RESEARCH ARTICLE

Spectrum of renin angiotensin aldosterone system disorders in young hypertensives

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Abstract

Objective: To analyse the spectrum of renin angiotensin aldosterone system disorders in young hypertensive patients in hospital settings.

Methods: This cross-sectional study was conducted at the Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, Pakistan, from January to December, 2016. It comprised hypertensive subjects aged 17-40 years of either gender presenting in the outpatient department. All subjects were having blood pressure more than 140/90mmHg and were not on any anti-hypertensive medicine. Blood sample was taken from each patient to analyse arterial blood gases, plasma renin, serum aldosterone and electrolytes. Association of qualitative variables like age, systolic and diastolic blood pressure with essential hypertension and primary hyperaldosteronism was explored.

Result: Of the 80 patients, 72(90%) were diagnosed with essential hypertension and 8(10%) with primary hyperaldosteronism. None of the patients had Liddle syndrome, apparent mineralocorticoid excess or Gordon syndrome. Mean age of patients having essential hypertension was 30.97±7.1 years, whereas, for those with primary hyperaldosteronism it was 29.25±7.1 years. Systolic blood pressure was significantly higher ($p = 0.000$) among all patients. No statistically significant association was found between age, systolic and diastolic blood pressure ($p<0.05$).

Conclusion: Primary hyperaldosteronism as compared to other renin angiotensin aldosterone system disorders was found to be the leading cause of hypertension in young population.

Keywords: Renin angiotensin aldosterone disorders, Primary hyperaldosteronism, Essential hypertension. (JPMA 68: 1179; 2018)

Introduction

Hypertension is one of the most prevalent non-communicable diseases in developed countries accounting for 7.1 million deaths per year and 92 million disability adjusted life years (DALY) worldwide.[1,2] Among young adults between18 to 39 years of age, 20% of men and 15% women are hypertensive.[3] Hypertension reflects a system of pathophysiological disturbances in our body, presenting itself in the form of high blood pressure. Documented mechanisms include increased sympathetic activity, renin angiotensin aldosterone system (RAAS) disorders, increased sodium conserving hormones, deficiency of vasodilators(nitric oxide, prostacyclin, natriuretic peptides), increased vasoconstrictors, abnormalities of the kallikrein-kinin system and renal micro vasculature.[4] Even though extensive research work and data has been collected on this subject, etiology of hypertension is still not well understood.[5] However, hypertension is one of the modifiable risk factors for cardiovascular and cerebrovascular morbidity and mortality.[6]

RAAS plays an important role in pathogenesis of hypertension. It regulates systemic vascular resistance and circulatory volume by water and electrolyte balance.[7] Renin is synthesised from precursor prorenin by the juxtaglomerular apparatus cells. It converts angiotensinogen to angiotensin I in the liver. Angiotensin converting enzyme (ACE), present in lung converts Angiotensin I into Angiotensin II.[8] This angiotensin II via G protein coupled receptor in the glomerulosa cells causes membrane depolarisation, activation and opening of calcium gated channels. Increased intracellular calcium, signals the production of aldosterone from the adrenal glomerulosa. Aldosterone in turn causes kidneys to reabsorb sodium ions and secrete potassium ions.[9]

Common disorders affecting the RAAS system and causing hypertension include primary hyperaldosteronism, apparent mineralocorticoid excess, Liddle syndrome and Gordon's syndrome.[10-14] Primary hyperaldosteronism is the leading hormonal cause of hypertension with a prevalence varying from 4.6% to

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16.6% among Greeks.[10] Majority of hypertensive patients with primary hyperaldosteronism reporting in primary and tertiary care settings have adrenal tumours or adrenal hyperplasia. Apparent mineralocorticoid excess is an autosomal recessive disorder, being the third most common cause of monogenic hypertension it is characterised by 11 β-hydroxysteroid dehydrogenase type 2(11β-HSD2) enzymes deficiency, responsible for the conversion of cortisol to cortisone.[11] Liddle syndrome, the second most common cause of monogenic hypertension, is an autosomal dominant disorder characterised by mutations in the β and - subunits of ENaC (epithelial sodium channels). It presents with hypokalaemia, metabolic alkalosis, salt-sensitive hypertension, suppression of plasma renin activity(PRA) and aldosterone secretion.[12] Gordon syndrome also known as pseudohypoaldosteronism type II is caused by mutations in any of the four genes; WNK1, WNK4, CUL3 and KLHL3 which are the regulators of the thiazide sensitive Na^+- Cl^- co transporter. It is characterised by hyperkalaemic metabolic acidosis and salt dependent hypertension.[13]

