

Disorders Causing Secondary Hypertension in Patients Less Than 45 Years of Age

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ABSTRACT

Objective: To determine the frequency of disorders causing secondary hypertension in patients less than 45 years of age.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Pathology and Medicine, Combined Military Hospital (CMH), Risalpur, Pakistan, along with Armed Forces Institute of Pathology (AFIP)and Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan from Apr 2017 to Apr 2019.

Methodology: A total of 50 patients, less than 45 years of age, newly diagnosed with hypertension (systolic blood pressure>140 mm Hg or diastolic BP>90 mm Hg) and reported to CMH Risalpur for the workup of HTN were included. Analysis of serum cholesterol, triglycerides, urea, creatinine, sodium, potassium, calcium, thyroid stimulating hormone, plasma glucose random, urine analysis and renal ultrasonography were carried out. In addition, serum cortisol, 24 hours urinary free cortisol, dexamethasone suppression test, growth hormone level, insulin-like growth factor-1,24 hours urinary vanillylmandelic acid, serum aldosterone and renin levels, Doppler renal ultrasonography, renal arteriogram, CT abdomen, MRI pituitary and MR/CT angiography were carried out.

Results: A total of 50 patients comprised of 82% males and 18% females with a mean age of 36.1±6.2years. Primary hypertension was observed in 31(62%) cases. Secondary causes of HTN in 19(38%) cases, were obstructive sleep apnea (4, 8%), primary hyperaldosteronism (3,6%), renal parenchymal hypertension (3,6%), renal artery stenosis (1,2%), Cushing's syndrome (2,4%), hyperthyroidism (2,4%), hypothyroidism (2,4%), pheochromocytoma (1,2%) and coarctation of aorta (1,2%) cases.

Conclusion: Obstructive sleep apnea primary hyper-aldosteronism and renal parenchymal diseases were the commonest causes of secondary hypertension, followed by Cushing's syndrome, hyperthyroidism and hypothyroidism.

Keywords: Obstructive sleep apnea, Primary hyperaldosteronism, Secondary hypertension.

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INTRODUCTION

Hypertension (HTN) is the highest contributor to the global disease burden. Unfortunately, most patients with essential hypertension do not have an identifiable cause. Therefore, exploring the secondary causes of hypertension is important, as they can be identifiable and potentially curable.¹ Secondary hypertension occurs in a significant number of patients less than 45 years of age (approximately 10-35%),^{2,3} by leaving undiagnosed, the cases of secondary hypertension may lead to resistant hypertension, cardiovascular and renal complications, multiple referrals and unnecessary burden on the healthcare system.

Obstructive sleep apnea, renal artery stenosis, renal parenchymal disease, coarctation of the aorta, drugs (NSAID, OCPs, sympathomimetics, erythropoietin) and some diets are non-endocrine causes. At the same

time, primary hyperaldosteronism,⁴ Cushing's syndrome, pheochromocytoma, hyperthyroidism, hypothyroidism, hyperparathyroidism and acromegaly are endocrine causes of secondary HTN.^{5,6} Recognition and early diagnosis of secondary causes of hypertension can help in effective treatment, better clinical outcomes and the possibility for reversal of end-organ damage and blood pressure control.³

The causes of secondary hypertension may differ in various regions, and management depends on the cause. So knowing the most common causes of secondary hypertension in our setup could be helpful in the early diagnosis and management of the patients. Therefore, this study aimed to determine the frequency of disorders causing secondary hypertension in patients reporting to Combined Military Hospital (CMH) Risalpur.

METHODOLOGY

This cross sectional study was conducted at the Department of Pathology and Medicine, CMH

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Risalpur, in collaboration with the Armed Forces Institute of Pathology (AFIP) and Pak Emirates Military Hospital (PEMH), Rawalpindi Pakistan, from April 2017 to April 2019 after approval of the Institutional Ethical Review Board (via IERB CMH Rsc-1/2017).

Inclusion Criteria: The patients less than 45 years of age newly diagnosed with hypertension (systolic BP > 140 mm Hg or diastolic B.P. > 90 mmHg) and reported to Combined Military Hospital, Risalpur for the workup of HTN were included in the study.

