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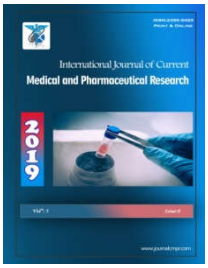

Research Article

PREVALENCE OF ESSENTIAL HYPERTENSION ASSOCIATED WITH ELEVATED ALDOSTERONE TO RENIN RATIO IN KASHMIR VALLEY. A CASE CONTROL STUDY

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ABSTRACT

Background: Despite growing burden of hypertension, its pathophysiology is still incompletely understood. Although implicated in pathogenesis of hypertension, the role of aldosterone and renin is not completely elucidated.
Aim: This study was aimed to acquire baseline data about the prevalence of essential hypertension associated with an elevated aldosterone to renin ratioby studying plasma aldosteroneconcentration and plasma renin activity.
Methods: One hundred hypertensive patients and fifty normal individuals were enrolled. All antihypertensive medications were stopped for four weeks before measuringaldosterone concentration and plasma renin activity. An aldosterone-renin ratio of ≥25 was taken as elevated.
Results: The prevalence of essential hypertension with elevatedaldosterone-renin ratiowas 19% in our population. Mean aldosterone concentration, mean plasma renin activityand aldosterone-renin ratio was 5.8ng/dl (range 1.1-15.9), 1.0 ng/ml/hr and 14.6 (range 0.5-69.6) respectively. Inaldosterone associated hypertension group, 68.4% (n=13) had systolic blood pressure of ≥160 mmHg while 52.6% (n=10) had diastolic blood pressure of ≥100 mmHg. The mean systolic blood pressure of patients with high aldosterone-renin ratio was 160.1mmHg (± 8.1) while mean systolic blood pressure of patients with normal aldosterone-renin ratio was 157.0mmHg (±10.6) which was statistically significant (p=0.04). In addition, relatively higher aldosterone-renin ratiowas observed in patients with stage II hypertension as compared to stage I hypertension.
Conclusion: One-fifth of essential hypertensive patients had elevated ARR (Aldosterone associated hypertension) in this study. Thus Aldosterone antagonists may be a more appropriate and cost effective antihypertensive drug for these patients. Further controlled trials capable of demonstrating the hypothesis are mandatory.

INTRODUCTION

In recent years, growing evidence has consistently supported the view that arterial hypertension due to primary aldosteronism is much more frequent than was previously suspected.[1-14] This change in the estimated prevalence has been mainly due to the widespread use of the aldosterone to renin ratio (ARR) as a screening test capable of detecting inappropriately high aldosterone secretion for the degree of renin-angiotensin system activation.[15] By means of this approach, which is generally followed by confirmatory tests, it has also been demonstrated that most of the affected patients are normokalemic and therefore clinically indistinguishable from patients with essential hypertension.[15, 16] In addition to its screening function, ARR elevation has been reported to be a useful predictor of patient susceptibility to spironolactone treatment regardless of the established diagnosis of primary aldosteronism.[17, 18]On the basis of all these considerations, the question still remains to be solved: should ARR measurement be reserved to specific, highly selected subgroups or extended to all hypertensive patients? If patients with elevated ARR are relatively frequent and clinically indistinguishable from those affected by common form of hypertension, then it would be logical to propose that at least one determination of ARR be performed in all individuals presenting with high blood pressure (BP). Despite being a subject of theoretical discussion, this issue has not been widely investigated and the true prevalence of high ARR in the general population is uncertain.[20] Clinical studies on ARR have generally been conducted in selected groups of patients referred to specialist hypertension units.[1-7, 8-14]Interestingly, the prevalence of elevated ARR was not found to be different from that in specialist referral clinics. This result, although very important, cannot be considered conclusive and the actual prevalence in an appropriate sample of general adult population, selected

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according to the criteria adopted in high quality epidemiological studies, needs to be established.

