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Retrospective evaluation of patients diagnosed with Primary Hyperaldosteronism

Abstract

Primary hyperaldosteronism (PA), despite being a common disease, is grossly underdiagnosed and undertreated. Though in primary care prevalence of PA is 4–6% in patients with hypertension, it is much higher in specialized hypertensive clinics, especially in resistant hypertension (RH). PA is associated with higher morbidity rates than matched essential hypertension patients. PA is classified as unilateral and bilateral disease, with adrenalectomy considered for unilateral disease and medical management with mineralocorticoid receptor antagonists (MRA) for bilateral disease. There is gross underdiagnosis of PA across the world with very limited literature on PA from India. We wanted to retrospectively evaluate the profile of patients diagnosed with PA from case records, in outpatient settings in a tertiary care hospital. Primary outcomes of the study will be to evaluate the presenting features of PA patients. This includes clinical, biochemical, radiological aspects in different subgroups like unilateral vs bilateral disease, diabetes/ prediabetes vs non-diabetes, and chronic kidney disease (CKD) vs no significant CKD. We also want to evaluate the treatment preferences (both surgical and medical) and follow-up data (for treatment outcomes / effectiveness if relevant records were available). Our main objective is to highlight the current state of PA presentation and management so that we can develop a pragmatic diagnostic approach to improve screening, case detection and empiric management of PA.

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Introduction and background

Primary hyperaldosteronism (PA) is the most common cause of surgically curable secondary hypertension. However, it is grossly underdiagnosed and undertreated. Estimated prevalence of PA is about 4-6% in primary care patients with hypertension and around 10% in specialized hypertension clinics.[1] Nearly 12.5% of hypertensive patients have resistant hypertension (RH). Among them, 20-25% have PA that is mostly undetected.[1] PA is characterized by autonomous inappropriately high plasma aldosterone secretion leading to suppressed feedback of the plasma renin system.[2] Increased aldosterone production leads to excessive activation of the mineral corticoid receptor (MR) significantly increasing the cardio metabolic and renal risk.[1,3] There is a higher morbidity rate in PA patients compared to matched essential hypertension patients.[4–8] Early diagnosis and specific medical or surgical management of PA decreases the associated risk of morbidity and can significantly alter the prognosis of PA.[9,10]

PA is classified into unilateral and bilateral forms of the disease, which has different treatment approaches.[1] Surgical treatment by adrenalectomy is considered the gold standard for unilateral disease, but medical treatment with MRA is the therapy of choice in bilateral disease.[1]

PA is grossly underdiagnosed across the world, even in developed countries, with the prevalence being five times less than the predicted estimates.[11] The presentation and management of PA in India is not very well illustrated. The limited literature on PA from India is attributable to lack of regulated practice in this context and limited access to specialized testing. We wanted to retrospectively evaluate the profile of patients diagnosed with PA from case records, in outpatient settings in a tertiary care hospital. Primary outcomes of the study will be to evaluate the presenting features of PA patients. This included variations in the clinical, biochemical, and radiological aspects, in different subgroups like unilateral vs bilateral disease, diabetes/ prediabetes vs non-diabetes, and chronic kidney disease (CKD) vs no significant CKD. The study also evaluates the treatment preferences (surgical and medical) and follow-up data (treatment outcomes / effectiveness if relevant records were available). The main objective of the study is to highlight the current state of PA presentation and management so that we can develop a pragmatic diagnostic approach to improve screening, case detection and empiric management of PA.

Lacunae in literature

Very limited literature on PA is available in India. The presenting features, clinical, biochemical, and radiological characteristics in PA are not well studied in our population leading to very low rate of detection and treatment. Moreover, treatment preferences and outcomes are unknown in our population.

Research questions

What is the clinical, biochemical, radiological presentation of patients with confirmed PA in our population?

Is there any difference in the presenting features of PA in different subgroups like unilateral vs bilateral disease, diabetes/ prediabetes vs non-diabetes, and chronic kidney disease (CKD) / no significant CKD?

What are the treatment preferences, both surgical and medical, and follow-up data regarding treatment outcomes/effectiveness in our population?

Aims and objectives

Primary hyperaldosteronism (PA), a common disease which is currently grossly underdiagnosed and undertreated, carries significantly higher cardiovascular and renal morbidity and mortality as compared to matched individuals with essential hypertension. The study aims to highlight the current state of PA presentation and management in the Indian population, to assist in developing a

pragmatic diagnostic approach to improve screening, case detection and empiric management of PA. The objective is to retrospectively evaluate the profile of patients diagnosed with PA from case records, in outpatient settings in a tertiary care hospital. Primary objectives of the study will be to evaluate the presenting features of PA patients including clinical, biochemical, radiological aspects in different subgroups like unilateral vs bilateral disease, diabetes/ prediabetes vs non-diabetes, and CKD vs no significant CKD. The secondary objectives will be to evaluate the treatment preferences (surgical and medical) and follow-up data (treatment outcomes/effectiveness if relevant records were available).

Study design

Retrospective study.

Study duration

Evaluation of Records from January 2010 to June 2023.