The current study was planned to analyse the spectrum of RAAS disorders in young hypertensive patients, as hypertension is one of the preventable risk factors for death and a predictor of future cardiovascular incidents.[3]

Patients and Methods

This cross-sectional study was conducted at the Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology (AFIP), Rawalpindi, Pakistan, from January to December, 2016. After approval from the institutional review board, hypertensive subjects with a blood pressure of more than 140/90mmHg who were not on any anti-hypertensive medicine, aged 17-40 years of either gender were enrolled from among those presenting at the outpatient department. Sample size was calculated after thorough literature review and calculated from given prevalence rate of the most common RAAS disorders (5%) in Asian population[15] from given formula of World Health Organisation (WHO) sample size estimation (n= z2p(1-p)/d2).[16] Besides, 165 hypertensive subjects, presenting in the outpatient department (OPD) of tertiary care hospital were recruited in the study. Patients with renal dysfunction, heart failure, pregnancy and secondary hypertension were excluded. Blood samples were collected from subjects by non-probability consecutive sampling technique after taking informed consent. To analyse plasma renin and serum aldosterone levels, 3.0 ml venous blood was collected in each ethylenediaminetetraacetic acid (EDTA) and gel tube. Furthermore, 3.0 ml arterial blood was collected in lithium heparin tube to measure pH, electrolytes-sodium and potassium and blood gases. Plasma rennin was analysed on DIASORIN LIASON® by sandwich chemiluminescence immunoassay and analysis of serum aldosterone was done by BIORAD PhD™ SYSTEM-enzyme-linked immunosorbent assay (ELISA). Arterial blood gases, pH, partial pressure of carbon dioxide (pCO2) and electrolytes-sodium, potassium were measured on COBAS b221 by potentiometry along with calculated bicarbonate. SPSS 24 was used to analyse the data. Mean and standard deviation was calculated for all the parametric quantitative variables while median and interquartile range (IQR) were calculated for non-parametric data (Systolic Blood Pressure in OPD with primary hyperaldosteronism). Chi-square was used to compute the association of age, systolic and diastolic blood in OPD and Endocrine Clinic AFIP (Laboratory), with primary hyperaldosteronism and essential hypertension. $P<0.05$ was considered significant.

Results

Out of 165 patients examined, 80(48.48%) fulfilled the inclusion criteria. Of them, 12(15%) were females and 68(85%) were males. In terms of age, 21(26.25%) subjects were aged 17-25 years, 22(27.5%) were aged 26-33 years, and group-37(46.25%) were aged 34-41years. Mean systolic blood pressure of all patients was 172.7±19.2 mmHg, whereas, diastolic blood pressure was

Table-1: Descriptive analysis of various study factors.

	All cases (Mean±SD)	With Essential Hypertension (Mean±SD)	With Primary Hyperaldosteronism (Mean±SD)/ Median(IQR) for non-parametric data
Age	30.8±7.1	30.97±7.1	29.25±7.1
Diastolic BP in OPD	100±8.3	100.41±8.2	96.25±9.1
Systolic BP in OPD	172.7±19.2	172.91±19.0	Median= 180 IQR=(162-241)
Diastolic BP in Endo Clinic	90±6.5	90.06±6.6	92.5±4.6
Systolic BP in Endo Clinic	142.7±10.5	142.70±10.5	143.12±11.6
Serum Sodium	137.8±6.5	137.5±6.5	140.6±6.3
Serum Potassium	4.23±0.6	4.29±0.6	3.73±0.4

OPD= Outpatient Department.

Table-2: Association of Systolic and Diastolic Blood Pressure in different age groups with essential hypertension and primary hyperaldosteronism patients.

	Systolic Blood Pressure						Diastolic Blood pressure					
	Outpatient department			Endocrine clinic			Outpatient department			Endocrine clinic		
Age groups	17-25y	26-33y	34-41y	17-25y	26-33y	34-41y	17-25y	26-33y	34-41y	17-25y	26-33y	34-41y
Essential Hypertension	0.3	0.4	0.3	0.3	0.5	0.2	0.3	0.3	0.3	0.3	0.7	0.4
Primary hyperaldosteronism	0.2	0.1	0.2	0.1	0.1	0.1	0.2	0.1	0.3	0.3	0.1	0.2

Table-3: Association of RAAS disorders (primary hyperaldosteronism) and essential hypertension with blood pressure.

