

Should all Hypertensive Patients be Screened for Primary Aldosteronism?

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Abstract

Our aim was to determine whether the prevalence of Primary Aldosteronism (PA) in a referral hypertensive population is high enough to warrant routine screening for PA amongst unselected hypertensive's in general practice. A retrospective clinical audit was conducted on 635 patients referred for specialist hypertension review, over a period of 33 months (March 2009 till December 2011).

We found a PA prevalence of (confirmed or probable) in 8/635 referred patients (1.25%) which is lower than the previously reported prevalence. Among the 178 patients who at discharge had met the JNC-7 criteria for resistant hypertension the prevalence was 4.5% (8/178). All the PA cases met the criteria for resistant hypertension, and in addition, all had unprovoked hypokalaemia.

We conclude that in our population, routine screening for PA amongst hypertensive individuals in general practice cannot be justified, and that even in a specialist hypertension clinic population investigation should likely be reserved for those with a combination of resistant hypertension and unprovoked hypokalaemia.

Keywords: Hypertensive; Primary aldosteronism; Hypokalaemia

Introduction

Primary Aldosteronism (PA) is defined as non-suppressible hypersecretion of aldosterone by adrenal glands, with consequent suppression of plasma renin activity. It was described by Jerome Conn in 1955 [1]. It is said to be an under diagnosed and important secondary endocrine cause of hypertension, and is one of the few potentially curable causes of hypertension using both medical and surgical interventions [2]. The most common subtypes of PA are bilateral adrenal hyperplasia (60%) and aldosterone-producing adenoma (30%). Other rarer causes include adrenal carcinoma (rare) and glucocorticoid suppressible hyperaldosteronism (rare).

The prevalence of PA has been reported to be 1-14% in the general hypertensive population and as high as 20% in specialist referral populations with resistant hypertension [2-4].

In the early descriptions, hypertension in primary aldosteronism was invariably accompanied by hypokalaemia [1]. However in recent years it has been reported that perhaps half are normokalaemic although diuretic-induced hypokalaemia may be more common in this group [5]. In the normokalaemic group therefore, the diagnosis may not be suspected unless plasma renin and aldosterone are checked.

There is ongoing debate as to the cost-effectiveness of screening for PA and who to screen, taking into consideration on one hand its relatively low prevalence, but on the other hand the potential for a surgical cure or specific medical therapy where the diagnosis is made [5,6].

Screening for PA is commonly undertaken in the specialist workup of difficult hypertension, but whether it should be utilised at the community/primary care level remains uncertain.

A specialist, publically funded, hypertension clinic was set up at North Shore Hospital (Waitemata District Health Board, WDHB) in March 2009 (WvdM and VvdM) in parallel with a private service (WvdM and VvdM) which accepts referrals for similar indications, for patients with health insurance, and operates under an identical model of care [7]. For the purposes of this review all the patients are considered together. In New Zealand, the majority of hypertension is managed by family practitioners.

The clinic accepts referrals for hypertensive patients with the following indications:

- Blood pressure not at target (using JNC-7 criteria) on ≥ 2 medications [8]
- Young patients with elevated office blood pressures not currently on treatment in whom the diagnosis of chronic hypertension and/or indication for treatment is uncertain
- The referrer suspects an underlying secondary cause of hypertension
- Multiple antihypertensive drug intolerances

An important part of the function of the clinics is to exclude secondary or treatable causes of hypertension, and as part of this there has been a liberal approach to screening for PA. We wished to review the yield of this liberal approach in terms of diagnosing PA, especially in those without hypokalaemia.

We conducted a retrospective clinical audit which objectives were

- To determine the incidence of PA in a specialist hypertension clinic population.
- To determine, in particular in this referral population, the incidence of normokalaemic PA, and whether this is high enough to warrant routine screening of normokalaemic hypertensive patients either in the specialist clinic or at primary care level.