Exclusion Criteria: Patients older than 45 years, pregnant women and patients already on treatment for hypertension were excluded from the study.

The sample size was calculated as 49 by WHO calculator 1.1, using a confidence level of 95%, absolute precision of 0.10 and population proportion 15%.⁷

Fifty samples were collected consecutively from all the patients after their informed consent for the workup of secondary hypertension. All samples were collected in vacutainer tubes. The blood samples were allowed to clot and centrifuged for 12 min at 2,000g. The serum was separated and then stored at -20°C until analysed. History of the disease, physical examination, demographic data and baseline investigations were carried out at the start of the study.

Serum was collected in plain tubes for analysis of cholesterol, triglycerides, urea, creatinine, calcium total, plasma glucose ® (on Microlab 300), sodium, potassium (on Easylite) and urine analysis at CMH Risalpur. In contrast, serum T3, fT4, and TSH, by chemiluminescent enzyme immunoassay on Immulite 2000 from AFIP and renal ultrasonography (USG) from PEMH Rawalpindi, were carried out in all patients.

If indicated or clinical features present for Cushing's syndrome, pheochromocytoma, acromegaly or coarctation of the aorta, then measure 24 hr urinary free cortisol, serum cortisol, dexamethasone suppression test, 24 hours (hrs) Urinary vanillyl mandelic acid (VMA), growth hormone (GH), oral glucose tolerance test (OGTT), insulin-like growth factor-1 (IGF-1) or aortography according to the indications. If serum potassium was low and other tests carried out so far were normal, then plasma renin levels were measured along with serum aldosterone, aldosterone to renin ratio, any one of the three; Frusemide stimulation test (FST), saline suppression test (SST), Captopril suppression test (CST)¹, performed at AFIP Rawalpindi. In addition, doppler renal USG, renal arteriogram, computerized tomography (CT) abdomen, CT adrenals,

magnetic resonance imaging (MRI) pituitary and MR/CT angiography were carried out to confirm the diagnosis at the Radiology Department of PEMH. In addition, other tests to confirm the diagnosis, including polysomnography, I123-MIBG, and echocardiography, were carried out according to the requirements.

Diagnostic criteria (Secondary HTN); In renal parenchymal disease, test urine analysis (proteinuria), urea, creatinine (more than ULR), sodium, potassium and renal USG. In renovascular disease (RVD), abdominal bruit, investigate with serum potassium (less than 3.5mmol/L), doppler renal USG, serum aldosterone (more than ULR), plasma renin levels (more than ULR), MR/CT angiography and renal arteriogram. In primary hyper-aldosteronism, tests serum potassium (less than 3.5mmol/L), serum aldosterone (more than ULR), plasma renin levels (less than LLR) (along with aldosterone to renin ratio > 50), any one of three; FST, SST, CST and C.T. scan of adrenals. In obstructive sleep apnea, obesity (BMI > 30), daytime somnolence, fatigue, test sleep study with oxygen saturation, polysomnography and apnea-hypopnea index (AHI) ≥ 5 events/hour sleep. In hyperthyroidism, tachycardia, increased systolic BP, test thyroid profile (TSH less than 0.4 mIU/L and fT4 more than 34 pmol/L). In hypothyroidism, increased diastolic B.P., test thyroid profile (TSH more than 4.5 mIU/L and fT4 less than 8pmol/L). In Cushing's syndrome, moon facies, acne, hirsutism, truncal obesity, striae and hyperglycemia test serum cortisol (more than ULR), 24 hrs urinary free cortisol (more than ULR), Dexamethasone suppression test, adrenal CT/MRI Pituitary. In pheochromocytoma, episodic headache, sweating, palpitations, tachycardia, flushing, visual disturbances, episodic HTN, 24 hrs urinary VMA (more than ULR), C.T. abdomen, I123-MIBG. In acromegaly, there are coarsening of facial features, sweating, headache, cardiac failure, arthritis and hyperglycemia, test growth hormone (G.H.) level (more than ULR), OGTT and IGF-1 (more than ULR). In coarctation of the aorta, there are weak lower extremity pulses, systolic BP in upper limbs more than 20mm of Hg greater than lower extremity BP, test CT angiography and echocardiography.