Moreover, some experts advocate screening all hypertensive individuals for this disorder to guide drug selection and improve treatment success.[19, 20]The prevalence of hypertension in Kashmir valley is about 20%.[21]The present study was aimed at acquiring baseline data about the prevalence of essential hypertension associated with an elevated ARR in this part of the country by studying the plasma aldosterone concentration and plasma renin activity (PRA) in patients of essential hypertension.

MATERIALS AND METHODS

This study was conducted in a tertiary teaching hospital from north India over a period of 15 months from January 2011 to March 2012. The study was approved by institutional scientific and ethical committees and informed consent was obtained from patients. Primary outcome of this study was to determine prevalence of essential hypertension with elevated ARR in this part of the country while the secondary outcome was to determine if there is any correlation between high ARR and severity of hypertension.

One hundred consecutive adult hypertensive patients who reported to hypertension clinic were enrolled in this study. Another 50 normotensive individuals of comparable baseline characteristics and devoid of any cardiovascular, renal, hepatic or metabolic disease and not on any drugs were recruited from general population who served as control. Secondary causes of hypertension were excluded by history, physical examination and appropriate investigations in proper clinical setting (Appendix I). Patients with malignant hypertension, congestive heart failure as well as women on oral contraceptives were excluded from the study.[22]All patients were allowed unrestricted salt intake while 24 hour urinary sodium excretion was used as an index of the state of salt balance. All antihypertensive medication were stopped for four weeks before measuring plasma aldosterone concentration and plasma renin activity. If necessary BP control was obtained by verapamil or α blockers because they don't affect ARR.[23]

Blood pressure was measured with a mercury sphygmomanometer in supine position, after taking rest for 15 minutes. Normal blood pressure was defined as systolic and diastolic blood pressures less than 120 mmHg and 80 mmHg respectively. Mean blood pressure (MAP) was calculated by adding diastolic blood pressure to one-third of pulse pressure. Hypertension was defined as systolic and diastolic pressures ≥ 140 mmHg and ≥ 90 mmHg as determined by mean of 3 readings on three different occasions.[8]

Venous blood sample was drawn for estimation of PRA and plasma aldosterone concentration between 0900-1100 hours after the patient had been ambulatory for at least 2 hours and a subsequent period of 10 minutes in seated position.[24] For PRA determination 5ml of blood was collected in pre-chilled tube containing 10mg of EDTA. Sample was centrifuged immediately and plasma frozen at -20° C for future use.[25] All samples were assayed in one step, using the same batches of reagents. For aldosterone estimation, 5ml of blood was collected in a separate EDTA tube and plasma was separated and stored under refrigeration for future use. On the day of sample collection for PRA and aldosterone estimation, a 24 hour urinary sample was also collected for determination of urinary sodium excretion.

PRA measurement was performed by generation of angiotensin I (AI) in aliquots of plasma specimens and radioimmunoassay of AI by the modification of method described by Haber *et al*. and standardized as per recommendation provided in AI RIA kit.[26] In this technique the amount of AI generated in vitro in plasma specimens under controlled conditions is assumed as an index of renin activity and is referred to as plasma renin activity (PRA). The differences in the amounts of AI before and after generation is used to determine PRA. Renin in plasma specimens is allowed to act under standardized conditions and generated AI is quantitated by RIA. Sodium azide, an enzyme inhibitor, was used to prevent AI metabolism further to AII and smaller peptides to assure precise quantification of the amount of AI generated.

