

Prospective Evaluation and Characteristics of Patients with Suspected Primary Hyperaldosteronism

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ABSTRACT

Primary hyperaldosteronism (PH), resulting in hypokalaemic hypertension, may be due to an aldosterone-producing adenoma (APA) or bilateral zona glomerulosa hyperplasia. Six patients with suspected PH were identified at the University Hospital of the West Indies and standardized screening was carried out. Plasma renin activity (PRA) and serum aldosterone concentrations (SAC) were measured, followed by confirmatory intravenous saline suppression test. The patients were all women, of median age 48 years (interquartile range, IQR: 41–51.7 years). They tended to be overweight with suboptimal blood pressure control. Median serum potassium was 3.1 mmol/L (IQR 2.7 – 3.3 mmol/l) and kaliuresis was elevated or inappropriately normal. All individuals had suppressed PRA (< 0.6 ng/ml/hr) and elevated SAC (> 30 ng/dl), with SAC/PRA ratios > 50. Five patients had confirmed PH (ie post-saline SAC > 10 ng/dl); PH could not be definitely excluded in the sixth patient (ie post-saline SAC 5 – 10 ng/dl). Imaging studies revealed normal adrenal glands in one patient, unilateral adrenal enlargement in three patients, and unilateral adrenal masses in two patients. Only one of these latter two patients was shown to have an adrenal adenoma on histological examination. In this series, there appears to be fewer cases of the APA subtype of PH than expected. It remains to be seen whether the distribution of PH subtypes in Jamaica is actually different from elsewhere. This, and the cost-effectiveness of different approaches to screening, identification and management of patients suspected of having PH in Jamaica are areas for further study.

Evaluación Prospectiva y Características de los Pacientes con Sospecha de Hiperaldosteronismo Primario

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RESUMEN

El hiperaldosteronismo primario (HP), que trae como resultado hipertensión hipocalémica, puede tener por causa un adenoma productor de aldosterona (APA) o una hiperplasia bilateral de la zona glomerulosa. Seis pacientes con sospecha de HP fueron identificados en el Hospital Universitario de West Indies, y se llevó a cabo un tamizaje estandarizado. Se realizaron mediciones de la actividad de renina plasmática (ARP) y las concentraciones de aldosterona en suero (CAS), seguidas de una prueba confirmatoria de supresión con salina por vía intravenosa. Los pacientes fueron en su totalidad mujeres, con una edad mediana de 48 años (rango intercuartil, IQR: 41–51.7 años). Tenían tendencia al sobrepeso y un control subóptimo de la presión sanguínea. La mediana de potasio sérico fue 3.1 mmol/L (IQR 2.7–3.3 mmol/l) y la caliuresis fue elevada o inadecuadamente normal. Todos los individuos presentaron ARP suprimida (< 0.6 ng/ml/hr) y CAS elevada (> 30 ng/dl), con proporciones CAS/ARP > 50. A cinco pacientes les fue confirmado HP (ie CAS post-salina > 10 ng/dl); el HP no pudo ser definitivamente excluido en el sexto paciente (ie CAS post-salina 5 – 10 ng/dl). Estudios de imagen revelaron glándulas suprarrenales normales en un paciente, agrandamiento suprarrenal unilateral en tres pacientes, y masas suprarrenales unilaterales en dos pacientes. Solamente uno de estos dos últimos pacientes mostró tener un adenoma adrenal al realizarse el examen histológico. En esta serie, parece haber menos casos del subtipo APA de HP que lo esperado. Queda por ver si la distribución de los subtipos de HP en Jamaica es en realidad diferente de la de otras partes. Esto, al igual que el costo-efec-

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tividad de los diferentes métodos de tamizaje, identificación y tratamiento de pacientes con sospecha de HP en Jamaica, son áreas que requieren ulterior investigación.

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INTRODUCTION

Primary hyperaldosteronism (PH) causes hypokalaemic hypertension and was first described by Litynski (1953) and Conn (1955) (1–3). Aldosterone-producing adenoma (APA, otherwise called Conn's syndrome) is the most common subtype of PH, accounting for ~60% of cases. The other common subtype of PH is due to bilateral zona glomerulosa hyperplasia (idiopathic hyperaldosteronism, IHA) and accounts for ~35% of cases (4). It is generally believed that PH is a rare cause of endocrine hypertension, occurring in <1% of individuals with hypertension (5, 6). Newer data suggest higher prevalence rates; 5–13% of hypertensive individuals in Europe, Southeast Asia and Australia have been shown to have biochemical evidence of PH (7–13). The true overall prevalence of PH and the relative occurrence of its different subtypes are unknown for the English-speaking Caribbean.

