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P Takkavatakarn

W. Polamaung

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Primary Aldosteronism at Prapokklao Hospital

Pratarn Takkavatakarn*

Waraporn Polamaung*

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- Background** : *Primary aldosteronism (PA) is a cause of secondary hypertension which characterized by hypertension, increased plasma aldosterone concentration (PAC), and suppressed plasma renin activity (PRA).*
- Objective** : *To study the prevalence of primary aldosteronism and clinical clue for diagnosis of PA.*
- Setting** : *Prapokklao Hospital, Chanthaburi Province.*
- Materials and Methods** : *All patients whose diagnoses of primary aldosteronism from October 2006 - March 2012 were reviewed.*
- Results** : *The prevalence of PA at Prapokklao Hospital was 0.15% (20 cases of PA) of HT. 70% of cases were female. The age at the diagnosis of HT ranged from 32.58 to 72.92 (mean = 46.47). The mean time to diagnosis of PA since HT was 78.85 months (range of 1 to 295 months). The mean of potassium level was 3.0 (2.1 to 3.8) mEq/dL. The prevalence of co-morbidities were as follow diabetes/ impair fasting glucose 30%, dyslipidemia 30%, chronic kidney disease 20%, obesity 15%. The aldosterone to rennin ratio (ARR) was 16.56 - 282.5 ng/mL to ng/mL/hr. The abnormalities of adrenal gland were demonstrated by CT with seven cases of unilateral macroadenoma, five cases of adrenal*

limb thickening, three cases of unilateral microadenomas. Medical or surgical treatment significantly resulted in improved hypokalemia and hypertension. Five cases underwent adrenalectomy and the others were treated by antihypertensive medication especially aldosterone antagonist. There were four cases that still require potassium replacement eventually at lower dosage.

Conclusion : *The prevalence of primary aldosteronism at Prapokklao hospital was 0.15% which extremely lower than that of the reviewed literatures. The most important clue that triggered the investigation was 'hypertension with hypokalemia'. The screening scheme might have to be initiated earlier, before patients present an obvious clinical of hypokalemia to include more cases.*

Keywords : *Primary Aldosteronism, aldosterone (PAC), plasma renin activity (PRA), hypokalemia, a secondary hypertension.*

Reprint request. Takkavatakarn P. Prapokklao Hospital, Chanthaburi Province.

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ประธาน ตรีภวาทการ, วราภรณ์ พลเมือง. ภาวะอัลโดสเทอโรนสูงแบบปฐมภูมิที่โรงพยาบาลพระปกเกล้า จังหวัดจันทบุรี. จุฬาลงกรณ์เวชสาร 2556 พ.ย. - ธ.ค.; 57(6): 667 - 79