	All cases		With Essential Hypertension		With Primary Hyperaldosteronism	
	n	p-value	n	p-value	n	p-value
Systolic BP in OPD	80	0.000	72	0.34	08	0.3
Diastolic BP in OPD	80	0.51	72	0.41	08	0.27
Diastolic BP in Endo Clinic	80	0.17	72	0.56	08	0.33
Systolic BP in Endo Clinic	80	0.17	72	0.61	08	0.31

RAAS= Renin Angiotensin Aldosterone System.

100.0±8.3mmHg. Similarly, mean systolic blood pressure in the Endocrine Clinic was 142.7±10.5mmHg and diastolic blood pressure was 90.3±6.5mmHg. Plasma renin and aldosterone levels were measured and aldosterone-to-renin ratio (ARR) was computed. Those having an ARR >130 pmol/mIU were diagnosed as having primary hyperaldosteronism, while patients having ARR <100pmol/mIU were having essential hypertension. Overall, 72(90%) patients were reported with essential hypertension, out of whom 60(83.3%) were males and 12(16.6%) were females, whereas 8(10%) patients were diagnosed with primary hyperaldosteronism and all were males. None of the patients had Liddle syndrome, apparent mineral ocorticoid excess and Gordon syndrome.

Mean age of all the patients was 30.8±7.1 years, while for patients having essential hypertension it was 30.97±7.1 years, whereas, for those with primary hyperaldosteronism it was 29.25±7.1 years (Table-1). Frequency of cases with essential hypertension in different age groups was: in 17-25years, 5(25%), in 26-33 years, 6(27.7%), in 34-41 years 17(47.2%); while with primary hyperaldosteronism, it was 17-21years 8(37.5%), 26-33 years 6(25%), 34-41 years 14(37.5%). Association of all of these age groups with essential hypertension and primary hypertension was also computed (Table-2). Association of Systolic blood pressure with all the patients reported in OPD was significant (p=0.000) (Table-3).

Discussion

Hypertension, the most prevalent non-communicable diseases affecting developed countries has a spectrum of etiologies, RAAS being one of the leading causes. RAAS regulates blood pressure by regulating systemic vascular resistance and circulatory volume by water and electrolyte balance.[7] Early diagnosis and treatment of hypertension is very important as it is a predictor of future cardiovascular events and a modifiable risk factor.[3] Primary hyperaldosteronism is the most prevalent RAAS disorder in our study population which is consistent with the data presented by Tsiavos et al[10] in a study conducted in University of Athens, Greece.

Frequency of primary hyperaldosteronism in our subjects was 10% (all in males) which is very close to the prevalence documented by Rossi et al[14] which is 11.2% without gender differences and same study population characteristics (e.g. age). Douma et al[17] in a study conducted in the Aristotle University of Greece reported a frequency of 11.3% of primary hyperaldosteronism in hypertensive population which is also very close to our results.

Mean age of patients having primary hyperaldosteronism in our study population was 29.25±7.1 years and those with essential hypertension was 30.97±7.1 years. However, in a study conducted by Douma et al[17] the mean age for primary hyperaldosteronism was 56.7±12.3 years and that for essential hypertension was 56.3±12.3 years. This difference was because our study was conducted in young hypertensives with age from 17-40 years and specified age group selection was not a criterion in their inclusion.

Another finding in our study was that patients presenting in OPD had a significantly higher systolic blood pressure

(p=0.000) as compared to those presenting in our Endocrine clinic. This was probably because of the stress and the long waiting hours that patients underwent in OPD as compared to the early morning appointment based sampling in our Endocrine clinic, without any wait. It can also be due to physical exertion and stairs climbing in hospital settings. This stress factor has been documented in a study by Artinian et al[18] and Hjortskov et al.[19] Another reason could be test protocol which is a fasting sample with patient comfortably seated for half-an-hour in our Endocrine clinic. Study conducted by Lutsey et al[20] in University of North Carolina and University of Minnesota also reported a positive association of food intake and a higher blood pressure. Similarly, another study by Tzoulaki et al[21] in Japan, China and USA also concluded the same results.

Although study reported very important results and served as a preliminary data for future information and studies but small sample size and single centre study were the limitations. Therefore, study with greater sample size, multi-centric approach and advanced study design will be able to generate more generalised and authentic results.

Conclusion

RASS plays a key role in blood pressure regulation and mineralocorticoid excess syndrome. Primary hyperaldosteronism among all the RAAS disorders is the most common in young hypertensives, while no cases of Liddle syndrome, Gordon syndrome and apparent mineralocorticoid excess syndrome were reported in our study.

