Maori	Y	N	Y	No (CKD 4)	-	Spironolactone		-
17.	54	M	European	Y	Y	Y	FST pos	N	Laparoscopic adrenalectomy	cured	cardiology
18.	43	M	African	Y	N	N	FSTpos	Y/bilat	Spironolactone	normotensive	internal medicine
19.	47	F	European	Y	Y	N	FST pos	Y/bilat	Spironolactone	normotensive	internal medicine
20.	32	F	Chinese	Y	Y	Y	FST pos	N	Laparoscopic adrenalectomy	cured	internal medicine
21.	30	F	European	N	N	N	FST / past SST neg	Y/bilat	Spironolactone	normotensive	endocrine
22.	42	F	European	N	Y	N	SST pos	Y/unilat	Laparoscopic adrenalectomy	cured	-
23.	45	F	Maori	N	Y	N	FST / SST neg	Y/bilat	Spironolactone	normotensive	renal
24.	46	F	Filipino	Y	N	N	FST pos	Y/bilat	Spironolactone	normotensive	-
25.	57	F	European	N	N	N	FST pos	Y/bilat	Spironolactone	normotensive	-
26.	47	M	Middle-East	Y	N	N	FST pos	Y/bilat	Spironolactone	normotensive	endocrine
27.	65	M	Pacific	Y	N	N	FST pos	Y/unilat	Laparoscopic	cured	-

									adrenalectomy		
28.	52	M	Filipino	Y	N	Y	FST pos	Y/bilat	Spironolactone	normotensive	renal
29.	60	F	European	N	N	N	FST pos	Y/bilat	Spironolactone	normotensive	endocrine
30.	40	M	Chinese	Y	N	N	FST pos	Y/bilat	Spironolactone	normotensive	-
31.	60	F	European	Y	N	N	FST pos	Y/bilat	Spironolactone	normotensive	-
32.	48	F	European	N	N	N	FST pos	Y/bilat	Spironolactone	normotensive	-
33.	50	F	Chinese	Y	Y	N	FST pos	Y/bilat	Spironolactone	normotensive	-

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