On the day of assay, frozen plasma samples of patients were thawed and 200 µL of each plasma sample was mixed to 200 µL of pre-cooled enzymatic inhibitor. Each sample was split into two 200 µL aliquots. First aliquot was placed in an ice-cold water bath in a refrigerator (for determination of background AI at 4°C) while the second aliquot was placed for one hour in a water bath at 37°C (for determination of generated AI at 37°C). All the aliquots were incubated at 37°C for 1 hour and then rapidly cooled to 4°C using ice water bath. Fifty microliter of calibrator (containing 0 to 30 ng/mL of AI in buffer with bovine serum albumin and sodium azide) was added to antibody coated tubes followed by control (containing AI in buffer with bovine serum albumin and sodium azide) and patient samples successively after enzymatic incubation at 37°C and at 4°C respectively. Two hundred microliters of tracer was added to the solution and incubated at 18-25°C for 2 hours at > 280 rpm. This was followed by aspiration from tubes and each was subsequently washed with 2 mL of wash solution and PRA was determined for 1 minute.

The results were calculated using a logit-log curve fit (weighted cubic regression) with B/T (%) or B/B0 (%) on vertical axis and the AI concentrations of calibrators on the horizontal axis (ng/mL). The curve serves for the determination of AI concentrations in samples assayed at the same time as the calibrators. Results were obtained from the standard curve by interpolation. For the control and samples incubated at 4°C or at 37°C, the B/T (%) or the B/B0 (%) value on the vertical axis was located and the corresponding AI concentration in ng/mL on the horizontal axis was obtained. The determination of PRA was performed indirectly by the measurement of the in vitro generation of AI per hour. Background AI, determined on plasma samples incubated at 4°C, was subtracted from the AI generated at 37°C for the calculation of PRA using the following equation:

$$\text{PRA ng of AI /mL/hr} = \frac{[\text{AI (37°C)} - \text{AI (4°C)}] \times 2}{\text{Enzymatic incubation time (hrs)}}$$

Where, AI (37°C): angiotensin concentration in ng/mL of sample incubated at 37°C and AI (4°C): angiotensin concentration in ng/mL of sample incubated at 4°C.

Plasma aldosterone was measured by radioimmunoassay as described by Mayes *et al*.[27] The radioimmunoassay of aldosterone is a competition assay. Samples and calibrators (containing 0 to 2000 pg/mL of lyophilized aldosterone in human serum with sodium azide) are incubated with an ^{125}I-labeled aldosterone, as tracer, in antibody-coated tubes. After incubation, the liquid content of the tube is aspirated and

bound radioactivity is measured. A standard curve is established and unknown values are determined by interpolation from a standard curve. The curve serves for the determination of aldosterone concentrations in samples measured at the same time as the calibrator. The results were calculated using a semi-logarithmic curve fit ("spline" mode) with B/T (%) or B/B0 (%) on vertical axis and the aldosterone concentration of the calibrators on the horizontal axis (pg/mL). Location for each sample (plasma) with B/T (%) or the B/B0 (%) on the vertical axis was determined and the corresponding aldosterone concentration in pg/mL on the horizontal axis was noticed.

Statistical Analysis

Standard statistical methods were used wherein continuous variables are shown in mean (±SD) or median (IQR) depending on underlying distribution of the data. Inter-group comparison was done by student's t-test, Mann Whitney U-test and Chi-square test. A P value of <0.05 was considered statistically significant. All the data were analyzed by SPSS 14.0 software from International Business Machines (IBM) Corporation.

RESULTS

A total of 100 hypertensive patients (52 males and 48 females) and 50 normotensive controls (26 males and 24 females) of comparable baseline characteristics were studied. ARR was determined in both the groups to determine the prevalence of aldosterone associated hypertension (ARR >25). The demographic, clinical and biochemical characteristics of 2 groups are shown in table 1.Both the groups were comparable in age and gender distribution (p> 0.05). Among hypertensive patients, 7% (n=7) were <40 years while 93% (n=93) were older than 40 years whereas in control group, 8% (n=4) were <40 years whereas 92% (n=46) were >40 years. The prevalence of aldosterone associated hypertension was 19% in our study population. There was statistically no significant difference in the biochemical characteristics of hypertensive patients and controls (p>0.05) in terms of blood urea, sodium, potassium or 24 hours urinary sodium except for serum creatinine which was high in hypertensive patients as compared to controls (p=0.01).