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Methods

We undertook a retrospective audit of 635 patients seen in the Hypertension Clinic over a period of 33 months (March 2009 – December 2011).

Most patients in the Hypertension Clinics were routinely screened for PA as part of workup for secondary causes of hypertension. Screening was not performed if the diagnosis of PA was deemed irrelevant to patient management; - for example, hypertension quickly responsive to simple therapy, clear evidence of alternative secondary causes, and the very elderly.

Renin and aldosterone were collected in hospital or community laboratories. The specimens were obtained in the resting seated position at any time of day. No antihypertensive medications were required to be discontinued prior to testing apart from spironolactone which (where applicable) was withheld for a month. (There is evidence that diagnostic accuracy may be enhanced by discontinuing other drugs which may affect renin and aldosterone measurements [9]). However, this is considerably cumbersome and time-consuming and would not be practical in the context of screening for PA in primary care. In addition, there is some evidence that, although theoretically useful, the failure to complex adjustments to drug therapy may not in fact make much difference to PA diagnostic rates [10]. Urea, creatinine, and electrolytes were always measured simultaneously. Aldosterone results obtained with simultaneous serum potassium of < 3.5 mmol/L were disregarded and the test repeated following correction of the serum potassium.

Renin and aldosterone were measured at the LabPlus™ laboratory at Auckland City Hospital. Renin was measured by chemiluminescence immunoassay on *Diasorin Liaison* analyser, and aldosterone by competitive radioimmunoassay using the *Siemens Coat-A-Count* Aldosterone assay. The reference range for renin is 4-46 mU/L and aldosterone 100-850 pmol/L (for adults).

A positive screening test for PA required a suppressed plasma renin (< 10 mU/l) and an elevated aldosterone (usually > 400 pmol/l) and an aldosterone-renin ratio ≥ 40 , with a simultaneous serum potassium ≥ 3.5 mmol/l. A positive screening result was usually followed by a definitive test, almost always a Saline Suppression Test (SST) [9]. For this test the patients come in to the Haematology Day Ward at 8.30am. An intravenous cannula is inserted and blood drawn for aldosterone, serum creatinine and electrolytes. Two litres of 0.9% sodium chloride are then infused intravenously over 4 hours and a repeat sample for aldosterone drawn at the end. A “negative” test (aldosterone suppresses normally) is defined as an end-aldosterone < 165 pmol/l. A “positive” test (aldosterone non-suppressible) is defined as an end aldosterone > 165 pmol/l. Rarely (in our cohort only one test was performed), a Fludrocortisone Suppression Test is performed if there is strong clinical suspicion of PA with a negative or equivocal SST [9]. Once the PA diagnosis was confirmed biochemically the usual next step is computed tomography (CT) imaging of the adrenals, and, if indicated Adrenal Vein Sampling (AVS) although this is a test we have rarely utilised in the past [9].

Information on patients was obtained from electronic clinical and laboratory records and the Hypertension Clinic electronic data. Through WDHB clinical portal system Concerto (*CHCA 1181 de l'Express St. Terrebonne, Quebec, Canada*), we extracted results for all renin and aldosterone measurements as well as simultaneously measured plasma electrolytes, including those done as part of SST.

Results

The clinical and laboratory data of 635 patients were reviewed. 368 (58%) were female. Mean age was 59 yr for females and 52 yr for males. Average BMI was 29.0 kg/m², waist circumference 105.5 cm (male) and 97.1 cm (female).

At each visit, careful resting blood pressure was measured according to JNC-7 guidelines using a *Microlife* automated office blood pressure monitor (*Microlife AG, Widnau, Switzerland*) [8]. Mean initial blood pressure was 154/87 mmHg and final blood pressure (at time of discharge from clinic) was 130/76 mmHg.

85% (540) of the patients were on a mean of 2.6 antihypertensive medications on referral and 15% (95) on no antihypertensive medication. At discharge, 90% (572) of the patients were on a mean of 2.9 medications and 10% (63) were on no medication. Those discharged on no medication either had a confirmed diagnosis of white coat hypertension, pre-hypertension, were normotensive after treatment of a secondary cause, or (rarely) were subject to multiple antihypertensive drug intolerances (Table 1).

