

Primary Aldosteronism among Adult Filipinos with Resistant Hypertension: A Pilot Study

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Abstract

Background: Primary aldosteronism (PA) was previously thought to be uncommon. With the utilization of plasma aldosterone concentration and plasma renin activity ratio (PAC/PRA) as a mode of screening, the frequency of its detection increased significantly. Among the population with an indication for PA screening, resistant hypertension has the highest prevalence. Detection of PA in this group is essential since it is associated with increased cardiovascular and cerebrovascular complications.

Objective: To determine the prevalence of PA among adult Filipinos at Capitol University Medical Center, Cagayan de Oro City, Misamis Oriental.

Methods: Adult Filipino patients with resistant hypertension underwent PA screening using the PAC/PRA. Patients with positive results were confirmed for PA either through IV saline infusion or using the following criteria: history of spontaneous hypokalemia or documented hypokalemia prior to screening, undetectable PRA (< 1 ng/ml/hour), and a PAC of ≥ 15 ng/dl.

Results: Twenty-one patients were recruited, but only fourteen participated in the study. Thirty five percent of those who participated screened positive for PA. Among those who screened positive, three patients were confirmed of having PA.

Conclusion: The prevalence of PA in adult Filipinos with resistant hypertension in Capitol University Medical Center, Cagayan de Oro City, Misamis Oriental is estimated to be 21.43%.

Key words: primary aldosteronism, Filipinos, resistant hypertension

Introduction

In its annual health statistics last 2013, the Department of Health recognized hypertension as the third of ten leading causes of morbidity in the Philippines¹. Of those with hypertension, about 80 to 95 percent are diagnosed of having a primary or essential cause, while the remaining 5 to 20 percent are due to secondary causes². Among the underlying disorders of secondary hypertension, primary aldosteronism (PA) is the most common endocrine cause³. Detection of PA is essential since it is associated with increased cardiovascular and cerebrovascular complications as compared with patients having primary hypertension⁴.

The prevalence of PA was previously thought to be uncommon ($< 1\%$) since the diagnosis of such condition was suspected only in the presence of hypertension and hypokalemia⁵. However, newer evidence indicated that only about 9 to 37 percent of patients with PA were associated with low potassium levels⁶, implying that more than half of such individuals were normokalemic upon

presentation. With the introduction of plasma aldosterone concentration to plasma renin activity ratio (PAC/PRA) as a mode of screening for PA in the 1990s, the case detection of PA became more frequent⁷. From less than 1%, the over-all prevalence rate of PA is between 5-10% according to the current Endocrine Society Clinical Practice Guideline in the Management of Primary Aldosteronism in 2016⁵. In another study done by Monticone et al in 2017, the overall prevalence of PA and its subtypes was 3.9% in hypertension stage 1, 9.7% in hypertension stage 2, and 11.8% in hypertension stage 3⁴. However, the population in published prevalence studies of PA were mostly Caucasians with few studies involving Asians. One study with Asian subjects was done by Loh et al in 2000 at Singapore which was predominantly represented by the Chinese population (85%), while the rest were Malays and Indians. In this study, the overall prevalence rate of PA among patients with hypertension in a primary care setting was suggested to be about 5%⁸. Another published retrospective study involving Filipinos was done at St. Luke's Medical Center, Philippines by Mejia et al in 2010. The prevalence of aldosterone producing adenoma among hypertensive patients admitted in this institution was 2.6%⁹.

Among the groups of patients with high incidence of PA, those with resistant hypertension comprised the highest prevalence rate which was between 17 to 23%⁵. Upon

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literature search, one study on the prevalence of PA among Asian individuals with resistant hypertension was retrieved. This was done by Sang et al in 2013 among patients with resistant hypertension in China. In this study, prevalence rate of PA was 7.1%⁷. In the Philippines, the true prevalence of resistant hypertension is still unknown and no local studies had been published¹⁰. The only study retrieved which determined the prevalence of PA among Filipinos was done by Mejia et al in 2010. However, all hypertensive patients were included and those with resistant hypertension were not specified⁹. Hence, this study will focus on the prevalence of PA in patients with resistant hypertension.