Table 1 Baseline Characteristics of 2 Groups

Variable	Hypertensive group (n=100) Mean (±SD)	Normotensive group (n=50) Mean (±SD)	P value
Age (years)	54.2 (±9.5)	54.2 (±10.4)	0.97
Weight (Kg)	67.7 (±5.3)	65.7 (±6.7)	0.06
Height (cm)	162.8 (±4.9)	161.0 (±6.9)	0.07
Body Mass Index (Kg/m2)	25.6 (±1.9)	25.4 (±2.2)	0.57
Systolic Blood Pressure (mmHg)	157.6 (±10.2)	121.3 (±7.7)	0.00
Diastolic Blood Pressure (mmHg)	95.5 (±5.2)	75.9 (±4.9)	0.00
Mean blood Pressure (mmHg)	116.2 (±6.2)	91.0 (±4.2)	0.00
Blood Urea (mg/dl)	30.0 (±5.8)	31.3 (±5.5)	0.19
Serum Creatinine (mg/dl)	0.9 (±0.3)	0.7 (±0.3)	0.01
Serum Sodium (meq/L)	137.8 (± 4.0	137.7 ± 3.9	0.93
Serum Potassium (meq/L)	3.9 (±0.6)	4.1 (±0.5)	0.11
24 hrs Urinary Sodium (meq/L)	126.7 (±14.6)	128.8 (±12.7)	0.41

Hypertensive patients had elevated aldosterone and ARR than normotensive individuals which was statistically significant while renin levels were comparable in 2 groups (Table 2)

Table 2 Aldosterone and Renin in 2 Groups

Hormone	Hypertensive group (n=100) Mean (±SD)	Normotensive group (n=50) Mean (±SD)	P value
Aldosterone (ng/dl)	5.8 (±3.4)	5.0 (±3.6)	0.02
Renin (PRA-ng/ml/hr)	1.0 (±1.1)	1.1 (±0.7)	0.57
Aldosterone-Renin Ratio	14.6 (±15.7)	6.0 (±4.1)	0.00

The mean systolic BP of patients with elevated ARR was significantly higher than patients with normal ARR (p=0.04). However diastolic BP and mean BP was comparable among hypertensive patients with raised and normal ARR (table 3).

Table 3 Age, BMI and BP distribution among Hypertensive Patients with High & Normal ARR

Variable	Raised ARR (> 25.0) n= 19 Mean (±SD)	Normal ARR (≤ 25.0) n= 81 Mean (±SD)	P Value
Age (years)	56.7 (±5.7)	53.6 (±10.1)	0.51
Body Mass Index (Kg/m^2)	25.4 (±2.0)	25.6 (±1.9)	0.99
Systolic Blood Pressure (mmHg)	160.1 (±8.1)	157.0 (±10.6)	0.04
Diastolic Blood Pressure (mmHg)	97.4 (±4.4)	95.1 (±5.3)	0.15
Mean Blood Pressure (mmHg)	118.3 ± 5.1	115.7 ± 6.3	0.07

Biochemical profile (urea, creatinine, sodium, potassium and 24 hrs urinary sodium) of individuals with high and normal ARR among hypertensive group was comparable (Table 4). In addition, ARR was correlated with the severity of hypertension wherein relatively higher ARR was observed in patients with stage II hypertension as compared to stage I hypertension.