The most commonly prescribed classes of medication on discharge were (in order of frequency) Dihydropyridine Calcium Channel Blockers (DHP-CCB), angiotensin converting enzyme inhibitors (ACE-inhibitor), beta blockers, thiazide diuretics and angiotensin receptor blockers (ARB). If considered as a single “super-class”, drugs which interrupt the renin-angiotensin-aldosterone axis (“RAS blockers” – ACE inhibitors + ARB’s), these drugs constituted the most frequently prescribed group.

40% of those discharged on medication were on a thiazide (229), and an additional 14% (80) had been prescribed a thiazide at some time but proven intolerant, mostly due to hyponatraemia. All patients with resistant hypertension were either discharged on a thiazide, or were thiazide-intolerant.

Because of the heterogeneity of hypertensive populations, the JNC-7 definition of resistant hypertension is a useful one to identify a group with more difficult, treatment - resistant disease [8]. This is also the group in which secondary causes of hypertension, particularly PA is reportedly much more common, even as high as 20% [10]. At the final visit, 178 of the 635 patients (28% of all patients and 31% of patients discharged on antihypertensive medication) had fulfilled the JNC-7 criteria for resistant hypertension. The majority of these achieved target blood pressure but generally required more than 3 drugs.

Renin and Aldosterone were performed on 453 patients (71%)

77 patients had renin <10 mU/L

78 patients had aldosterone >400 pmol/L

52 had ARR ≥ 40 but with non-suppressed renin (> 10 mU/l)

15* had renin <10 mU/L, aldosterone >400 pmol/L and ARR ≥ 40 :

Co-morbidities	n	%
Diabetes mellitus	95	15
Ischaemic heart disease	51	8
Cerebrovascular disease	44	7
Peripheral vascular disease	19	3
Dyslipidaemia	463	73
Heart failure	70	11
Current smoker	70	11

Table 1: Co-morbidities of patients studied.

these patients were subjected to Saline Suppression Testing (SST), in addition to another 5 with high aldosterone and ARR and plasma renin (with one exception) only modestly above the 10mU/l cutoff (Total 19 SST) (Table 2).

Saline Suppression Test (SST) was performed on 19* (this included 6 with equivocal renin levels and 2 with high ARR excluded because of old age and comorbidities. The biochemical parameters of these patients are outlined in Table 3.

5 patients had positive SST (i.e. post SST Aldosterone >200 pmol/L). 3 had Aldosterone-Producing Adenoma (APA) diagnosed radiologically, 2 Bilateral Adrenal Hyperplasia (BAH), (Figure 1).

1 patient (no.17) with rennin <10, aldosterone >400 and ARR >40 interestingly had a negative SST result (post SST aldosterone 156 pmol/L). This was probably due to the effect of incompletely corrected plasma potassium. Subsequently, following liberal potassium supplementation he had a positive fludrocortisone suppression test which confirmed a PA diagnosis. On CT scan he had a 8mm left adrenal adenoma, and lateralisation of aldosterone secretion to the left adrenal was confirmed on adrenal vein sampling. He underwent a laparoscopic left adrenalectomy and achieved a clinical and biochemical cure.

In total therefore, there were 6 confirmed PA, with 4 APA and

two BAH one of which was presumptive. Patient 1 had a confirmed biochemical diagnosis of PA with normal adrenal CT. The diagnosis of BAH was confirmed by absence of lateralisation on selective AVS. Patient 16 had a positive SST and no obvious adenoma on CT. She declined AVS and elected for medical therapy. She was treated successfully with spironolactone and was labelled presumptive BAH (although functional APA below the limits of radiological resolution cannot be definitively excluded without AVS).