Definite determination of PA as an underlying cause of resistant hypertension will provide several benefits such as: sparing these patients from the costly lifetime treatment with 3 or more anti-hypertensive medications, preventing the associated cardiovascular and cerebrovascular sequelae, and providing a definite cure from hypertension itself.

Objective

To determine the prevalence of PA with resistant hypertension among adult Filipinos at Capitol University Medical Center, Cagayan de Oro City, Misamis Oriental, between January to December 2018.

Operational Definitions

1. Resistant hypertension: systolic blood pressure of > 140 mmHg and diastolic blood pressure of > 90 mmHg despite treatment with three anti-hypertensive medications, including a diuretic⁵.
2. Primary aldosteronism: a group of disorders in which aldosterone production is inappropriately high for sodium status, relatively autonomous of the major regulators of secretion (angiotensin II, plasma potassium concentration), and non-suppressible by sodium loading⁵.
3. Positive PA screening: plasma aldosterone concentration to plasma renin activity ratio of ≥ 30 ng/ml/hr with a plasma aldosterone level of ≥ 15 ng/dl⁵.
4. Intravenous saline loading test: a confirmatory test for PA wherein a patient stays in a recumbent position during the infusion of 2 liters of 0.9% saline IV over 4 hours⁵.

Methods

The study was conducted at Capitol University Medical Center (CUMC), Cagayan de Oro City, Misamis Oriental, Philippines. Letters were distributed to the internal medicine (IM) outpatient department (OPD), private clinics of physicians, and all visiting consultants who manage hypertension in the institution. Physicians were requested to refer all adult (18 years old and above) Filipino patients with resistant hypertension to the IM OPD for registration. Patients who were pregnant, with estimated glomerulo-filtration rate of < 60 mL/min/1.73 m², with histories of adverse reactions upon withdrawal

of aldosterone antagonist according to the attending physician, and with documented ejection fraction of less than 40% by two-dimensional echocardiography or with signs of heart failure based on the Framingham Criteria for Heart Failure were excluded in the study.

After securing an informed consent, qualified patients were assigned codes to ensure confidentiality. Personal data, medical history, and physical examination were obtained. An average blood pressure of $\geq 140/90$ mmHg after 3 consecutive measurements in the sitting position using an aneroid sphygmomanometer was required. Baseline serum creatinine and potassium were also taken. Documented hypokalemia was corrected with oral potassium chloride. Prior to screening for PA, participants were advised liberal sodium diet and to continue any anti-hypertensive medications, except for aldosterone antagonist (which was discontinued for at least 4 weeks). Patients with persistent hypokalemia despite potassium replacement and on aldosterone antagonist were allowed to proceed with screening without discontinuation of such medications. Those who were non-adherent to prescribed anti-hypertensive medications based on history were advised strict compliance for at least a week.

Plasma aldosterone concentration (PAC) and plasma renin activity (PRA) determination were conducted in the morning after participants had ambulated for at least 2 hours, then seated for at least 5 to 15 minutes. Individuals with positive screening test for PA, but with no history of hypokalemia, was scheduled for an in-patient confirmatory testing using intravenous saline loading test. Confirmatory testing started at around 8 to 9:30 AM, and vital signs were monitored throughout the test. A post saline infusion PAC was taken after the procedure, in which a level of > 10 ng/dl was considered confirmatory for PA. Aldosterone antagonist was then resumed. Confirmatory testing was no longer required in the presence of the following: history of spontaneous hypokalemia or documented hypokalemia prior to screening, undetectable PRA (< 1 ng/ml/hour), and a PAC of ≥ 15 ng/dl, since PA is already confirmed in this clinical setting. Methods for the screening and confirmatory testing were adapted from the Endocrine Society Clinical Practice Guidelines in the Management of Primary Aldosteronism 2016 and UpToDate^{5,6}.

Using the PA prevalence of 23% among patients with resistant hypertension⁵ and the estimated number of hypertensive patients seen at CUMC OPD in 2018 (which was about 336), the relevant sample size for this study (at 95% confidence interval) was determined to be 151. This calculation was based on The Methods in Observational Epidemiology Open-Source Calculator by Sullivan K et al¹¹.

The prevalence rate computation was based from The Center for Disease Control and Prevention's Principles of Epidemiology in Public Health Practice (3rd edition), an Introduction to Applied Epidemiology and Biostatistics¹².