Statistical Package for Social Sciences (SPSS) version 22.0 was used for the data analysis. Frequencies and percentages were calculated for qualitative variables like age groups, gender, smoking, obesity and disorders causing secondary HTN. Mean and S.D. were calculated for quantitative variables like age, pulse, systolic BP, diastolic BP, serum cholesterol,

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triglycerides, urea, creatinine, sodium, potassium, calcium total, TSH and plasma glucose. The quantitative variables were compared between two groups using an independent sample t-test. The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

Out of 50 patients with hypertension, there were 41(82%) males and 9(18%) females. The mean age of the patients was 36.1±6.2 years (ranging from 21 to 45 years). In addition, 15(30%) patients had a family history of HTN, 6(12%) were smokers, 2(4%) had diabetes mellitus, 6(12%) had a history of renal stones, and 15(30%) were obese.

Primary or essential hypertension was found in 31(62 %) patients. Secondary causes of HTN in 19(38 %) cases, out of which obstructive sleep apnea (4,8%), renal parenchymal hypertension (3,6%), primary hyperaldosteronism (3,6%), renal artery stenosis (1,2%), Cushing's syndrome (2,4%), hyperthyroidism (2,4%), hypothyroidism (2,4%), pheochromocytoma (1, 2%) and coarctation of aorta (1,2%)(Figure).

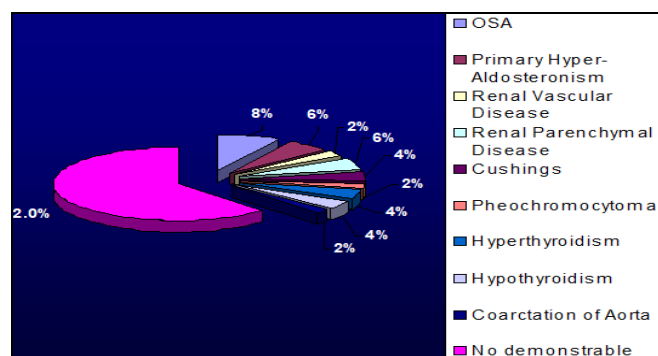


Figure: Different Types of Disorders Causing Secondary Hypertension (n=50)

Comparison of quantitative variables between the patients diagnosed with secondary hypertension and essential hypertension showed significant differences for age but insignificant for a pulse, systolic BP, diastolic BP, serum cholesterol, triglycerides, urea, creatinine, sodium, potassium, calcium total, TSH and plasma glucose (Table).

DISCUSSION

To investigate secondary HTN in younger patients, renal parenchymal disease, coarctation of the aorta and fibromuscular dysplasia may be considered.^{7,8} In contrast, adult patients should be evaluated for endocrine disorders, especially primary hyperaldosteronism, obstructive sleep apnea,^{9,10} and renal artery stenosis.^{11,12} Endocrine causes of secondary hypertension include Cushing's syndrome, pheochromocytoma, hyperthyroidism (causing elevated systolic BP), hypothyroidism (causing elevated diastolic B.P.), hyperparathyroidism and acromegaly are less common. Conversely, primary hyper-aldosteronism occurs with sufficient frequency (5–12%),¹³ to be considered "top of the list" for secondary endocrine causes in resistant or hypokalemia-associated hypertension.^{11,14,15}

Wang *et al.* in 2017 showed essential hypertension as 61.5%, primary hyper-aldosteronism (10.7%), OSA (24.7%), renal parenchymal HTN(1.8%), renovascular HTN (0.8%), Cushing's syndrome (0.1%), pheochromocytoma (0.1%), hyperthyroidism (0.1%), hypothyroidism (1.1%), others (0.1%).¹⁶ Camelli *et al.* in 2015 showed essential hypertension as 70.4%, primary hyper-aldosteronism (7.4%), renovascular HTN (5.8%), pheochromocytoma (3.9%), others (12.5%).¹⁷ Rossi *et al.* in 2013 showed essential hypertension as 76%, primary

