

Primary hyperaldosteronism among Chinese hypertensive patients: how are we doing in a local district in Hong Kong

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Objectives To estimate the point prevalence of primary hyperaldosteronism in a government out-patient setting and to compare associated patient characteristics with those having essential hypertension.

Design Case series with external comparison.

Setting A single public hospital (Caritas Medical Centre) and all five associated general out-patient clinics in Sham Shui Po district in Hong Kong.

Patients All patients with confirmed primary hyperaldosteronism and randomly selected patients with essential hypertension from a medical specialist clinic and general out-patient clinics, retrieved from a computer database for the period January 2007 to December 2008.

Main outcome measures Estimated point prevalence of primary hyperaldosteronism among hypertensive patients treated in the public sector of Sham Shui Po district. Patient age when hypertension was diagnosed, number of antihypertensive drugs used for treatment, and the presence of target organ damage in the patients with primary hyperaldosteronism and those with essential hypertension were compared.

Results Among the 46 012 patients receiving antihypertensive treatment, 49 were confirmed to have primary hyperaldosteronism. The estimated point prevalence of primary hyperaldosteronism among these hypertensive patients was 0.106% only, which was far smaller than figures from other countries. When compared with the 147 patients with essential hypertension by multivariate analysis, those with primary hyperaldosteronism were: (1) associated with longer durations of hypertension (odds ratio=1.14; 95% confidence interval, 1.06-1.24) despite being younger at the time of study, (2) likely to be taking three or more antihypertensive drugs (odds ratio=2.51; 95% confidence interval, 1.59-3.95), and (3) more likely to have left ventricular hypertrophy (odds ratio=5.01; 95% confidence interval, 1.83-13.69). All primary hyperaldosteronism patients studied presented with hypokalaemia. The need for antihypertensive drugs was markedly reduced after adrenalectomy for adrenal adenoma.

Conclusions Primary hyperaldosteronism, which is potentially a surgically curable cause of hypertension, appeared to be underdiagnosed in our locality. Screening by aldosterone-renin ratio of high-risk individuals may help improve patient outcomes.

Key words

Adrenal cortex neoplasms; Aldosterone; Hyperaldosteronism; Hypertension; Prevalence

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New knowledge added by this study

- Primary hyperaldosteronism was probably underdiagnosed among hypertensive patients in our locality.
- Patients with primary hyperaldosteronism are more likely to be younger and more drug-resistant than those with essential hypertension.

Implications for clinical practice or policy

- Instead of only screening hypokalaemic hypertensive patients, we suggest screening high-risk individuals by aldosterone-renin ratio, especially those with young age of onset and/or resistant hypertension.

高血壓華籍患者的原發性醛固酮增多症： 香港的情況

目的 評估原發性醛固酮增多症（以下簡稱原醛症）在政府門診的時點患病率，並把此症的患者與原發性高血壓患者作特徵比較。

設計 與其他醫院比較的病例系列。

安排 香港一所公立醫院（明愛醫院）及深水埗區其餘五間政府門診部。

患者 從醫院的電腦檔案中抽取2007年1月至2008年12月期間所有確診為原醛症患者的紀錄，以及從一所專科診所及其他政府門診隨機抽樣的原發性高血壓患者的紀錄。

主要結果測量 估計從深水埗區公立醫院所處理的高血壓患者中出現原醛症的時點患病率，並比較原醛症患者及高血壓患者在以下幾方面的分別：患者確診為高血壓時的年齡、服食降壓藥物的數量，以及是否有器官損壞的情況。

結果 服食降壓藥物的46 012名病人中，49人確診患有原醛症，其時點患病率為0.106%，數字遠低於其他國家。與147名原發性高血壓患者比較，多元回歸分析結果顯示原醛症患者雖然年齡較輕，他們患有高血壓的年期卻較長（比數比=1.14；95%置信區間：1.06-1.24）。此外，原醛症患者較大機會服食多於三種或以上降壓藥物（比數比=2.51；95%置信區間：1.59-3.95），他們左心室肥厚的機會亦較高（比數比=5.01；95%置信區間：1.83-13.69）。所有原醛症患者均有低血鉀症，他們因腎上腺腺瘤而接受腎上腺切除術後，都會大大減少對降壓藥物的需求。

結論 原醛症雖會引致高血壓，但適合手術治療。在香港，原醛症以乎出現診斷不足的情況。使用血漿醛固酮 / 腎素活性比值把高風險人士進行篩檢可以改善患者的治療結果。

comprised 5.3% of the total Hong Kong population.⁵ Although only about 5 to 10% of patients with hypertension are thought to have a secondary form, hypertension is so common that secondary hypertension will be encountered frequently in primary care.^{6,7} However, the management may be very different if secondary hypertension is identified, and most importantly it is possible to offer patients a cure.