Table 4 Biochemical Profile of Hypertensive Patients with High and Normal ARR

Variable	High ARR (> 25.0) n=19 Mean (±SD)	Normal ARR (≤ 25.0) n=81 Mean (±SD)	P Value
Blood Urea (mg/dl)	31.8 (±7.0)	29.5 (±5.4)	0.21
Serum Creatinine (mg/dl)	0.9 ± 0.3	0.8 ± 0.3	0.40
Serum Sodium (meq/L)	138.1 (±3.9)	137.7 (±4.0)	0.93
Serum Potassium (meq/L)	3.6 (±0.6)	4.0 (±0.6)	0.38
24 hrs Urinary Sodium (meq/L)	123.1 (±14.2)	127.6 (±14.7)	0.15

Among hypertensive patients, 19% (n=19) were having high ARR (≥25). Out of these 19% patients of aldosterone associated hypertension, 63.2% (n=12) comprised of females mostly in age group of 45-65 yrs (89.5%, n=17). Among this aldosterone associated hypertension group, 68.4% (n=13) and 52.6% (n=10) were having systolic and diastolic BP of ≥160 mmHg and ≥100 mm Hgrespectively while 63.2% (n=12) were having BMI of > 25kg/m^2. Further in this group, 57.9% (n=11) were having 24hr urinary sodium excretion between 100-129mEq/L/24hr.

The aldosterone concentration was significantly higher in hypertensive patients with elevated ARR than hypertensive patients with normal ARR. It was observed that patients with high ARR have significantly lower level of renin as compared to patients with normal ARR (Table 5).

Table 5 Aldosterone and Renin profile in Hypertensive Patients with High and Normal ARR

Hormone	High ARR (> 25.0) n=19 Mean (±SD)	Normal ARR (≤ 25.0) n=81 Mean (±SD)	P Value
Aldosterone (ng/dl)	8.4 (±3.4)	5.2 (±3.1)	0.00
Renin (PRA, ng/ml/hr)	0.2 (±0.1)	1.2 (±1.2)	0.00

DISCUSSION

The essential hypertension is one of the most common chronic diseases affecting humans and yet the pathogenesis of this disease is far from being complete. Among the various systems suspected to be of etiological significance, renin-angiotensin-aldosterone system (RAAS) is the most studied one. There has been a paradigm shift in our understanding of the actions of aldosterone. The initial description by Conn of primary aldosteronism proved the existence of a direct relationship between elevated levels of aldosterone with the development of hypertension. Such an association was initially considered a rare cause of secondary hypertension, with a prevalence of < 1%. However, recent data indicate the possible existence of an unrecognized epidemic of aldosterone associated hypertension. In fact, a prospective study by Rossi *et al*. investigated a group of 1125 patients and found 11.2% prevalence of aldosterone associated hypertension.[28]The contribution of aldosterone to the development of hypertension in general population has been shown recently by the Framingham Offspring Studyin which aldosterone level in normotensive individuals predicted subsequent risk of hypertension.[29, 30]The fact that aldosterone associated hypertension is more common than previously thought, led to the use of ARR as a more sensitive method of screening for aldosterone associated hypertension. Despite wide variation in sample population in studies found in literature, most of these studies have reported prevalence rate of aldosterone associated hypertension within the range of 5% to 15%.[25, 31-33]

We investigated essential hypertensive patients to know the prevalence of aldosterone associated hypertension in this part of the country by measuring ARR. An ARR of ≥25 was taken as elevated. In addition, we assessed the characteristics (demographic as well as biochemical) of patients of essential hypertension with high and normal ARR. Further, the occurrence of high ARR in hypertensive patients correlated with the severity of hypertension.

In our study, the prevalence of aldosterone associated hypertension was 19%. In literature the prevalence of aldosterone associated hypertension varies widely. Olivieri *et al*., Loh *et al*., Lim *et al*., Fardella *et al*., Fogari *et al*. and Strauch *et al*. reported that an elevated ARR was observed in 32.4%, 18%, 16.6%, 9.5%, 22.8% and 21.6% of essential hypertensive patients respectively.[24, 25, 31-34]

