SCREENING AND DIAGNOSIS OF PRIMARY HYPERALDOSTERONISM AMONG EGYPTIAN PATIENTS AT RISK

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Abstract

Background: Hypertension (HTN) affects between 10 to 40% of the general population and is considered as risk factor for premature death in the world. Primary aldosteronism (PA) is the most common form of secondary hypertension. Primary aldosteronism causes more end-organ damage and is associated with excess cardiovascular morbidity and strokes. Screening is simple and readily available. Also, targeted therapy improves blood pressure control and decreases mortality rates.

Aim of the work: to screen primary aldosteronism in hypertensive patients at high risk with an estimation of PA prevalence within the Egyptian hypertensive population and to identify "low renin hypertension" patients as a subset in need of specific preventive and therapeutic strategy.

Patients and methods: One hundred (100) hypertensive Egyptian patients in high-risk groups for PA. patients were subjected to clinical assessment, routine laboratory measures, and the aldosterone/ direct renin ratio (ADRR). Plasma aldosterone Active renin concentration (ARC) was used as a component of measurement during the calculation of ARR in our study. Fludrocortisone Suppression Testing (FST) is one of the confirmatory tests which was used in our study in patients with positive ADRR.

Results: there was a highly statistically significant relation between potassium level and plasma aldosterone to direct renin ratio (ADRR) (P<0.000). One hundred patients were included:8 of them (8%) had a positive ADRR >2. 39, low renin hypertension was prevalent in 19 patients out of 100(19%) in the overall study group. Fludrocortisone confirmation test was done,2 patients from 8 were positive test. Abdomen and pelvis CT were done for the patients with positive fludrocortisone confirmatory test and revealed the first case had RT bulky suprarenal gland while the second case had RT well-defined suprarenal mass.

Conclusion: Primary aldosteronism is a frequent cause of secondary hypertension, ADRR is used as a screening test. Hypokalemia has been considered one of the hallmark signs in the diagnosis of primary aldosteronism; however, estimates showed that less than 37 percent of patients who had primary hyperaldosteronism would present with hypokalemia. The diagnosis should be considered in a patient with drug-resistant hypertension and hypokalemia in a patient starting a low dose of diuretic.

Keywords: Noradrenaline, terlipressin, and hepatorenal syndrome

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1. INTRODUCTION

Hypertension is a major correctable risk factor causing worldwide cardiovascular mortality. Primary aldosteronism (PA) is one of the commonest causes of secondary hypertension and is characterized by high persistent levels of aldosterone due to hyperplasia or tumors secreting aldosterone in zona glomerulosa of the adrenal cortex. The estimated prevalence of primary aldosteronism was about five to ten percent among all hypertensive patients (1,2) and it represents about twenty percent of resistant hypertensive cases (1,3)

It was suggested that persons with PA had four to twelve times higher rates of myocardial infarction, myocardial fibrosis, diastolic dysfunction, stroke, and arrhythmias (4) as well as a very poor life quality (5) than people with primary hypertension irrespective of the degree of blood pressure (6)).

Additionally, aldosterone in excess causes dysfunction of the endothelial layer of blood vessels together with increased stiffness of arteries. Increased aldosterone secretion was found to enhance collagen synthesis producing high rigidity on vascular smooth muscles and patients with PA have been shown to have atherosclerosis and stiffness measured by pulse wave velocity and

thickened carotid intima-media (7). Studies showed patients with PA usually present with hypertension without a decrease in potassium level, so the diagnosis of PA may be missed (8,9). The aldosterone to renin ratio (ARR) is the most advisable screening test for PA (3). However, many factors influence the ARR such as posture (10), time of blood sampling (11), age (12), salt intake (13), presence of hypokalemia (14), sex (15), use of contraceptives (16), NSAIDs and some selective serotonin reuptake inhibitors (17). All these factors make the diagnosis of PA a challenge for clinicians.

2. PATIENTS AND METHODS

This study included 100 hypertensive patients aged from eighteen to sixty-five years. Their systolic blood pressure exceeding 140 mmHg or diastolic blood pressure over ninety mmHg although two antihypertensive drugs were subscribed to patients admitted in the internal medicine department in kasr El- Ainy and the Out-Patient Endocrinology Clinic in Kasr El -Ainy Hospitals. They were considered high-risk groups for PA screening if there are hypertension resistant to three conventional antihypertensive drugs, hypertension with hypokalemia, adrenal mass with hypertension, blood pressure controlled by 4 or more drugs, hypertension with sleep apnea, early-onset hypertension or cerebrovascular stroke at a young age (less than forty) or presence of 1st-degree relatives with primary aldosteronism.

Patients were excluded when they developed heart failure or cardiac chest pain or cerebrovascular stroke within six months before starting our study. Exclusion also if patients had liver cirrhosis, renal failure, congenital adrenal hyperplasia, diabetes, and pregnancy. Additionally, Patients with secondary etiology of hypertension such as pheochromocytoma, Cushing's syndrome, and renal artery stenosis. The study protocol was approved by the local Ethical Committee and informed consent was obtained from study participants.