Material and methods

Out-patient setting records of clinical presentation including base line and follow-up records of blood pressure (BP), plasma aldosterone concentration (PAC), Plasma Renin Activity (PRA)/Direct Renin, Aldosterone Renin Ratio (ARR), sodium, potassium, creatinine, bicarbonate, aldosterone concentration post salt loading confirmatory test, CT scan of adrenal glands, Adrenal Venous Sampling (if done), complications, management preferences and treatment outcome records, if available can be considered. Calculation of corrected ARR (Aldosterone divided by PRA) can be utilized to correctly estimate ARR by avoiding a factitious inflation ARR when PRA<0.20ng/ml/h, by fixing minimum PRA value at 0.20ng/ml/h. Calculation of Aldosterone potassium (Aldo: K) ratio and validation indices like Aldo: K, ARR, PAC, and risk scores in predicting PA diagnosis or lateralization can be estimated. Prevalence of hypokalemia including diuretic induced hypokalemia, hypokalemic periodic paralysis (HPP), duration and number of anti-hypertensives, duration, and treatment of diabetes/prediabetes are to be recorded. CT scan findings especially the scan is indicative of normal/ hyperplasia/ adenoma are to be noted. Prevalence of complications like chronic kidney disease (CKD) by eGFR, left ventricular hypertrophy (LVH) by ECG or ECHO, coronary artery disease (CAD), atrial fibrillation (AF), cerebrovascular accident (CVA), obstructive sleep apnea (OSA) are to be noted. Difference in profile between diabetes / prediabetes/ non-diabetes subjects, unilateral / bilateral disease, significant CKD / non-significant CKD are to be noted. Post-treatment or post-operative features including clinical, biochemical specially BP, potassium, creatinine, PAC are to be observed. Post-operative outcomes especially biochemical cure: normalization of potassium & PAC<5ng/dl; clinical cure: no anti-hypertensive medicines or partial cure are to be documented. Adequacy and the effect of medical management with MRA are to be noted.

Statistical analysis

SPSS will be used for statistical analysis. Normally distributed variables will be expressed as mean and standard deviation (SD) analyzed by Student's test; variables with a skewed distribution will be expressed as median (interquartile range [IQR]) analyzed by the Mann-Whitney U test; categorical variables will be described as percentages analyzed by the χ^2 test. Multiple logistic regression analyses will be used to identify prediction factors related to diagnosis of PA. To assess the diagnostic accuracy of the criteria, parameters including the sensitivity and specificity will be calculated. P<0.05 (2-tailed) is to be considered as statistically significant.

Eligibility criteria

Inclusion criteria: Patients with confirmed diagnosis of PA aged more than 18 years. Availability of baseline clinical, biochemical, and radiological (at least CT scan of adrenal glands), management and follow-up records.

Exclusion criteria: Age<18 years; secondary hyperaldosteronism; records of confirmatory test or CT scan of adrenal gland is not available or not done.

Discussion

Prevalence of PA is high and largely unrecognized. Unregulated aldosterone production (high ARR) is seen in 5-10% of patients with hypertension and 20% of resistant hypertension patients.[1] Hallmark presentation and diagnosis of PA is hypertension with hypokalemia, with autonomous inappropriate production of aldosterone leading to suppression of renin.[2] Current literature suggests that most patients of PA have normokalaemia.[2] PA is a common syndrome, manifesting with a broad spectrum of presentation from mild severity like hypertension to more severe presentations like resistant hypertension with hypokalemia. Clinical manifestations depend on the severity and duration of the renin-independent aldosteronism, genetic makeup and dietary composition. Direct and sustained MR activation in different target organs causes inflammation, necrosis, and fibrosis.[1,3] PA increases the risk of adverse outcomes independent of high BP.[4,5] There is increased end organ damage and mortality when compared to age and sex-matched individuals with essential hypertension (with a similar degree of elevated BP). At diagnosis, PA has significantly higher left ventricular hypertrophy (LVH), atrial fibrillation (AF), heart failure (HF), coronary artery disease (CAD), stroke, metabolic syndrome, and diabetes.[4–8] A pragmatic diagnostic approach can maximize sensitivity, early detection, and management of PA, leading to improved outcomes.

Unilateral and bilateral forms of PA must be distinguished, as treatment approaches differ.[1] In unilateral disease, surgical management via adrenalectomy is the gold standard treatment, while in bilateral PA, medical treatment with MRA is the therapy of choice.[1] Despite controversy regarding superiority of adrenalectomy to adequate medical treatment with regard to cardiovascular outcomes, recent evidence from observational studies suggests superiority of surgery in unilateral disease.[9,12–16] Medically treated PA patients compared to those adrenalectomized, have higher risk of AF.[17] PA subjects undergoing adrenalectomy require lesser number and lower dose of antihypertensive medications (non-MRA) after 6 to 12 months post-operation. They also had better quality of life compared to medically managed patients.[18,19] Clinical blood pressure remission occurs in 17-62% and biochemical remission of aldosterone excess is seen in 93-100% after adrenalectomy.[1,15] Clinical success after adrenalectomy depends on predictive factors like duration of hypertension, sex, number and dose of antihypertensive medications, BMI, target organ damage and size of the largest nodule as detected by imaging.[15]