The current accepted approach in North America and Europe for patients suspected of having PH consists of biochemical screening followed by confirmatory testing and imaging studies (14, 15). Screening consists of the determination of plasma renin activity (PRA) and serum aldosterone concentration (SAC) without any restriction on dietary intake or the posture of the patient at the time of sampling. An SAC \geq 20 ng/dl, with a corresponding SAC/PRA ratio $>$ 20, constitute a positive screening test for PH (16). A diagnosis of PH is confirmed by demonstrating inappropriate (*ie* non-suppressible) aldosterone secretion with either the intravenous saline suppression test or measurement of 24-hour urinary aldosterone while the patient is on a high-sodium diet (17). Imaging studies may then be employed to identify the anatomical cause and surgery may be offered if a suitable lesion is identified.

The standard screening and confirmatory tests are not available in Jamaica and anecdotal evidence suggests that evaluation of such patients has been limited in the past. In order to gain some insight into the question of whether the outcomes of patients who were strongly suspected of having PH would be altered by performing standard screening tests, a prospective observational study was carried out. Screening and confirmatory tests were performed utilizing commercial laboratory facilities outside of Jamaica on several patients attending either the Hypertension or Endocrine Outpatient Clinics at the University Hospital of the West Indies (UHWI), Mona, Jamaica. All of these patients had chronic spontaneous hypokalaemia and hypertension and were suspected to have PH. This is a report on their clinical characteristics and the results of tests for PH.

SUBJECTS AND METHODS

Patients who were taking spironolactone or angiotensin-converting enzyme inhibitors had these medications replaced by α -methyl dopa and/or calcium channel blockers 6–12 weeks prior to biochemical testing. Potassium supplements were continued. One patient was asked to continue ACE inhibitor therapy up to 48 hours prior to testing due to concerns about her blood pressure control. Subjects were asked to fast from 11 pm and were seen at the Tropical Metabolism Research Unit (TMRU) by 07.45 h. On arrival, the procedure was explained and patients gave written, informed consent. Body weight, height and body fat (using bioelectrical impedance, BIA) were measured using a standardized protocol (18).

After voiding the urinary bladder and lying supine for 10 minutes, blood pressure was measured with an oscillometric device (DINAMAP, General Electric, Waukesha, Wisconsin, USA). A 20-gauge cannula was sited in an antecubital vein and locked with normal saline. After a further 15 minutes, 35 ml of blood was collected for plasma renin activity (PRA), into pre-chilled tubes, and also for serum aldosterone concentration (SAC), glucose, electrolytes and creatinine. Samples were centrifuged at 4°C and the sera were frozen at -20°C until assays were carried out. Samples were kept on ice prior to centrifugation.

A saline suppression test was then performed. Two litres of normal saline were infused at ~600 ml/hour. Vital signs were measured hourly and patients were monitored for signs of volume overload. After completion of the infusion, 8 ml of blood was taken for SAC measurement.

Plasma/serum samples were shipped to the Mayo Labs, Rochester, MN, USA, on dry ice. PRA was measured using a two-step radioimmunoassay (RIA) and SAC was measured by RIA with a sensitivity of <1 ng/dl. Glucose, electrolytes and creatinine were measured on an Abbott Architect C8000 Autoanalyzer (Abbott Laboratories, Illinois, USA) in the Chemical Pathology Laboratory, UHWI. Samples for PRA and SAC assays (the primary outcomes of this study) were processed as a batch approximately 4 months after samples were collected. Serum and plasma samples were subsequently retrieved from repository storage (approximately 4.7 years after initial collection) and were used for estimation of electrolytes and glucose in order to explore whether there might have been evidence of impaired glucose tolerance or renal function at the time of screening.