A clinical examination of the subjects of the studied group was performed. Blood pressure was obtained as 3 successive readings in a sitting position with time intervals of five minutes at least. Then we calculate the mean of the readings preferably, the last 2.

Body mass index was calculated according to the height and weight of the patient expressed in units of kg/m2.

Serum urea, creatinine, sodium, and potassium were assessed in all the patients included in the study considering the following:

Patients should be advised not to restrict salt intake and hypokalemia should be treated before testing as low levels of potassium suppress the secretion of aldosterone.

Aldosterone antagonists were discontinued at least 6 weeks before the investigation; angiotensin-converting enzyme inhibitors and Ang II receptor blockers were discontinued 4 weeks before; β-blockers, dihydropyridine-type calcium antagonists, and clonidine were progressively reduced and withdrawn 2 weeks before. Medications that might interfere with the renin-ALD axis, such as steroids, sex hormones, liquorice, or non-steroidal anti-inflammatory drugs were also withheld for at least 3 weeks

The random antihypertensive medication regimen was replaced by one or more of the following drugs: Verapamil, Hydralazine, Prazosin, Doxazosin mesylate, and Terazosin hydrochloride.

Spironolactone, eplerenone, amiloride, triamterene, Potassium wasting diuretics, and products derived from licorice root were discontinued at least 4 weeks before the start of the study protocol. NSAIDS and other anti-hypertensive medications were discontinued three weeks before the start of the study protocol.

Blood was collected in a vacutainer plain tube. Vein tapping and fist-clenching were avoided. Separation of serum from cells within 30 min of collection.

On the next visit, ADRR was calculated at the outpatient clinic by measuring both aldosterone concentration (expressed in ng/dL) and direct renin concentration (expressed in mU/L). Both Aldosterone and direct rennin concentrations were measured by Human ALD (Aldosterone) ELISA kit Cat No: SEH4705 and Human REN (Renin) ELISA kit Cat No: SEH0268 supplied by Cloud – Clone Corp technical service which employs a double–antibody sandwich enzyme–linked immunosorbent assay.

• Blood collection was done 8-10 am after the patient had been up (sitting, standing, or walking) for at least 2 h and seated for 5–15 min.

• Blood collection was done carefully and samples were kept at room temperature during delivery to the laboratory centrifugation was done for 10 t0 15 min then separation of centrifuged serum and freezing at -20 till assay

Patients with positive ADRR were admitted to the internal medicine department in kasr El- Ainy for fludrocortisone suppression test (FST) in patients with no medical contraindications.

Patients are administered 0.1 mg of fludrocortisone orally every 6 hours for 4 days. Potassium is supplemented with KCl to keep serum level close to 4.0 mmol/L and is measured every 6 hours.

In addition, supplementation with slow-release sodium chloride tablets is used to maintain urinary sodium excretion greater or equal to 3 mmol/kg body weight.

Plasma aldosterone, ARC, and plasma cortisol are measured. If the cortisol level at 10 AM is decreased compared to 7 AM, then the test can be considered valid as it excludes any possible confounding ACTH effect. Serum aldosterone of >6 ng/dL (170 nmol/L) with ARC less than 8.3 mu/l to confirm the diagnosis of PA (3).

Patients with a positive fludrocortisone confirmatory test underwent a high-resolution, thin-section CT scan of the adrenal gland and computed tomography (CT) scan of the adrenals to screen for the presence of an aldosterone-producing adenoma (APA).

3. RESULTS

Table (1): The characteristics of the 100 investigated patients with hypertension

	Median /range
SBP (mmHg)	160(110-220)
DBP (mmHg)	100 (70-130)
Age (years)	35(18-45)
SEX (male/female) number	51/49
BMI (kg/m^2)	29(15-52)
Serum potassium (mEq/l)	3.9 (2.3-5.9)
Creatinine(mg/dl)	0.9(0.5-1.2)
Plasma aldosterone (ng/dl)	11.75(0.53-175)
Direct renin concentration (mU/l)	31.96(1.5-276)
ADRR (ng/dl/mU/l)	0.5(0.01-7.01)

SBP: systolic blood pressure, **DBP:** diastolic blood pressure, **BMI:** body mass index and **ADRR:** aldosterone/direct renin ratio

The serum K levels were normal in 72 (72%), and only 28 (28%) were hypokalemic

There is debate over the optimal methods for detecting PA. To obtain an accurate ADRR, we investigated 100 subjects with plasma aldosterone concentration expressed in ng/dl and direct renin concentration in mu/l.

- Plasma aldosterone concentration (PAC) of the study group ranged between 0.53 and 175 ng/dL with mean ± SD = 19.29± 24.66ng/dL.
- Direct renin concentration (DRC) ranged between 1.5 and 276 mU/L with mean ± SD = 47.21± 53.19 mU/L.
- Aldosterone/Direct renin concentration ratio (ADRR) ranged between 0.006 and 7.009 with mean ± SD = 0.93±1.28.
- In our study; 8(8%) patients out of a total of 100 patients had a positive ADRR (>2.34ng/dl/mu/l).