Of the 4 confirmed cases of APA, three had successful laparoscopic unilateral adrenalectomy. The fourth declined surgery and opted for long-term treatment with spironolactone. Both patients with BAH were treated successfully with spironolactone.

We have also included 2 other cases of probable PA who were not subjected to confirmatory testing. They were older (84 and 71 years respectively) and had multiple medical co-morbidities. They both presented with resistant hypertension, hypokalaemia, and plasma renins <2 mU/l and 6 mU/L respectively, and aldosterones 558 pmol and 1004 pmol/L respectively. Confirmatory testing with SST was not thought warranted, and both were treated empirically with spironolactone to which both made an excellent response.

Most of the studied patients had essential hypertension, with other secondary causes identified being shown in Table 4.

Discussion

Primary Aldosteronism (PA) is defined as autonomous aldosterone production by the adrenal glands, with the classical manifestations of hypertension and hypokalaemia [1].

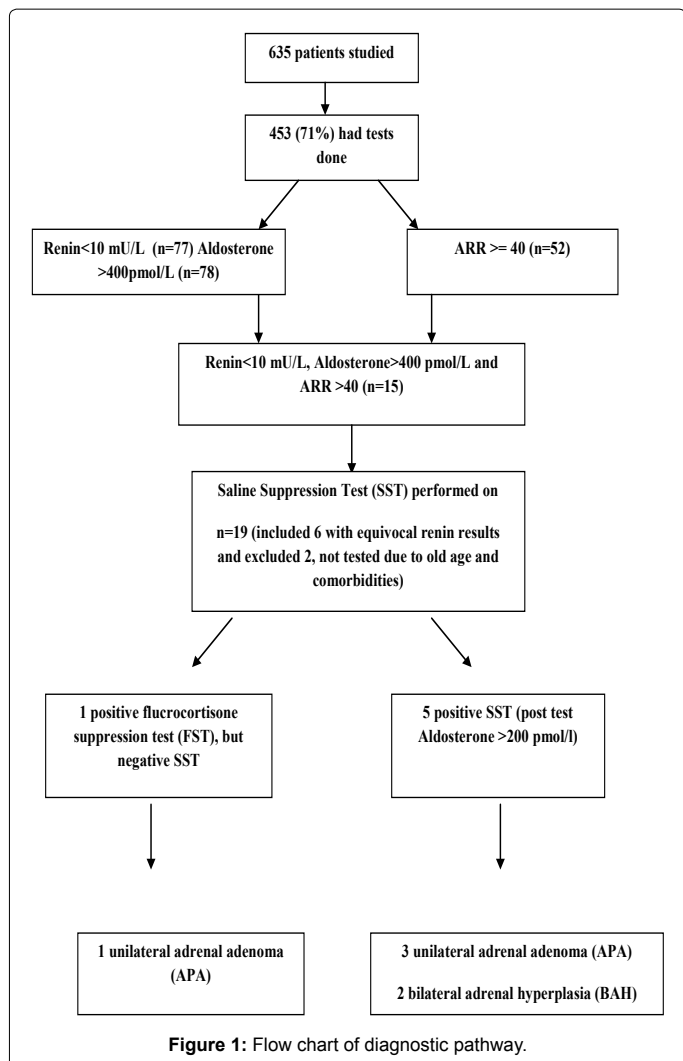
It has been reported as a relatively uncommon secondary cause of hypertension, with prevalence of 1-2% among unselected individuals with hypertension, although some groups have suggested this may be as high as 10-14% [3,4]. Its prevalence is reportedly as high as

Investigations (Average)	
Potassium (mmol/L)	5.0
Sodium (mmol/L)	139
Creatinine (umol/l)	85
eGFR (ml/min/1.73m2)	79
Microalbuminuria	n=121
24-hour ambulatory BP monitor use	n=173

Table 2: Relevant laboratory parameters on patients studied.