- เหตุผลของการทำวิจัย** : ภาวะอัลโดสเทอโรนสูงแบบปฐมภูมิเป็นสาเหตุของความดันโลหิตสูงแบบที่มีระดับอัลโดสเทอโรนในพลาสมาสูงและระดับเรนินต่ำ
- วัตถุประสงค์** : เพื่อศึกษาความชุกของภาวะอัลโดสเทอโรนแบบปฐมภูมิและศึกษาลักษณะทางคลินิกที่ช่วยในการวินิจฉัย
- รูปแบบการวิจัย** : การศึกษาวิจัยเชิงพรรณนา
- สถานที่ทำการศึกษา** : โรงพยาบาลพระปกเกล้า จังหวัดจันทบุรี
- ตัวอย่างและวิธีการศึกษา** : ทบทวนเวชระเบียนผู้ป่วยทุกรายที่วินิจฉัยภาวะอัลโดสเทอโรนสูงแบบปฐมภูมิ ในระหว่างช่วงตุลาคม 2549 ถึงมีนาคม 2555
- ผลการศึกษา** : ความชุกของภาวะอัลโดสเทอโรนแบบปฐมภูมิ (ร้อยละ 0.15 ของความดันโลหิตสูง (20 ราย เป็นผู้หญิงร้อยละ 70 อายุที่ได้รับการวินิจฉัยว่ามีความดันโลหิตสูงระหว่าง 32.58 ถึง 72.92 ปี (เฉลี่ย 46.47 ปี) ระยะเวลาเฉลี่ยตั้งแต่วินิจฉัยความดันโลหิตสูงจนกระทั่งวินิจฉัยภาวะอัลโดสเทอโรนสูงแบบปฐมภูมิเท่ากับ 78.85 เดือน (ระหว่าง 1 ถึง 295 เดือน) ระดับโพแทสเซียมในซีรัมเฉลี่ย 3.0 มิลลิกรัม/เดซิลิตร (2.1 ถึง 3.8 ไร่รวมที่พบได้แก่เบาหวานน้ำตาลก่อนอาหารเริ่มสูงพบร้อยละ 30, ภาวะไขมันในเลือดผิดปกติพบร้อยละ 30, โรคไตเรื้อรังพบร้อยละ 20 และโรคอ้วนพบร้อยละ 15 อัตราส่วนของระดับความเข้มข้นอัลโดสเทอโรนใน พลาสมาต่อกิจกรรมเรนินในพลาสมา มีค่าระหว่าง 16.56 ถึง 282.5 นาโนกรัม/เดซิลิตรต่อนาโนกรัม/มิลลิลิตร/ชั่วโมง ภาพถ่ายรังสีคอมพิวเตอร์พบความผิดปกติของต่อมหมวกไต โดย 7 รายพบเนื้องอกขนาดใหญ่ที่ต่อมหมวกไตข้างเดียว, 5 รายพบการหนาตัวของรังไข่ต่อมหมวกไตข้างเดียว, 3 รายพบเนื้องอกขนาดเล็กที่ต่อมหมวกไตข้างเดียว ผู้ป่วยได้รับการรักษาด้วยการผ่าตัดทั้งหมด 5 ราย และที่เหลือใช้ยาลดความดันโลหิตสูงโดยเฉพาะยากุ่มต้านอัลโดสเทอโรน ผู้ป่วย 4 ราย ยังต้องได้รับโพแทสเซียมคลอไรด์ทดแทนในขนาดที่ลดลง

- สรุป** : ความชุกของภาวะอัลโดสเทอโรนสูงแบบปฐมภูมิในโรงพยาบาลพระปกเกล้า ร้อยละ 0.15 ของความดันโลหิตสูงซึ่งต่ำกว่าที่เคยมีการทบทวนวรรณกรรม ลักษณะทางคลินิกที่ช่วยทำให้สงสัยคือการที่มีความดันโลหิตสูงร่วมกับการมีระดับโพแทสเซียมต่ำ เพื่อให้ให้เพิ่มการค้นพบภาวะนี้เพิ่มขึ้นควรมีการส่งเสริมการค้นหาตั้งแต่แรกเริ่มนอกเหนือจากการดูแต่ระดับโพแทสเซียมที่ต่ำเพียงอย่างเดียว
- คำสำคัญ** : ภาวะอัลโดสเทอโรนสูงแบบปฐมภูมิ, ระดับอัลโดสเทอโรนในพลาสมา, ระดับเรนิน, ระดับโพแทสเซียมต่ำ, ความดันโลหิตสูงแบบมีสาเหตุ.

Primary aldosteronism (PA) was first described in 1955.⁽¹⁾ It is a clinical syndrome characterized by hypertension, suppressed plasma renin activity (PRA), and increased aldosterone production. In the past, clinicians would not consider for the diagnosis of primary aldosteronism unless the patient presented with spontaneous hypokalemia, and then the diagnostic evaluation would require discontinuing of antihypertensive drugs. This approach resulted in predicted prevalence rates of less than 0.5% of hypertensive patients. However, in 1981, plasma aldosterone concentration [PAC]-to-plasma renin activity [PRA] ratio (Aldosterone-to-Renin Ratio; ARR) was first proposed as a case-finding test.⁽²⁾ The screening can now be completed with a simple blood test, while the patient is taking antihypertensive drugs (only with some exception). The predicted prevalence is about 5% to 13% of hypertensive patients.⁽³⁻⁶⁾

The endocrine society has published a most widely used clinical practice guidelines for the case-detection, case-confirmation, subtype classification and treatment of primary aldosteronism in September 2008.⁽⁷⁾ They recommended screening with ARR in population where PA prevalence is high. They are 1. Hypertension (HTN) with Joint National Commission (JNC) stage 2 and 3 (SBP \geq 160 mmHg, DBP \geq 100 mmHg); 2. Resistant Hypertension; 3. Hypertension with hypokalemia *regardless of* diuretics; 4. Hypertension with adrenal incidentaloma; 5. Hypertension with family history of early-onset HTN or CVA (<40 years); 6. All first-degree relatives of patients with PA.