There was a significant correlation between both SBP and DBP with serum potassium levels (P 0.024 and 0.013 respectively)

we also found a statistically significant correlation between serum aldosterone/ renin ratio (ADRR) and serum potassium (K) with (P-value 0.000)

There was a significant correlation between serum aldosterone/ renin ratio (ADRR) and both SBP and DBP (P-value 0.000)

In our study; 8(8%) patients out of a total of 100 patients had a positive ADRR (>2.39 ng/dl/mU/l). fludrocortisone confirmation test was done (2 patients from 8 were positive), and serum cortisol was suppressed at 10 a.m. than 7 a.m. in all 8 patients **Table (2).**

Table (2): value of PAC and ARC before and after fludrocortisone suppression test in patients suspected PA

	Before Fludrocortisone Suppression Test			**After Fludrocortisone Suppression Test**	
No	**PAC** (ng/dl)	**DRC** (mU/l)	**ADRR**	**PAC**	**DRC**
1	6.8	2.28	2.9	4.9	2.0
2	8.8	1.77	4.9	5.6	1.0
3	8.3	3.33	2.5	5.0	3.0
4	8.3	1.80	4.6	4.8	1.5
5	6.8	1.52	4.4	4.7	1.2
6	8.0	1.53	5.2	4.9	1.2
7	12.5	2.27	5.5	8.0	1.8
8	15	2.14	7	10	1.0

After the fludrocortisone suppression test, CT abdomen and pelvis was done for the patient who had positive fludrocortisone suppression test, the first case had RT bulky suprarenal mass while the second case had RT well-defined suprarenal

4. DISCUSSION

Primary aldosteronism is common but underestimated. Patients with primary aldosteronism have more morbidity than patients with essential hypertension, but on diagnosis and appropriate treatment, these patients are potentially cured and may have a reversal of target organ damage (18).
The aldosterone to direct renin ratio (ADRR) is the best screening test for PA (19). However, the ratio has not been standardized due to different analytical methods for aldosterone and renin (20).
In the present study, we investigated the prevalence of PA among hypertensive Egyptians with the ADRR
Our study included 100 hypertensive patients, who were considered high-risk groups for PA screening
In our study, 100 patients were included and 8 of them (8%) had a positive ADRR >2.39 (21)

This was in agreement with Monticone et al who stated that PA is a common cause of secondary hypertension so hypertensive patients should be screened for PA (22)
In a recent large population-based study, Hannemann discovered0.2-7.0% of hypertensive patients with positive ADRR. (23)
The variations are due to different cut-off limits for the ADRR, salt intake, ethnicity, and sampling conditions.
Although primary aldosteronism presented with the triad of hypertension, hypokalemia, and metabolic alkalosis, this presentation is considered an extreme form of the condition. Only 9% to 37% of patients presented with hypokalemia, and the most common presentation is normokalemic hypertension (3). the clinician often alerts with a diagnosis of primary aldosteronism when patients presented with hypokalemia; however, the absence of hypokalemia gave a poor negative predictive value for diagnosis and should not be used to exclude the presence of primary aldosteronism.
Hypokalemia (defined as serum K+ <3.6 mEq/l) was prevalent in 28 patients out of 100 (28%) in the overall study population. Patients with a positive ADRR (8%) had K levels ranging from 2.7 to 3mEq/l.
There was a highly statistically significant negative correlation between potassium level and plasma aldosterone to direct renin ratio (ADRR) (P<0.000).
Patients with spontaneous hypokalemia must be screened for PA. However, part of these patients are not hypokalemic So ADRR is used as a screening test among both hypokalemic and normokalemic hypertensives have resulted in much higher prevalence estimates for this disease (24)

In addition, there was a statistically significant correlation between ADRR and both systolic blood pressure (SBP) and diastolic blood pressure (DBP) (P<0.000).
This was in agreement with Newton-Cheh et al,2005higher ADRR was associated with an increased risk of BP progression and hypertension(25).

In our study, there was also a statistically significant correlation between serum potassium (K) and both systolic blood pressure (SBP) and diastolic blood pressure (DBP) (P <0.024, P < 0.013 resp.).
This was in agreement with Maria al ,et al who observed a reverse relationship between serum potassium and BP which supports a close pathophysiological connection between serum potassium and essential hypertension (26)
In our study; 8 patients out of a total of 100 patients (8%) had a positive ADRR (>2.39 ng/dl/mu/l), after the fludrocortisone confirmation test was done,2 patients 8 were a positive test, this was in agreement with Volpe et al prevalence of PA was 1.6 and 3.8 % after confirmatory test among hypertensive patients who were positive for ADRR in the screening of primary aldosteronism (27)
our results indicate the necessity to encourage PA screening which is crucial for early diagnosis and preventing cardiovascular and renal morbidity in many high-risk patients with HTN.
One key limitation of our study is the lack of dietary salt intake modifications which affect aldosterone, renin, and BP.
The small sample size is another limitation, Future larger studies are needed to establish the true prevalence of PA in Egyptian hypertensive patients.

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