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References

1. Sarafidis PA, Li S, Chen SC, Collins AJ, Brown WW, Klag MJ, et al. Hypertension awareness, treatment, and control in chronic kidney disease. Am J Med 2008; 121: 332-40.
2. Mohan S, Campbell NR. Hypertension management: time to shift gears and scale up national efforts. Hypertension 2009; 53: 450-1.
3. Johnson HM, Thorpe CT, Bartels CM, Schumacher JR, Palta M, Pandhi N, et al. Undiagnosed hypertension among young adults with regular primary care use. Int J Hypertens 2014; 32: 65-74.
4. Samson R, Lee A, Lawless S, Hsu R, Sander G. Novel Pathophysiological Mechanisms in Hypertension. In: Islam MS, (eds). Hypertension: from basic research to clinical practice. Advances in Experimental Medicine and Biology. Springer, Cham, 2016.
5. Saleem F, Hassali AA, Shafie AA. Hypertension in Pakistan: time to take some serious action. Br J Gen Pract 2010; 60: 449-50.
6. K?z?l?rmak P, Uresin Y, Ozdemir O, Avci BK, Tokgozoglu L, Ongen Z. Renin-angiotensin-aldosterone system blockers and cardiovascular outcomes: a meta-analysis of randomized clinical trials. Turk Kardiyol Dern Ars 2017; 45: 49-66.
7. Bavishi C, Bangalore S, Messerli FH. Renin Angiotensin Aldosterone System Inhibitors in Hypertension: Is There Evidence for Benefit Independent of Blood Pressure Reduction? Prog Cardiovasc Dis 2016; 59: 253-61.
8. Thethi T, Kamiyama M, Kobori H. The link between the renin-angiotensin-aldosterone system and renal injury in obesity and the metabolic syndrome. Curr Hypertens Rep 2012;14:160-9.
9. Choi M, Scholl UI, Yue P, Björklund P, Zhao B, Nelson-Williams C, et al. K+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. Science. 2011;331:768-72.
10. Tsiavos V, Markou A, Papanastasiou L, Kounadi T, Androulakis II, Voulgaris N, et al. A new highly sensitive and specific overnight combined screening and diagnostic test for primary aldosteronism. Eur J Endocrinol. 2016;175:21-8.
11. Ardhanari S, Kannuswamy R, Chaudhary K, Lockette W, Whaley-Connell A. Mineralocorticoid and apparent mineralocorticoid syndromes of secondary hypertension. Adv Chronic Kidney Dis 2015; 22: 185-95.
12. Wang LP, Yang KQ, Jiang XJ, Wu HY, Zhang HM, Zou YB, et al. Prevalence of Liddle syndrome among young hypertension patients of undetermined cause in a Chinese population. J Clin Hypertens 2015; 17: 902-7.
13. Glover M, Ware JS, Henry A, Wolley M, Walsh R, Wain LV, et al. Detection of mutations in KLHL3 and CUL3 in families with FHHt (familial hyperkalaemic hypertension or Gordon's syndrome). Clin Sci 2014; 126: 721-6.
14. Rossi GP, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J Am Coll Cardiol 2006; 48: 2293-300.
15. Loh KC, Koay ES, Khaw MC, Emmanuel SC, Young Jr WF. Prevalence of primary aldosteronism among Asian hypertensive patients in Singapore. J Clin Endocrinol Metab 2000; 85: 2854-9.
16. Pourhoseingholi MA, Vahedi M, Rahimzadeh M. Sample size calculation in medical studies.Gastroenterol Hepatol Bed Bench 2013; 6: 14-7.
17. Douma S, Petidis K, Doumas M, Papaefthimiou P, Triantafyllou A, Kartali N, et al. Prevalence of primary hyperaldosteronism in resistant hypertension: a retrospective observational study. Lancet 2008; 371: 1921-6.
18. Artinian NT, Washington OG, Flack JM, Hockman EM, Jen KL. Depression, Stress, and Blood Pressure in Urban African?American Women. Prog Cardiovasc Nurs 2006; 21: 68-75.
19. Hjortskov N, Rissén D, Blangsted AK, Fallentin N, Lundberg U, Søgaard K. The effect of mental stress on heart rate variability and blood pressure during computer work. Eur J Appl Physiol 2004; 92: 84-9.
20. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome. Circulation 2008; 117: 754-61.
21. Tzoulaki I, Brown IJ, Chan Q, Van Horn L, Ueshima H, Zhao L, et al. Relation of iron and red meat intake to blood pressure: cross sectional epidemiological study. BMJ 2008; 337: a258.