In clinical practice at Prapokklao Hospital, PA patients were not common. We might oversee this

subgroup of hypertensive patients and letting them face the negative effects of aldosterone silently, despite a chance they could be cured from hypokalemia and greatly improved in hypertension.⁽⁸⁻¹²⁾ The prevalence of primary aldosteronism has never been evaluated. A retrospective study should be conducted to determine the prevalence and distribution in each subtype of primary aldosteronism and the characteristic of the cases at Prapokklao Hospital, including factors that lead the clinicians to initiate their screening tests.

Methods

Descriptive retrospective study;

Target population:

1. All diagnosed cases of primary aldosteronism at Prapokklao Hospital from October 2006 to March 2012
2. All diagnosed cases of any type of hypertension at Prapokklao Hospital from October 2006 to March 2012 according to the computerized database of the hospital

Inclusion criteria: Every patient who is diagnosed with any type of aldosteronism according to the computerized database of the hospital and the registry of aldosterone patients of the Endocrine Unit.

Exclusion criteria:

1. The medical record could not be obtained.
2. The results of plasma aldosterone concentration (PAC) and plasma renin activity (PRA) were not obtained.
3. A confirmed alternative diagnosis other than PA that contributed to the clinical syndrome of hyperaldosteronism

Definition of Terms:

Resistant hypertension: SBP >140 and DBP >90 despite treatment with three anti-hypertensive medications

Adrenal incidentaloma: an adrenal mass detected incidentally during imaging performed for extra-adrenal reasons.

Diuretics: drugs that help promote the rate of urination. When not specified in this study, diuretics referred to drugs of any class with such effect EXCEPT for aldosterone antagonist, which will be explicitly referred to as the name of the drug.

Statistical Analysis

The data collected by the questionnaire were then analyzed statistically using the application software "IBM SPSS Statistics 19".

1. Prevalence of PA among HTN patient =

$$\frac{\text{All cases diagnosed with PA at PPK}}{\text{All cases diagnosed with any type of HTN at PPK}}$$

2. Ages of patients were calculated as of March 1, 2012. If the exact date of birth was not known, January 1 of the year of birth was assumed.
3. Nominal data were analyzed and presented as frequency and percentage.
4. Ordinal and scale data were analyzed and presented as mean and standard deviation, or median.
5. Comparison of mean of paired data (e.g. dose of potassium supplement before and after treatment, and serum potassium level before and after treatment.) was calculated by paired-sample T Test.

Results

From the computerized database of the Prapokklao hospital from October 2006 to March 2012, there were 13,732 diagnosed cases of any

type of hypertension. Total of 20 confirmed cases of primary aldosteronism were included in the study so the prevalence of PA was 0.15%. Medical records of all patients were obtained. No one was excluded from the study. They were 6 males (30%) and 14 females (70%); their ages were between 36.17 and 76.17 (55.81 ± 13.05) years. The age at the diagnosis of HT ranged from 32.58 to 72.92 (46.47 ± 12.68) years. The shortest duration from diagnosis of HT to the diagnosis of PA was 1 month, and longest was 295 months, with mean = 78.85 ± 86.21 months. However, most cases (8 out of 20, 40%) were diagnosed within the first year after the diagnosis of hypertension: about 50% of the cases were diagnosed during the first 5 years after HT (Figure 1.) One of these even had a hypokalemic periodic paralysis after doses of a diuretic drug. There were two cases that were diagnosed with PA after many years of hypertension (>20 years): one had follow-up visits with general practitioner clinic for hypertension, serum potassium was only slightly low (3.44), serum creatinine was 1.3 mg/dL, The other was misdiagnosed with idiopathic renal tubular acidosis for 15 years and was replaced with oral potassium regularly.