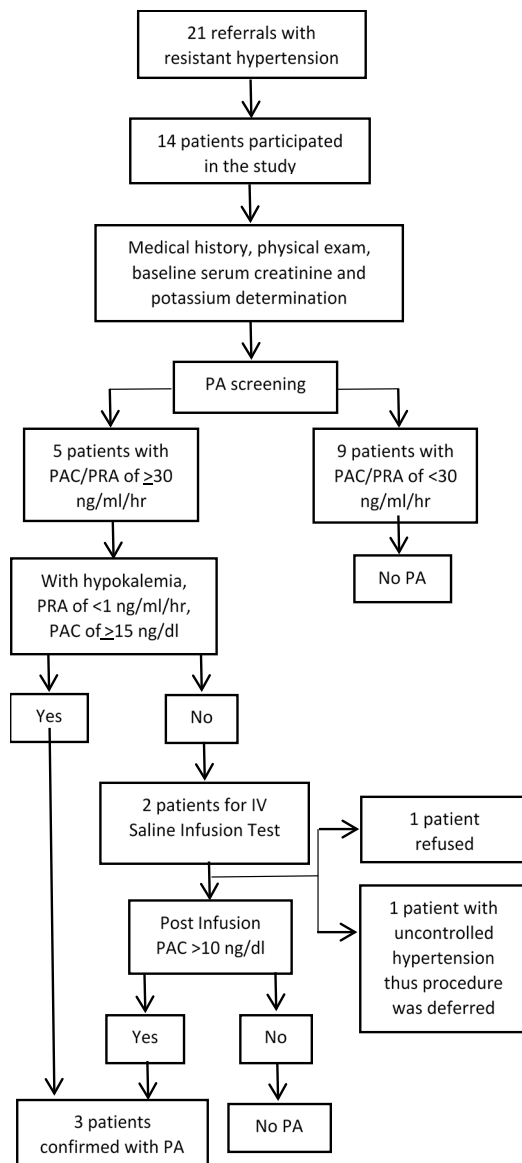


Figure 1: Study Design

Results

A total of 21 referrals were received in 2018, but only 14 patients with resistant hypertension agreed to participate in this study (see Figure 1). The demographic and clinical characteristics of the population are summarized at Table I. Of those who were included, 35% (5 patients) screened positive for PA. Among those who screened positive for PA, four patients had spontaneous hypokalemia while one had a normal potassium. All with positive screening results had PAC/PRA of ≥ 30 ng/ml/hr, but only three patients had PACs of > 15 ng/dl. Since those three patients with PACs of > 15 ng/dl already fulfilled the criteria of spontaneous hypokalemia, undetectable PRA (< 1 ng/ml/hr), and a PAC of > 15 ng/dl, the performance of the saline infusion test was no longer necessary. Upon further investigation, two of those patients who were confirmed of having PA underwent CT

scan of the adrenals, while one did not pursue further diagnostic work-up. CT scan results of both patients showed nodules on the adrenal glands.

For those patients with PACs of < 15 ng/dl, confirmatory testing was contemplated but not implemented. One patient refused the procedure due to financial concerns while the other had an uncontrolled blood pressure that saline infusion was considered risky. The latter, however, proceeded with computed tomography (CT) scan of the adrenal glands. Interestingly, the imaging result showed a nodule at the right adrenal gland with enhancement pattern compatible with an adenoma.

In this study, the overall prevalence rate of PA was 21.43% (see Table II).

Discussion

To the researchers' knowledge, this is the first study to estimate the prevalence of PA in adult Filipinos with resistant hypertension. Although the data in this study should be interpreted with prudence due to its small sample size, the results notably showed that PA is more common than expected in just a portion of adult Filipinos with resistant hypertension, with a prevalence rate of 21.43%. Since there are no local studies reported on the prevalence of PA in resistant hypertension, the closest comparison done to an Asian population was a study by Xiaojing Sang and his colleagues last 2013 to patients with resistant hypertension in China which yielded a lower prevalence rate of 7.1%. However, this was a multicenter epidemiologic study conducted among 1,656 patients with resistant hypertension in 11 provinces of China⁷, as compared to our study which was conducted in a single tertiary hospital in one of the regions in the Philippines.