It is suggested that primary hyperaldosteronism (PH) is a common cause of secondary hypertension. This is important not only because it is potentially curable by surgery but also because it is associated with higher cardiovascular morbidity and mortality than in age- and sex-matched patients with essential hypertension (EH) having the same degree of blood pressure elevation.⁸ Moreover, generally, it is associated with higher rates of target organ damage than in patients with EH.⁹

In the past, when we used to screen for PH in hypertensive patients with spontaneous hypokalaemia only, its prevalence among hypertensive patients was estimated to be less than 1%.^{10,11} However, recent studies using plasma aldosterone-renin ratio (ARR) as a screening test for PH in hypertensive populations suggested a prevalence as high as 5 to 13%, though over half of those affected are normokalaemic.^{6,12-17} According to the only Asian prevalence study of PH (using ARR screening) performed in Singapore, its estimated prevalence was about 5%, only 38% of whom were hypokalaemic.¹⁸ The ARR was calculated as the ratio of plasma aldosterone concentration (PAC in ng/dL) to plasma renin activity (in ng per mL/h). A positive screening test was defined as a ratio of >20 and with a PAC of >15 ng/dL (416 pmol/L). The latest guideline has also concluded that hypokalaemia has low sensitivity and specificity, and a low positive predictive value for the diagnosis of PH, and recommends ARR as currently the most reliable means of screening.^{19,20}

The prevalence of PH may be as high as 20% in patients with resistant hypertension,¹³ and in about half of these patients it may be potentially curable, there being a unilateral aldosterone-producing adrenal adenoma.¹⁸ A local study in Hong Kong confirmed that surgical excision of an adrenal adenoma can cure hypokalaemia in all cases and can cure persistent hypertension in 77% of patients.²¹ The procedure was also proven to be cost-effective in the long run.²²

To date, there are no local data on the prevalence of PH in Hong Kong. In our locality, most of us screen for PH in hypertensive patients, only when we encounter unexplained hypokalaemia. We therefore undertook this study to review the situation in our locality, and especially from the screening for PH in primary care.

Introduction

The Population Health Survey 2003-04 of the Department of Health revealed that around 27% of the population aged 15 years or above had increased blood pressure.¹ Hypertension is the second most common problem encountered in Hong Kong primary care (10% of all health-related issues).² It is commonly encountered in general out-patient clinics (GOPCs) accounting for 43% of attendees,³ and medical/geriatric specialty out-patient clinics (SOPCs) accounting for 47% of attendees⁴ of the Hong Kong Hospital Authority, which is similar among all districts of Hong Kong.³ In the Sham Shui Po (SSP) Community Diagnoses Study conducted by the City University of Hong Kong in 2002, hypertension was the major chronic disease among residents of SSP, and affected 14.4% of its 372 000 residents and

Thus, the objectives of this study were: (1) to estimate the point prevalence of PH among hypertensive patients treated in public sector in SSP; (2) to compare the presentation of PH patients to that of patients with EH; and (3) to review the outcome of adrenalectomy in patients with aldosterone-producing adrenal adenomas.

Methods

A retrospective observational study was performed on patients diagnosed to have PH and EH, and to review the situation in our locality. Patients coded PH (International Classification of Diseases [ICD] 10-255.1[0-5]) or secondary hypertension (ICD10-405) during attendance at the Department of Medicine and Geriatrics of Caritas Medical Centre from 1 January 2007 to 31 December 2008 were retrieved from the Clinical Data Analysis and Reporting System of the Hong Kong Hospital Authority. Confirmed PH cases were identified by record review.