The co-morbidity found in these patients is listed as follows:-

Glucose intolerance was found in 6 out of 20 cases (30%); 3 had impaired fasting glucose (IFG) and the other 3 had type 2 diabetes mellitus. 6 in 20 (30%) had dyslipidemia. Chronic kidney disease (CKD) was complicating 4 of 20 (20%). Obesity was found in 3 out of 20 (15%). Others were coronary artery disease (CAD), hypertensive retinopathy, benign prostatic hyperplasia (BPH), Cervical Cancer, Graves' disease and psoriasis. Each of which was found in 1 case (15%).

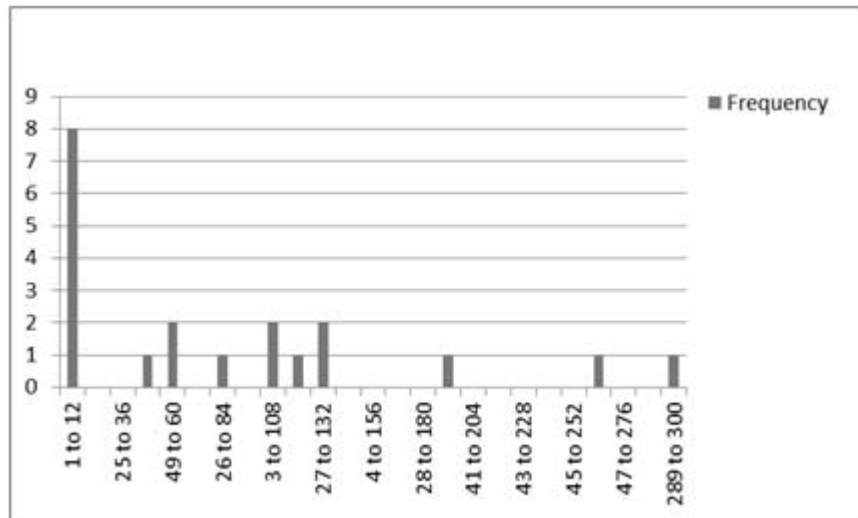


Figure 1. Duration to diagnosis (since DX of HTN).

The most frequent reason that the patients were suspected of the condition was 'hypertension with hypokalemia', which contributed to the diagnoses of 17 of these 20 cases (85%). Hypertension in the young was the clue in 2 cases (10%). In one case, the investigation was started because of severe hypertension.

Serum potassium level during the time before the initiation of the investigation ranged between 2.10

and 3.80 with the mean statistic of 3.00. The standard deviation of serum potassium was 0.43. Although almost all patients had hypokalemia, there were only a small number of patients who had severe hypokalemia (Figure 2). The average creatinine at baseline was 0.92 ± 0.29 . The minimum and maximum were 0.20 and 1.50 respectively.

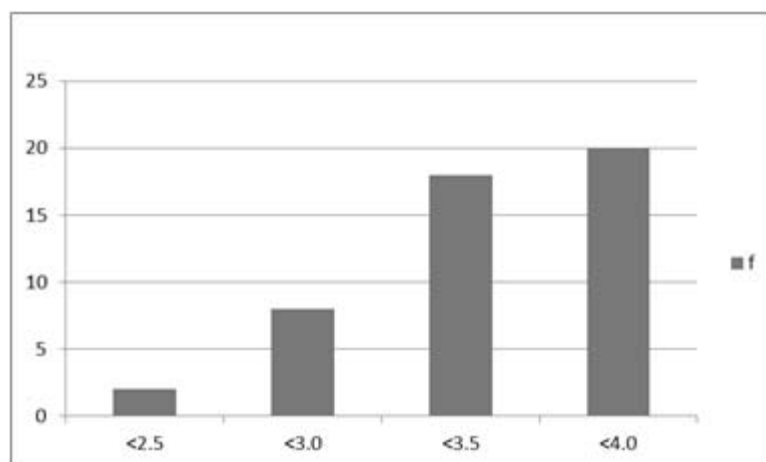


Figure 2. Number of patients at each K level before diagnosis.

Most patients (9 in 20) were able to control their blood pressure with only one medication. Four and five patients received 2 and 3 types of drugs for their blood pressure control. Only two received 4 medications. The dose of replaced potassium chloride ranged from 0 to 240 mEq/day, with the mean of 68.81 ± 61.30 mEq/day.