This study would like to emphasize the rationale of the inclusion of two patients to those who screened positive for PA despite having PACs of < 15 ng/dL. In the Endocrine Society Guidelines on Primary Aldosteronism 2016, investigators considered a minimum PAC of ≥ 15 ng/dL recognizing the limitations of PAC/PRA. This screening test becomes elevated in the presence of low renin levels (PRA of 0.1 ng/ml/hr), yielding false positive results. In certain studies, a PAC of < 15 ng/dl (but not < 6 ng/dl) was considered positive for PA screening since low renin levels appeared to be common in bilateral adrenal hyperplasia (BAH) than aldosterone producing adenoma (APA), which are both subtypes of PA. The lower likelihood of missing PA counterbalanced the possibility of a higher false positive results in this situation¹. For this reason, confirmatory testing was offered to these individuals despite their PAC levels of < 15 ng/dl.

Our study had several limitations. First, this study did not reach the relevant sample size of 151 patients determined at 95% confidence interval. Problems encountered that may have contributed to such small recruits were the passive participation of most private physicians, added costs of the diagnostic tests, and the limited time of data collection. Second, our participants

Table I. Demographic and Clinical Characteristics of the Study Population

| Parameters | Without PA (N=11) | | Confirmed PA (N=3) | | P-value |
|----------------------------------|-------------------|-------|--------------------|--------|---------|
| | Mean | S.D. | Mean | S.D. | |
| Age in years | 47.45 | 14.40 | 49.33 | 11.06 | 0.7692 |
| Gender | | | | | |
| Male | 7 | | 0 | | 0.1923 |
| Female | 4 | | 3 | | |
| Duration of hypertension (years) | 9.49 | 11.55 | 15.33 | 8.02 | 0.8095 |
| BMI in kg/m ² | 28.35 | 8.04 | 27.99 | 5.39 | 0.9435 |
| Systolic BP in mmHg | 144.45 | 7.92 | 144.33 | 5.13 | 0.8095 |
| Diastolic BP in mmHg | 82.00 | 7.56 | 80.00 | 10.00 | 0.6404 |
| Serum potassium in meq/L | 3.63 | 0.32 | 2.94 | 0.82 | 0.0343 |
| Serum creatinine in mg/dL | 0.74 | 0.19 | 0.82 | 0.19 | 0.5245 |
| PAC in ng/dL | 17.35 | 13.43 | 28.42 | 11.80 | 0.2215 |
| PRA in ng/ml/hr | 6.98 | 7.35 | 0.12 | 0.09 | 0.1424 |
| PAC/PRA in ng/ml/hr | 17.77 | 31.11 | 708.63 | 996.64 | 0.0232 |

T-test was used for normally distributed variables, Mann-Whitney U Test for the non-normally distributed variables, and Fisher Exact Test for less than 3 samples. A confidence level of 95% (alpha = 0.05) was utilized.

Table II. Prevalence of Primary Aldosteronism in the Study Population

| Total Study Population | Total Number of Patients with Positive Screening for PA | Total Number of Patients with Confirmed PA | Prevalence Rate |
|------------------------|---|--|-----------------|
| 14 | 5 | 3 | 21.43% |

did not represent a random sample of all people with resistant hypertension in the Philippines. Thus, caution in interpreting the results in this study was emphasized. Data and subgroup analysis may require confirmation with a large-scale investigation. Third, a thorough clinical profile of the individuals who were enrolled in the study was not determined. The costly diagnostics hindered its actualization. Lastly, identification of those who pursued further diagnostic work-up and treatment after this study was not done. The allotted time was limited and realization of this objective would entail a longer period.

Nonetheless, this study highlights the need for our local physicians and public health workers to focus their efforts on screening for PA in hypertensive individuals, especially those with resistant hypertension.

Conclusion

In conclusion, the prevalence of PA in adult Filipinos with resistant hypertension in Capitol University Medical Center, Cagayan de Oro City, Misamis Oriental is estimated to be 21.43%. This represents a significantly higher prevalence rate as compared to existing studies done to Asians. Physicians and public health workers should exert efforts on screening for PA in such a high risk group since this condition is virtually a curable disease.

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