The list of hypertensive patients who had received equal to or more than 180 days of antihypertensive drugs during the same period with regular follow-up in the Department of Medicine and Geriatrics of the Caritas Medical Centre's SOPC and all the five GOPCs in SSP was retrieved. A total of 147 patients were randomly selected as the comparison group to provide a 1:3 ratio for comparison. They were drawn by using stratified random sampling after excluding PH patients. The total number of patients drawn from each clinic was determined by its relative proportion of hypertensive attendees. Among the 45 963 hypertensive patients, this amounted to 34.5% from the medical SOPC and 65.5% from GOPCs (Fig 1). Different GOPCs and medical SOPCs were looking after various numbers of primary hypertensive patients. The patients from our five GOPCs were essentially similar to those in other districts,² which were representative of hypertensive patients in 59 GOPCs in Hong Kong. The patient list was arranged by numerical order of a unique out-patient number

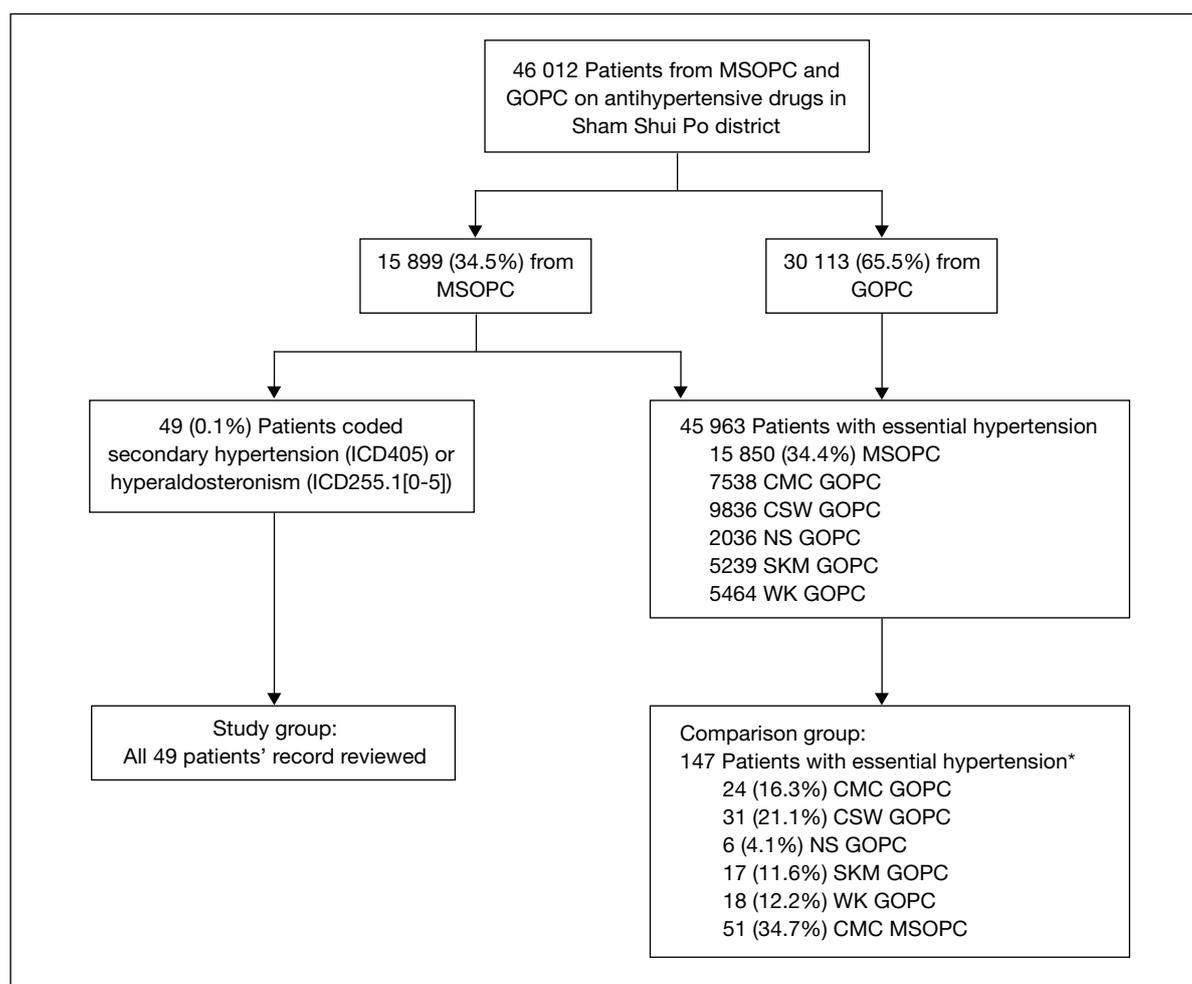


FIG 1. Study flowchart

CMC denotes Caritas Medical Centre, GOPC general out-patient clinic, ICD International Classification of Diseases, CSW Cheung Sha Wan, NS Nam Shan, SKM Shek Kip Mei, WK West Kowloon, and MSOPC medical specialty out-patient clinic

* According to proportion of patients followed up in various clinics randomly selected for record review

assigned to each patient chronologically by the computer during the patient's first registration. Repeated sampling of the same subject was avoided by checking for duplicate out-patient numbers. Each patient was given a number according to the order in the list. The required patients were then drawn randomly using a random number generator. Headcount by antihypertensive treatment instead of headcount by ICD-10 and International Classification of Primary Care coding was used as the coding for hypertension was incomplete in SOPCs.

Clinical notes of PH patients and the comparison group (EH patients) until the last visit record were reviewed for demographic data, diagnosis, presentations, antihypertensive drug treatment, and the presence of target organ damage. The outcome of adrenalectomy was also reviewed.

Data were analysed by the Statistical Package for the Social Sciences (Windows version 16; SPSS Inc, Chicago [IL], US). All continuous data were expressed as medians or means with standard deviations (SDs). In univariate analysis, the *t* test was used for comparisons of continuous data while the χ^2 test was applied to comparisons of categorical data. In the multivariate analysis, forward stepwise logistic regression was used to determine the effect of socio-demographics (gender and age) and disease (year of hypertension diagnosis, receipt of antihypertensive drugs, and presence of target organ damage) on each hypertension type. All estimates were accompanied with a 95% confidence interval (CI). Any *P* value of less than 0.05 was regarded as statistically significant.