Serum potassium level during the investigation for PAC/ PRA was 2.87 to 4.62. Mean of 3.75 mEq/dL was calculated from 19 samples due to unknown data of one female patient referred from Sa-kaew Hospital.

Medication used before the diagnosis of PA was made, during the investigation for, and after the diagnosis was made, are listed in Table 1.

The plasma aldosterone concentration (the previous one if ever repeated) was between 11.55 and 113.00 ng/dL: the mean was 45.83 ± 31.87 ng/dL

The plasma renin activity was between 0.1 and 2.2 ng/ml/hr. The mean was 0.85 ± 0.63 ng/ml/hr.

PAC/ PRA ratio was at least 16.56, and the maximum for this population was 282.5 ng/dL to ng/ml/hr. The mean was 85.43 ± 82.63 ng/dL to ng/mL/hr

PAC/ PRA were repeated in four patients. All of them had the ratio more than 20 ng/dL to ng/mL/hr. Of these, PRA were not suppressed in two cases (1.89 and 4.23 ng/ml/hr)

The confirmatory test was not done on 7 of 20 cases. Intravenous normal saline loading test was chosen for the other 13 cases. Among the 7 cases, only one had ARR of less than 20 ng/dL to ng/mL/hr. He changed his mind and refused surgery (case#9). Further investigation was then withheld. The test showed an unsuppressed PAC (more than 5 ng/ml) in every case.

Table 1. List of medication used before diagnosis, during investigation, and after diagnosis.
(Number of patients being treated with)

Medication	Before diagnosis	During investigation	After diagnosis
Verapamil	1	1	
Diltiazem	4	17	14
Nifedipine	2	1	
Amlodipine	6	2	5
Felodipine	1		
Atenolol	7		1
Propranolol	1		
Enalapril	10		2
Losartan			1
Valsartan	1		
Spironolactone	1		12
HCTZ	4		
ISMN	1	2	
Prazosin	2	4	4
Doxazosin		3	1

As for the subtype investigation, the CT study of the adrenal gland showed unilateral macroadenoma in 7 cases. Five were found to be minimal unilateral adrenal limb thickening. Three patients had unilateral microadenoma. Three were normal. The study was not done on two patients: the one refused surgery, and the other developed ST elevation myocardial infarction in November 2011.

Adrenal venous sampling (AVS) was done on 2 cases only. The result was found to be lateralized to the same side of the adenoma in one case. The other was inconclusive because an adrenal vein was unable to be catheterized.

Four patients underwent laparoscopic adrenalectomy. One of these needed comparably the same amount of medication and potassium supplement prior to surgery. AVS was not done to this patient before their scheduled surgery. After the diagnosis and specific treatment was given to the patients, at least one medication was still needed for hypertension in every patient.

The mean serum potassium level after diagnosis was 3.80 ± 0.49 which ranged between 2.34 to 4.30. Sixteen out of twenty cases did not need any supplement potassium at all.

Paired t test was used and showed that serum potassium was significantly greater after diagnosis with 95% CI of +0.47 to +1.11.

Dose of supplemental potassium was significantly lower as well with 95% CI -85.40 to -13.94.

Discussion

The prevalence of PA at Prapokklao Hospital was extremely low (0.15%) when comparing to 5-10% of hypertensives in other studies.⁽¹³⁾ Limitation of this

study is that not all of hypertensive patients were screening for PA so it may not be the true prevalence. The most frequent reason (85%) for screening of PA in this study was 'hypertension with hypokalemia' and the others reason was hypertension in the young. So we should encouraged clinicians to screen of PA in other reason e.g. severe hypertension, resistant hypertension, hypertension with adrenal incidentaloma, hypertension with family history of early-onset HTN and first-degree relative diagnosed with PA.⁽¹⁴⁾

The durations from diagnosis of HT to the diagnosis of PA were 1 month to 295 months. The result show that once the clinical syndrome was recognized by the physician and the screening process was initiated, the diagnosis can be made very early. On the other hand, when not recognized, it could be more than fifteen years.