Emerging evidence suggests that glucocorticoid co-secretion is seen in both aldosterone producing adenomas (APA) and bilateral hyperplasia (BAH) PA patients.[20,21] This is associated with increased cardiovascular morbidity and mortality in PA and can provide a biologically plausible explanation for observations that favors adrenalectomy over medical treatment, as it removes excess glucocorticoid and aldosterone.[9,13,14] Glucocorticoid secretion is associated with BMI, insulin resistance,[20] left ventricular hypertrophy[21] and impaired glucose tolerance.[22] Surgical patients with

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PA after adrenalectomy have higher rates of persistent hypertension if preoperative renin levels are not suppressed.[23]

Medical treatment options for PA are very limited, with MRA such as spironolactone and eplerenone being the treatment of choice.[1] Treatment with MRA in PA patients, has a strong correlation with cardiovascular outcomes and PRA, with non-suppressed PRA (≥1µg/l/h) having risk profile similar to essential hypertension while PA with suppressed PRA having nearly three times higher risk, despite similar mean BP control.[3,24] Thus, non-suppressed PRA is suggestive of adequacy of MRA treatment in PA and can be a predictor of treatment effectiveness in terms of cardiovascular outcomes. Spironolactone, with its affinity to androgen receptor and its anti-androgenic action causes dose-dependent adverse effects like painful gynecomastia and erectile dysfunction in men, and menstrual irregularity in women, contributing to non-compliance.[25] In SPARTACUS study, high (57%) incidence of anti-androgenic adverse effects occurred in spironolactone group in both genders, including mastopathy, gynecomastia, erectile dysfunction, menstrual disturbances, and decreased libido, requiring a switch to alternate treatment, eplerenone in 34% of PA patients. Eplerenone is an alternative option in PA patients with antiandrogenic complications with spironolactone treatment. Eplerenone, is a better selective MRA, with equal efficacy as spironolactone at appropriate dose. Advantage of eplerenone over spironolactone is its relative selectiveness on MR, with no antiandrogenic effects. Eplerenone, in contrast to spironolactone, with lower plasma protein-binding affinity is not converted into active metabolites. Eplerenone has a significantly shorter half-life compared to spironolactone, with short lasting (3-6 h) biological effects, requiring twice-daily administration.[25,26] Eplerenone (maximal dose 100mg/day), is approved for treatment of hypertension including PA in Japan and USA, but not in Australia and Europe. In PA, an adequate aldosterone antagonism requires at least twice daily administration, but in case of an insufficient response, three times per day administration may be considered. In general, eplerenone must be dosed twice as high as spironolactone for therapeutic equivalence with 25 mg eplerenone twice daily starting dose.[25] Most PA subjects achieve sufficient aldosterone blockade with 50 mg twice daily, doses up to 300 mg/day have been used although maximal approved dosage is 100 mg/day.[25] In severe hepatic or renal impairment, MRA titration must be monitored very carefully because of reduced drug clearance and enhanced risk of hyperkalemia. If blood pressure control is suboptimal despite maximum tolerated MRA dose, adding further antihypertensive drugs should be considered.[1] PRA is an additional marker to ascertain successful aldosterone blockade.[3] If persistent renin suppression is present, increasing MRA dose may be considered when there are no contraindications (e.g., elevated serum potassium levels, hypotension, or antiandrogen side effects).

Animal studies have observed that Mineralocorticoid Receptor Blockers (MRBs) exert renoprotective effects by attenuating glomerulosclerosis, podocyte injuries, and interstitial fibrosis by suppressing inflammation and oxidative stress in CKD.[27–29] However, hyperkalemia is a major concern with the use of MRBs and is the most common reason for withdrawal of MRBs. One of primary strategies employed to utilize the therapeutic benefits of MRBs while reducing the risk of hyperkalemia is reducing the dose of MRBs used in treatment.[30,31] The reduction in dosage also minimizes the effectiveness of treatment. Conversely, patients at risk for hyperkalemia are recommended low potassium intake.[32] In recent years, drugs such as Patiromer, containing calcium sorbitol complex which reduce serum potassium levels by binding to potassium released from food intake can also suggested to reduce the risk of hyperkalemia in patients with MRBs.[33]

Conclusion

There is gross under diagnosis of PA across the world with very limited literature on PA from India. We wanted to retrospectively evaluate the profile of patients diagnosed with PA from outpatient case records in a tertiary care hospital. Primary outcomes of the study were to evaluate the presenting feature of PA patients including clinical, biochemical, radiological aspects in different subgroups like unilateral vs bilateral disease, diabetes/ prediabetes vs non-diabetes, and CKD vs no significant CKD. Treatment preferences (surgical and medical) and follow-ups (treatment outcomes/effectiveness) were evaluated. Our main objective is to highlight the current state of PA presentation and management to develop a pragmatic diagnostic approach to improve screening, case detection and empiric management of PA.

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Conflicts of interest

Authors declare that there is no conflict of interest exists.

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