Table: Baseline Characteristics of Patients with Disorders Causing Secondary Hypertension and those with no Demonstrable Cause of Hypertension (n=50)

| Parameters | No Demonstrable Cause of Hypertension (n=31) (Mean±SD) | Secondary Hypertension (n=19) (Mean±SD) | <i>p</i> -value |
|---|--|---|-----------------|
| Age (years) | 38.0±5.2 | 33.3 ± 6.0 | 0.01 |
| Pulse (/min) | 85.9±7.0 | 87.2 ± 9.2 | 0.35 |
| Systolic B.P (mm of Hg) | 162.4±15.8 | 158.0 ± 18.1 | 0.40 |
| Diastolic B.P (mm of Hg) | 103.6±9.0 | 104.7 ± 14.2 | 0.69 |
| Serum Cholesterol (mmol/L) | 4.3±0.6 | 4.5 ± 0.7 | 0.59 |
| Serum Triglycerides (mmol/L) | 1.5±0.4 | 1.8 ± 0.6 | 0.09 |
| Plasma glucose random (mmol/L) | 5.1±0.8 | 5.5 ± 1.5 | 0.36 |
| Serum urea (mmol/L) | 4.6 ± 0.7 | 4.7 ± 1.1 | 0.50 |
| Serum creatinine (umol/L) | 77.0 ± 12.2 | 80.2 ± 19.4 | 0.56 |
| Serum sodium (mmol/L) | 138.1 ± 3.0 | 140.5 ± 6.3 | 0.29 |
| Serum potassium (mmol/L) | 4.2 ± 0.3 | 4.1 ± 0.8 | 0.28 |
| Serum Calcium (mmol/L) | 2.2 ± 0.2 | 2.2 ± 0.2 | - |
| Serum Thyroid stimulating hormone (mIU/L) | 1.7 ± 0.7 | 7.5 ± 19.2 | 0.21 |

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hyper-aldosteronism as 15.7%, OSA as 26.5% (overlap on other causes as well), renovascular HTN (5.4%), Cushing's syndrome (1%), hyperthyroidism (1.5%), others (0.4%).¹⁸

Our study showed higher rates of secondary HTN (38%), possibly attributable to the gradual availability and improvement in the screening skills of secondary hypertension. Out of secondary HTN, renal parenchymal hypertension, Cushing's syndrome, hyperthyroidism and hypothyroidism were higher and primary hyper-aldosteronism, and obstructive sleep apnea (OSA) were similar in other studies. In contrast, renal artery stenosis and pheochromocytoma were lesser compared to other literature studies.

In our study, HTN was presented in younger age groups, (36%) between 20 to 35 years, while 64% were between 36 to 45 years. Risk factors in HTN patients are also important to consider. In our study, 12% of cases had a history of renal stones, and 30% had obesity overlapping the recognized causes of HTN. Therefore, renal stones and obesity should always be considered while investigating the causes of secondary HTN in younger patients. Obstructive sleep apnea (OSA), primary hyper-aldosteronism and renal parenchymal diseases were the commonest causes of secondary hypertension, followed by Cushing's syndrome, hyperthyroidism and hypothyroidism. The measurement of various hormone levels was very sensitive in ruling out secondary hypertension. This workup will help in the early diagnosis of secondary HTN and further management accordingly.

LIMITATIONS OF STUDY

The limitation of the study was that complete tests were not carried out in all the patients. However, only required investigations were carried out step by step to diagnose secondary hypertension. Further studies are required to find and compare frequencies of all causes of secondary hypertension in various regions of Pakistan, aiming to manage the diagnosed cases of secondary hypertension well in time accordingly.

CONCLUSION

Obstructive sleep apnea, primary hyper-aldosteronism and renal parenchymal diseases were the commonest causes of secondary hypertension, followed by Cushing's syndrome, hyperthyroidism and hypothyroidism in patients who reported to CMH Risalpur.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

STAG: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

GI: Study design, data analysis, critical review, drafting the manuscript, critical review, approval of the final version to be published.

SL & BA: Critical review, drafting the manuscript, approval of the final version to be published.

SARSB & AB: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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