The hypokalemia were found in this study (19 out of 20 cases). Serum potassium level during the time before the initiation of the investigation ranged between 2.10 and 3.80 with the mean statistic of 3.00. Even through diuretic can cause hypokalemia, 4 cases of hypokalemic patients in this study were screened of PA like in suggestion from the guideline. One of these even had a hypokalemic periodic paralysis after doses of a diuretic drug. Periodic paralysis is a very rare presentation in white patients, but it is not an infrequent presentation in patients of Asian descent.⁽¹⁵⁾ The one normokalemic patient in this study had the impaired renal function which influences to increase serum potassium levels, so the baseline may be hypokalemia. The diagnosis of PA in the year 2008 and 2009 (as shown in figure 3) were higher than the others. The increased screening of

PA may due to the problem about the blood chemistry analysis at Prapokklao hospital in the periods showed slightly lower potassium level than it actually was. So the most important clue in this study was hypokalemia. When compare with the recent studies, only a minority of patients with PA (9% to 37%) had hypokalemia.⁽¹⁶⁾ It might be too late to wait until hypokalemia occurs to initiate the screening test.

The ARR which is the means of screening for PA were done. The false positive or negative ratio was decrease with the avoidance of interfering from hypokalemia or drugs e.g. beta-blocker, ACEI and diuretics as shown in table 1. The PRA was not suppressed in 2 cases, the diagnosis was confirmed later in these cases though. It is critical to keep in mind that PAC/ PRA ratio is only a screening or case-finding test and the assay is affected by a list of drugs and conditions. Even physical environment, e.g. cold, does have effect on the results.⁽¹⁷⁾ A medication-contaminated evaluation is unavoidable. So there were 4 cases that were repeated ARR in this study.

The confirmation of PA is the intravenous saline infusion tests which were the main. Normal subjects show suppression of PAC after volume expansion with isotonic saline; subjects with primary aldosteronism do not show this suppression. PAC levels in normal subjects decrease to less than 5 ng/dL; most patients with primary aldosteronism do not suppress to less than 10 ng/dL.^(18 - 20) None of the cases in this series showed a suppressible PAC.

In general, patients with APAs have more severe hypertension, more frequent hypokalemia, higher plasma (>25 ng/dL) levels of aldosterone, and are younger (younger than 50 years) than those with IHA. Patients fitting these descriptors are considered

to have a "high probability of APA". In this study, nearly all of the patients had hypokalemia, the mean of plasma aldosterone 45.8 ng/dl and the mean age 46.5 years. So it is not surprised when the subtype differentiation was done by CT of adrenal gland, mainly diagnosis were aldosterone-producing adenoma (APA). Patients fitting these descriptors are considered to have a "high probability of APA" regardless of the CT findings. 41% of patients with "high probability of APA" and a normal adrenal CT scan prove to have unilateral aldosterone hypersecretion. On the other hand, nonfunctioning unilateral adrenal macroadenomas are not uncommon, especially in older patients (older than 40years).⁽²¹⁾ There was a case of IHA which had clinical of "high probability of PA" and a unilateral microadenoma from CT which underwent surgery without AVS. The clinical outcomes after surgery were not improved so we should decision making follow by the algorithm as shown in Figure 4.

After treatment with laparoscopic adrenalectomy and medical treatment, the significant improvement of blood pressure control and potassium levels. In the literatures, the adrenalectomy for PA results in cure of HT in 50 - 60% of patients⁽¹³⁾ but anyone was not cure in this study. Even though sixteen out of twenty cases did not need any supplement potassium at all and the remainders need the lower dosage of potassium supplement. The antihypertensive drugs prescriptions were significantly increased in aldosterone antagonist group after diagnosis of primary aldosteronism as shown in Figure 5 in the aim of normokalemia, deleterious effect on the cardiovascular and kidney independent of effect on blood pressure.^(13, 22-23)