The study was approved by the Clinical Research Ethics Committee of the Kowloon West Cluster of Hospital Authority of Hong Kong.

Results

During the study period, the number of patients with hypertension treated in the public sector in SSP using headcounts based on antihypertensive treatment was found to be 46 012. The numbers of EH patients drawn from various GOPCs and SOPCs were based on the proportion of hypertensive patients fulfilling our inclusion criteria (Fig 1).

A total of 49 patients were confirmed to have PH in this period. All were Chinese. The estimated percentage of PH among our hypertensive patients in the SSP public sector was therefore 0.106% only. The characteristics of these 49 PH and 147 EH patients are shown in Table 1.

All cases of PH were confirmed biochemically with baseline serum renin and aldosterone levels and their response to sodium loading, postural change and cortisol rhythm, together with radiological support by computed tomography of the adrenal glands. Among them, 19 (39%) were confirmed to

have adrenal adenomas (Conn's syndrome), which were defined as group A; 20 (41%) were confirmed to have bilateral adrenal hyperplasia, defined as group B; and the remaining 10 (20%) had no clear-cut subtype classification and were defined as group C. Adrenal venous sampling was offered to PH patients when the subtype classification was uncertain; nine out of ten declined such sampling. Adrenal venous sampling was performed in one case only, in which the right adrenal vein could not be successfully cannulated due to wedging.

Concerning their presentation, all our PH patients presented were investigated for unexplained hypokalaemic hypertension. Of the 49 PH patients, 19 (39%) were referred from GOPCs. Five (10%) patients were admitted through the accident and emergency department for medical problems and incidentally found to have hypokalaemia. Three patients were admitted as emergency cases for a sudden rise in blood pressure. One patient was admitted because of a cerebrovascular attack, and one was referred from a private general practitioner for unexplained hypokalaemia. The other patients were being followed up in the Department of Medicine and Geriatrics of Caritas Medical Centre for medical reasons, including hypertension.