Patient	Sex	Age	Renin (mU/L)	Aldosterone (pmol/L)	Aldosterone-renin ratio (ARR)	Post-SST Aldosterone (pmol/L)	Baseline K+ (mmol/L)	Diagnosis/outcome
1	F	43	7	894	128	401	3.3	BAH
2	F	39	122	2502	21	370	4.6	Non-suppressed renin makes PA unlikely
3	M	41	<2	811	405	1319	2.5	APA
4	M	50	12	744	65	<70		Normal
5	M	72	6	361	66	110		Normal
6	F	43	12	468	39	<70		Normal
7	F	42	2	420	175	206	3.2	APA
8	M	57	15	719	48	102		Normal
9	F	61	<2	324	162	<70		Normal
10	F	58	4	295	78	103		Normal
11	M	52	17	1196	70	100		Normal
12	F	49	14	854	61	89		Normal
13	F	48	6	311	56	<70		Normal
14	F	62	14	804	57	<70		Normal
15	M	48	9	626	70	457	2.8	APA
16	F	41	10	720	65	207	3.2	BAH (presumptive)
17	M	61	4	540	135	156	3.1	APA
18	F	62	<2	438	219	159		Normal
19	F	69	5	429	86	<70		Normal

Table 3: Relevant clinical and laboratory datas on patients undergone SST.



	n
Essential hypertension	319
<i>Secondary hypertension</i>	
Primary renal disease	54
Renovascular disease	20
Obstructive sleep apnoea	31
White coat hypertension	58
Others	13

Table 4: Other causes of hypertension.

10-20% amongst selected specialist clinic populations with resistant hypertension [5]. Diagnosis of PA is important as it is potentially treatable by either medical therapy using aldosterone antagonists, or surgical adrenalectomy [6]. Although the majority of patients with PA have bilateral adrenal hyperplasia and are not amenable to surgical cure, there is accumulating evidence that specific treatment of hypertensive individuals with PA (whether by adrenalectomy, or medically with aldosterone receptor antagonists) results in better long-term outcomes than conventional antihypertensive drug therapy, even for similar levels of blood pressure control [11,12].

In our series of 635 patients referred for specialist assessment of difficult hypertension, 453 (71%) were screened for PA. Of these a

diagnosis of PA was confirmed in 6 patients (4 adrenal adenomas and 2 bilateral adrenal hyperplasia). Of the 4 with adenomas, three had successful laparoscopic adrenalectomies and the 4th patient elected for long-term medical treatment with spironolactone. The two patients with BAH were also treated with spironolactone. In addition, we have included in our tally two patients with probable PA, who were not further investigated due to age and co morbidities, but were treated empirically and successfully with spironolactone.

All 8 of the patients with confirmed or probable PA presented with stage 2 hypertension, met the criteria for resistant hypertension and had all had significant unprovoked hypokalaemia. No patients with normokalaemic PA were identified from our cohort [8,13].

From our study, the prevalence of (confirmed and probable) PA was .1.25% in our referral hypertension population. Among those who on discharge had met the JNC-7 criteria for the definition of resistant hypertension, the prevalence rose to 4.5% (8/178). Furthermore, all PA patients met the criteria for resistant hypertension, and in addition, all exhibited significant unprovoked hypokalaemia. Some reports suggest that the even the majority of individuals with PA are in fact normokalaemic but this was not our experience [6].

In summary, the prevalence of confirmed PA in a specialist hypertension clinic population of 635 consecutive patients was low at 1.25%, but increased to 4.5% among those meeting the strict criteria for resistant hypertension. Furthermore, all PA cases exhibited significant unprovoked hypokalaemia, and we detected no cases of normokalaemic PA.

PA in our hypertensive population appears to be less common than reported elsewhere. Based on our data, we cannot recommend widespread screening for PA among hypertensive patients in primary care. Furthermore, our results suggest that even in the hypertension clinic population screening should be confined to individuals who both fulfil the criteria for diagnosis of resistant hypertension, and have unprovoked hypokalaemia.

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