Our finding of high ARR in hypertensive patients compared to normotensive individuals was in agreement with other investigators.[25, 31, 33] We also found that high ARR was more prevalent in patients with systolic BP of > 160 mmHg, a finding similar to other studies.[24, 31-33]The findings in our study that patients of essential hypertension with high ARR were mainly females and in the age group of 45-65 years, were also found by Olivieri *et al*. who reported that 67% of patients with high ARR were in 45-65 years and 64.4% were females.[25]Our study found that 63.2% of patients with high ARR were having BMI of more than 25kg/m^2 which was in accord with other investigators.[35-37]

We found that 73.7% and 26.3% of patients with high ARR have serum potassium of 3.3-4.0 meq/L and more than 4 meq/L respectively. Thus it is more likely that patients with high ARR may have their serum potassium in lower normal range as compared to the hypertensive patients with normal ARR. A number of patients in the hypertensive group were on antihypertensive drugs (drugs affecting ARR were stopped 3 weeks prior to determination of ARR). However, no significant difference between hypertensive patients with high ARR who were on drugs as compared to hypertensive patients with normal ARR who were not on antihypertensive medication.

In our study the mean serum aldosterone concentration in hypertensive patients with high ARR was significantly higher as compared to hypertensive patients with normal ARR. Also, there was statistically significant difference in renin levels between hypertensive patients with high ARR as compared to hypertensive patients with normal ARR. The hypertensive patients with high ARR were having significantly low levels of renin as compared to hypertensive patients with normal ARR as determined by PRA. Olivieri *et al*. in 2004 reported similar findings.[25]There was statistically no significant difference between the hypertensive patients with high ARR as compared to patients with normal ARR in relation to serum creatinine, serum sodium or blood urea. These findings were in accord with those of Olivieri *et al*.[25]

The high prevalence of aldosterone associated hypertension reflects inappropriately elevated levels of aldosterone in relation to renin activation. It is pertinent to mention here that the study did not allow us to quantify the prevalence of primary aldosteronism, but only that of an elevated ARR. In particular, this does not mean that an equal proportion of patients with raised ARR should be considered as being affected by aldosteronism as no diagnostic tests were performed. Although high ARR and aldosteronism are very often concomitantly present, the study aims did not include establishing the extent of this association in our population.

Nevertheless, other implications of ARR that are potentially relevant in terms of human health have to be taken into account. There is probably the need to extend ARR screening more widely and more frequently to hypertensive patients. In this connection the methodological procedure used in present study is suitable model in general practice without major undesirable consequences. The potential impact of such a diagnostic approach in terms of subsequent workup for aldosteronism and possible surgical cure of hypertension due to aldosterone-producing adenomas is relevant.

The final consideration stems from Lim's concept that an elevated ARR may serve as a guide for targeting drug therapy in hypertensive patients independent of the established diagnosis of aldosteronism.[38, 39]Although this option was recommended for patients with resistant hypertension or those requiring more than two agents for BP control.[40, 41]Our results suggest that a larger population could take advantage of such a therapeutic option. Once validated by controlled trials and adequately extended to all sensitive patients, this approach should prove highly cost effective in terms of public health, taking into consideration the low cost of spironolactone treatment and availability of selective aldosterone receptor antagonist, Eplerenone. Future controlled trials capable of demonstrating the hypothesis are therefore mandatory, so that a substantial proportion of individuals affected by hypertension can receive appropriate treatment based on underlying pathogenic cause.

CONCLUSION

The patients of essential hypertension without any underlying etiology forms a heterogeneous group having different

biochemical and hormonal profile. A subcategory of hypertensive patients who, besides having high ARR, don't have clinical or biochemical features of primary aldosteronism, are said to have aldosterone associated hypertension. Screening of hypertensive patients revealed that there is a high prevalence of aldosterone associated hypertension. Although many such patients may not have the primary aldosteronism, they have demonstrable abnormalities in RAAS dynamics. So aldosterone antagonists may be more appropriate antihypertensive drug for such patients and such an approach may be more cost effective. Future large controlled trials capable of demonstrating the hypothesis are needed.

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