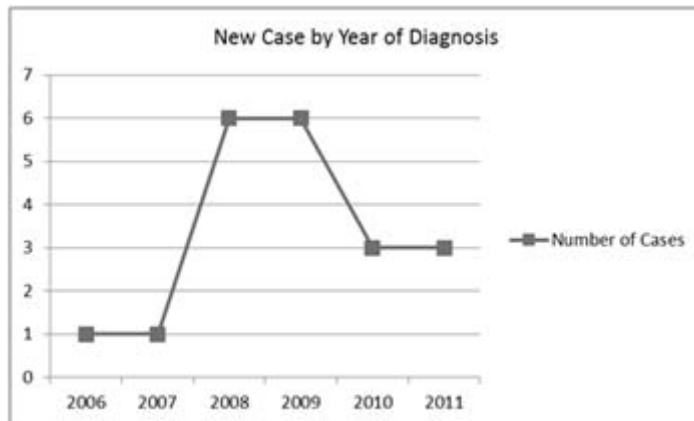


Figure 3. Number of new cases by year of diagnosis.

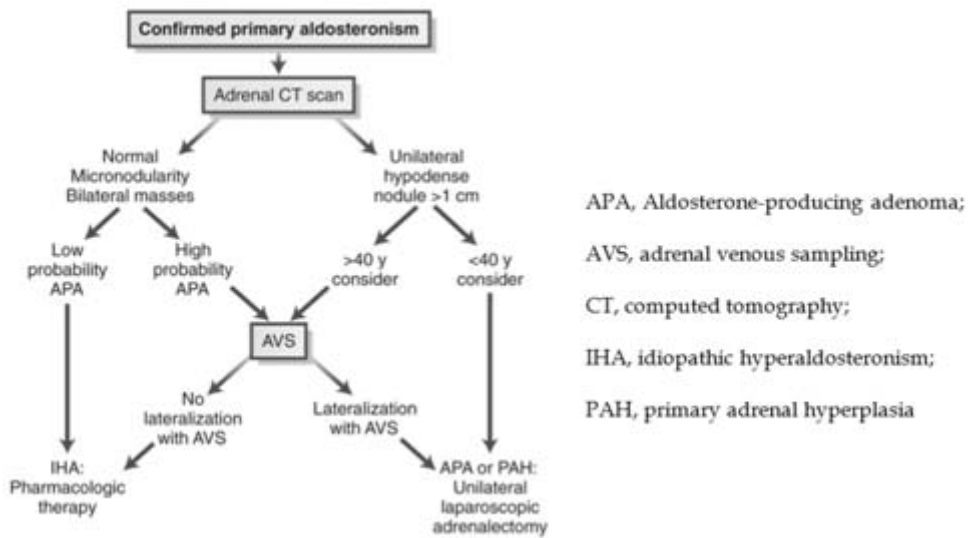


Figure 4. Algorithm for subtype evaluation of PA.

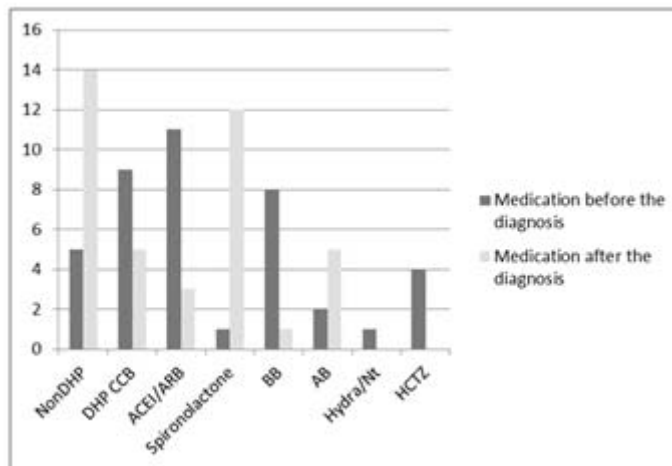


Figure 5. Number of patients using each group of antihypertensives.

Conclusions

The prevalence of primary aldosteronism among hypertensive patients at Prapokklao Hospital was extremely lower than that of the reviewed literatures. The endocrine society's screening scheme might have to be initiated earlier, before patients present an obvious clinical of hypokalemia to include more cases.

Key to prompt diagnosis is the awareness of the physician and follows clinical guideline. The most important clue that triggered the investigation was 'hypertension with hypokalemia'. Also, hypokalemia was a key characteristic of these patients that was found in almost every cases, only one was with K of 3.80 mEq/dL. However, the severity of hypokalemia was not severe in most cases.

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