The age at diagnosis was significantly younger in PH than EH patients ($P < 0.001$). The respective mean (SD) and median ages were 49.1 (10.9) and 49 years for PH patients, compared to 63.7 (12.3) and 66 years for those with EH. Among the PH patients, 20% had hypertension diagnosed before age of 40 years. The mean number of years with hypertension diagnosed was significantly higher in the PH than EH group (9.3, SD 5.1 years vs 6.3, SD 4.3 years).

There was no statistically significant difference in the male-to-female ratio between the groups.

Regarding the 49 PH patients, 22 (44.9%) were taking three or more antihypertensive drugs for control of hypertension, before they received specific treatment for PH. Among them, six (12%) had JNC VII (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) stage III hypertension ($>180/100$ mm Hg) despite treatment with three antihypertensive drugs.²³ In contrast, only 11.6% of EH patients were taking three or more antihypertensive drugs for control of their hypertension. The mean number of antihypertensive drugs used were 2.3 and 1.7 for PH and EH patients, respectively ($P < 0.001$). After adjusting for age and gender differences, the PH patients were associated with longer durations of diagnosed hypertension compared to EH patients (odds ratio [OR]=1.14; 95% CI, 1.06-1.24), despite being younger at the time of study (Table 2). Similarly they were more likely to be taking three or more antihypertensive drugs (OR=2.51; 95% CI, 1.59-

TABLE 1. Characteristics of the 49 primary aldosteronism (PH) patients and 147 essentially hypertensive (EH) patients studied

Characteristic*	A: Aldosterone- producing adrenal adenoma (n=19)	B: Adrenal hyperplasia (n=20)	C: Primary hyperaldosteronism with subtype not classified (n=10)	PH group: total primary aldosteronism patients, ie A+ B+C (n=49)	EH group: essentially hypertensive patients (n=147)	P value
Age when HT was diagnosed (years)						
Mean ± SD	51.2 ± 14.5	47.8 ± 8.3	48 ± 7.1	49.1 ± 10.9	63.7 ± 12.3	<0.001
Median	48	48.5	50	49	66	
Range						
≤30	1	0	1	2	0	
31-40	3	5	0	8	5	
41-50	8	7	6	21	23	
51-60	2	7	3	12	32	
61-70	2	1	0	3	36	
71-80	3	0	0	3	45	
≥81	0	0	0	0	6	
Actual age at the beginning of study period (years)						
Mean ± SD	59.3 ± 16.2	58.5 ± 6.2	56.6 ± 7.2	58.4 ± 11.2	70.0 ± 12.6	<0.001
Median	56	57	57	57	73	
Range	31-82	49-72	39-66	31-82	42-97	
Years of diagnosing HT						
Mean ± SD	9.1 ± 5.8	10.7 ± 5.0	8.6 ± 3.3	9.3 ± 5.1	6.3 ± 4.3	<0.001
Median	8	9.5	7.5	8	6	
Range	1-26	2-20	4-15	0-26	0-27	
Sex (M/F)	0.9	1.2	2.3	1.2	1.3	0.16
No. of types of antihypertensive drugs						
Mean	2.6	2.1	2.4	2.3	1.7	<0.001
Proportion on ≥3 drugs	58%	30%	50%	45%	12%	<0.001
1	3	5	1	9 (18%)	65 (44%)	
2	5	9	4	18 (37%)	65 (44%)	
3	9	5	5	19 (39%)	13 (9%)	
4	1	1	0	2 (4%)	4 (3%)	
5	1	0	0	1 (2%)	0	
Presence of target organ damage† (No. of patients)						
Proteinuria‡	1	2	1	4 (8%)	8 (5%)	0.16
CHF	2	0	0	2 (4%)	10 (7%)	0.49
IHD	2	1	0	3 (6%)	20 (14%)	0.16
CVA	1	1	2	4 (8%)	16 (11%)	0.59
LVH	7	4	1	12 (25%)	10 (7%)	0.001
Referral source (No. of patients)						
GOPC	4	11	4	19	-	
A&E	7	1	1	9	-	
Private practitioner	1	0	0	1	-	
MSOPC (FU for other reason)	7	8	5	20	-	

* HT denotes hypertension, SD standard deviation, CHF congestive heart failure, IHD ischaemic heart disease, CVA cerebrovascular attack, LVH left ventricular hypertrophy, GOPC general out-patient clinic, A&E accident and emergency department, MSOPC medical specialist out-patient clinic, and FU follow-up