RESULTS

There were six women with hypokalaemic hypertension. A review of their clinical characteristics and biochemistry, extracted from their clinical records, is given in Table 1. The

Table 1: Clinical and biochemical characteristics of patients (n = 6): outpatient data

Variable	Median	Interquartile range
Age at diagnosis (years)	31.5	25.0 – 34.0
Number of antihypertensive medications	3.5	2 – 4
Systolic blood pressure (mm Hg)	155.1	140.3 – 157.4
Diastolic blood pressure (mm Hg)	90.8	84.0 – 96.6
Serum sodium (mmol/l)	143.0	141 – 146
Serum potassium (mmol/l)	3.5	3.2 – 3.7
Total serum CO ₂ (mmol/l)	30.5	26 – 33
Serum creatinine (µmol/l)	88.5	88 – 94

median age at diagnosis of hypertension was relatively young with only one patient being diagnosed after age 35 years. Target blood pressures (< 140/90 mmHg) were not achieved within the six-month period prior to screening despite the use of a median of 3.5 antihypertensive medications. Antihypertensive medications included spironolactone in all but one case. Hypokalaemia tended to be mild and there was an associated metabolic alkalosis. Unlike classical descriptions of Conn's syndrome, serum sodium concentrations were high-normal rather than in the hypernatraemic range. Urinary potassium excretion studies were performed at different times during outpatient follow-up (patients had discontinued use of thiazides, ACE inhibitors and spironolactone for these studies). The median urinary potassium excretion was 84.0 mmol/24 hour (interquartile range, IQR 48– 87 mmol/24 hour) and in all cases the levels of kaliuresis were either above the upper reference limit or were inappropriately normal given the level of hypokalaemia (median 3.1 mmol/l, IQR 2.7–3.3 mmol/l).

Table 2 shows clinical and biochemical data for all patients at the time of screening and confirmatory testing for

Table 2: Clinical and biochemical characteristics of patients (n = 6) at the time of screening

Variable	Median	Interquartile range
Age (years)	48.0	41.0 – 51.7
Duration of hypertension (years)	17.3	14.2 – 21.0
Systolic blood pressure (mm Hg)	169.5	146 – 180.0
Diastolic blood pressure (mm Hg)	99.3	84 – 102.0
Mean arterial pressure (mm Hg)	126.0	110.3 – 130.0
BMI (kg/m ²)	28.4	25.8 – 30.6
Per cent body fat	42.3	42.0 – 42.7
Serum potassium (mmol/l)	2.9	2.9 – 3.0
Serum sodium (mmol/l)	141.5	140 – 142.0
Fasting plasma glucose (mmol/l)	4.5	4.2 – 6.0
Serum creatinine (µmol/l)	84.5	76 – 91.0

PH. At this stage, the patients had been diagnosed as having hypertension for approximately 17 years. On average, they were overweight (median BMI of 28.4 and median per cent body fat of 42.3). At the time of screening, there was evidence of hypokalaemia (median serum potassium 2.9, IQR 2.9–3) without evidence of severe renal impairment (median

serum creatinine 84.5 µmol/l). Blood pressure readings were above target, but it is likely that this was due to changes in prescribed medications to facilitate the procedure. Primary hyperaldosteronism is associated with glucose intolerance and decreased insulin sensitivity (19) and two of the patients had impaired fasting glucose (*ie* 5.6 – 6.9 mmol/L) by the criteria of the American Diabetes Association (20). It is possible that these two patients also have impaired glucose tolerance but a 75-gram oral glucose tolerance test was not performed (21).

All individuals had suppressed PRA (< 0.6 ng/ml/hr) as well as SAC levels greater than 30 ng/dl (Fig.1). Conse-

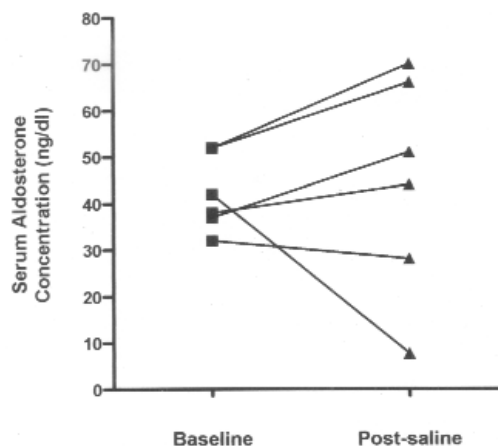


Fig. 1: Serum aldosterone concentrations at baseline and post-saline infusion.

quently, the SAC/PRA ratio in all cases was > 50. After volume expansion with saline loading, five individuals demonstrated non-suppressible aldosterone levels and had serum concentrations >10 ng/dl, thus confirming the diagnosis of primary hyperaldosteronism (Fig. 1). One individual suppressed to 7.7 ng/dl suggesting the alternative diagnosis of primary hypertension.

Of the five individuals with biochemically confirmed PH, unilateral adrenal masses (1.9 cm and 2.0 cm) were reported on CT scans of two patients; unilateral adrenalectomy via laparotomy was performed in both cases. The outcome for one patient was normokalaemia and excellent blood pressure control using only a small dose of α-methyldopa as monotherapy. The histology of her surgical specimen confirmed an adrenal adenoma. In the other patient, hypokalaemia and hypertension persisted post-surgery. In this case, no adrenal adenoma was identified in a gland that weighed 2.2 g. This patient subsequently developed Type 2 diabetes mellitus and has also been shown to have non-Cushing's hypercortisolaemia. It remains uncertain, in the absence of data from adrenal vein sampling prior to surgery, whether PH in this case could be due to a microadenoma in the remaining adrenal gland. Two patients had unilateral adrenal enlargement but no clear adenoma and a third had normal adrenals on a CT scan. These four patients, in whom the APA subtype

of PH was not demonstrated, have continued on antihypertensive medications including spironolactone (100–200 mg/day in two divided doses), ACE inhibitors and oral potassium supplements. The single patient who had suppressible SAC after saline loading had only very mild unilateral adrenal has thickening and continues to have mild hypokalaemia. Her medications include an ACE inhibitor and potassium supplement; spironolactone, which she was unable to obtain, was discontinued.

DISCUSSION

Screening and confirmatory tests were performed on six patients suspected to have PH. All six patients had a positive screening test for PH and five of these had definite evidence of PH, in the form of non-suppression of SAC after volume expansion with normal saline. One of the patients with a unilateral adrenal mass on CT scan was “cured” after unilateral adrenalectomy.

These cases illustrate that a provisional diagnosis of PH can be made using appropriate biochemical screening tools even in a relatively resource-poor setting. While it is not rigorously clear which screening test is best, the use of a low PRA, an elevated SAC or PAC ($> 15\text{--}20$ ng/dl) and an SAC/PRA ratio $> 20\text{--}30$ is the most favoured (16). In order to improve the positive predictive value of the diagnostic evaluation, angiotensin-converting enzyme inhibitors and spironolactone were discontinued prior to biochemical screening. Several authorities suggest, however, that screening may take place while the patient is on his/her usual antihypertensive therapy, except for spironolactone which needs to be discontinued 6 weeks prior to screening (22–24).

There is some controversy about using aldosterone/renin ratios. A recent systematic review which included 16 studies was not able to confirm reported values for sensitivity, specificity or likelihood ratios at different cut-off values (25). Most of the studies did not provide enough data to give valid estimates of the test characteristics. There is also concern that difficulties associated with proper sample collection and processing might contribute to reduced inter-laboratory reproducibility of PRA which in turn would affect reproducibility of aldosterone/renin ratios (26). Nevertheless, the use of the SAC/PRA ratio has a sound physiological basis and combined with an elevated serum aldosterone is probably the most valid non-invasive method of screening. Another group has suggested a logistic multivariate model for screening (27) but this is probably too unwieldy for routine use.

A saline suppression test was used as a confirmatory test for PH although suppression using dietary salt loading, captopril or fludrocortisone have been proposed as viable alternatives (6). With volume expansion, persons with PH fail to suppress below an SAC of 10 ng/dl. One of the subjects in the present study had suppressible hyperaldosteronism which suggests that she has primary low-renin hypertension which occurs in approximately 30% of hypertensive

Jamaicans (28). Holland *et al* (29), however, proposed that after saline infusion, an SAC value of < 5 ng/dl is a better threshold especially when PH is due to idiopathic hyperaldosteronism. It remains uncertain, therefore, whether this patient has idiopathic hyperaldosteronism or essential hypertension, so she continues to be monitored.

Despite these uncertainties, this approach is preferred to a procedure which might appear to be attractive in settings where biochemical testing is not readily available and where imaging of the adrenals is offered to patients with chronic spontaneous hypokalaemia and hypertension or an elevated SAC. The principal reason for not utilizing this approach is the likely low positive predictive value for PH; individuals with IHA often have normal imaging studies and non-functional adrenal masses (adrenal incidentalomas) are not infrequent. In studies where computerized tomography (CT) of the abdomen was done for evaluation of non-adrenal conditions, adrenal masses > 1 cm were seen in 0.4–5.0% of individuals (30). Prevalence rates for incidental adrenal tumours are even higher in autopsy studies; rates of 6.8–8.7% have been reported for unselected series and rates of up to 12% have been reported for hypertensive individuals (31, 32). Finally, there are other causes of hyperaldosteronism (*eg* renal artery stenosis, aortic coarctation, malignant phase hypertension and diuretic use) and hypokalaemic hypertension (*eg* syndrome of apparent mineralocorticoid excess) where a CT scan of the abdomen is unlikely to be helpful. Thus, in order to avoid mistakenly assigning clinical importance to an incidentaloma and/or wasting time and money on unhelpful imaging studies, it is crucial to confirm the biochemical diagnosis of PH prior to anatomical imaging.

Individuals with confirmed PH should have an abdominal CT scan with adrenal cuts. The accuracy of this procedure has been estimated to be 73% (33); patients shown to have a unilateral adrenal macroadenoma (*ie* > 1 cm) can undergo adrenalectomy (4, 34). The current recommendation for individuals with normal adrenals, adrenal masses < 1 cm, unilateral limb thickening or bilateral masses on CT imaging is to proceed with adrenal vein sampling for aldosterone (14). In approximately 40% of such cases, there is lateralization indicating a unilateral aldosterone producing microadenoma (35). Unfortunately, this is a difficult procedure and not readily available in the English-speaking Caribbean. It is possible that the three patients with unilateral adrenal enlargement could be harbouring surgically amenable lesions, but this cannot be proven at present. It is unlikely that they could have glucocorticoid-remediable aldosteronism (GRA), direct molecular screening has suggested that this disorder is likely to be extremely rare in Jamaica (36). Surgery is curative for hypokalaemia although older age, long duration of hypertension, severe hypertension and a family history of hypertension tend to predict persistence of hypertension after adrenalectomy (37).

The cost-effectiveness of screening for PH remains undetermined. Individuals with symptomatic hypokalaemia

are probably aided by a biochemical diagnosis and, if possible, surgical correction. Relatively young patients and patients with resistant hypertension may also benefit (38). Once an APA is identified, adrenalectomy results in significant long-term reduction in blood pressure in nearly 100% of patients and is less expensive than long-term medical therapy alone (39). In our setting where adrenal vein sampling is not readily available, medical therapy for any lesion which is not an adrenal macroadenoma is probably appropriate. In the present series, one patient benefitted from surgery and it is possible that another with indeterminate results after saline loading might have benefitted from avoidance of imaging. Nevertheless, these limited results are not a sound basis for making judgements on this matter.

Even if screening is cost-effective, the most appropriate method of screening remains undetermined in Jamaica. It is possible that less expensive, more readily available methods might be utilized in resource-poor settings. For instance, in this small series of patients, it appears that elevated or inappropriately high levels of kaliuresis were 100% concordant with tests for PH which relied on PRA and SAC. A further unresolved matter is the nature of the distribution of subtypes of PH in Jamaica. The probability (given by the binomial distribution) of observing as many cases of PH due to a non-APA cause in a series of six patients with PH is 0.037. This suggests that the observation in this study is significantly different, at the 5% level, from the three or four patients with APA that might have been expected. Better estimates of the prevalence of PH and of its subtypes in Jamaica are required before concluding that there are differences between Jamaican patients with PH and patients with PH in other countries. This, and the cost-effectiveness of different approaches to screening, identification and management of Jamaican patients suspected of having PH, requires systematic evaluation before firm conclusions can be drawn.

In summary, it appears that individuals with suspected PH in Jamaica can be screened with a combination of PRA and SAC. The biochemical diagnosis can be confirmed by demonstrating non-suppression of aldosterone secretion after saline loading. Individuals who are then shown to have a unilateral adrenal macroadenoma can consider unilateral adrenalectomy. All other categories of patients should be treated medically.

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