† Some patients had >1 type of target organ damage

‡ Proteinuria was defined as persistent urine protein excretion of ≥300 mg/day

TABLE 2. Factors associated with hypertensive type (primary hyperaldosteronism [PH] vs essential hypertension [EH]) by logistic regression analysis

Variable*	Odds ratio†	95% Confidence interval	P value
Years with hypertension diagnosis	1.14	1.06-1.24	<0.001
Types of hypertensive drug ≥3	2.51	1.59-3.95	<0.001
Left ventricular hypertrophy	5.01	1.83-13.69	0.002

* Only significant variables by forward stepwise logistic regression were reported

† Odds ratio <1 = less likely than the EH patients, odds ratio >1 = more likely than the EH patients; the Hosmer-Lemeshow test (P=0.589) indicates the good fit of data to logistic regression

3.95), and had a higher likelihood of left ventricular hypertrophy (OR=5.01; 95% CI, 1.83-13.69) [Table 2].

Difference in the presence of other target organ damage, including cerebrovascular attack, ischaemic heart disease, congestive heart failure, and proteinuria (defined as persistent urine protein excretion of ≥300 mg/day) in the PH and EH patients were not statistically significant. Some patients had more than one target organ showing damage (5/49 PH and 15/147 EH patients).

The drugs used to treat PH patients with bilateral adrenal hyperplasia included aldosterone antagonists (eg spironolactone) or other potassium-sparing diuretics (eg amiloride). For PH due to unilateral aldosterone-producing adenoma, the patients underwent unilateral adrenalectomy.

Among our 19 patients with confirmed Conn's syndrome, 14 had adrenalectomies, four refused operation, and one defaulted follow-up. After adrenalectomy, pathology reports were available in 13 of our cases; all were confirmed to be adrenal adenomas. The operation was performed in China for the single case for which the pathology report was not available.

Postoperatively, 93% (13/14) had their potassium levels normalised. Regarding the single case of persistent hypokalaemia after unilateral adrenalectomy, about 1 year later the patient was found to have an adrenal adenoma on the other side and considered to have bilateral nodular adrenal hyperplasia. On the other hand, 93% (13/14) had improved blood pressure control after adrenalectomy (defined as a reduction of either ≥10 mm Hg systolic or ≥5 mm Hg diastolic). Moreover, 86% (12/14) enjoyed a reduction in the number of antihypertensive drugs they were taking; evidently 50% (7/14) did not require any antihypertensive treatment. Before adrenalectomy, more than half of the patients with adrenal adenomas were taking three or more antihypertensive drugs for control of their hypertension, but after adrenalectomy the number was significantly reduced (P<0.001). Figure 2 summarises the comparison of the antihypertensive drug use before and after adrenalectomy in patients with adrenal adenomas.

Discussion

The estimated percentage of PH among hypertensive patients in our locality was obviously very low compared to that in other countries, which may have been due to several contributing factors. First, ours was a retrospective estimate based on a computer coding system, the problem of under-coding of PH could have affected our findings. Second, we used to screen for PH in hypertensive patients only if they had unexplained hypokalaemia. Yet, studies showed that only about 38% of such patients present with hypokalaemia.¹⁸ Moreover, plasma ARR is currently recommended as the most reliable means of screening for PH.¹⁷⁻²⁰ Third, our figure only included patients encountered in the public sector, whereas a proportion of PH patients could have been followed up in the private sector or seeing alternative medical practitioners. Fourth, ethnic differences could contribute to the apparent discrepancy, though the latest study from Singapore (only on Chinese patients) suggested a point prevalence of about 5%.¹⁸ Notwithstanding above factors, there is a high probability that PH was significantly under-diagnosed in our locality.

Insufficient awareness of PH may have contributed to the situation of underdiagnosis. Increasing the awareness of the condition by primary care doctors and specialists appears necessary. Latest guidelines suggest that screening by ARR (not only those with hypokalaemia) can yield a relatively higher prevalence of PH.^{19,20} This should be undertaken for patients with drug-resistant hypertension, hypertension with spontaneous or diuretic-induced hypokalaemia, hypertension with adrenal incidentaloma, young-onset hypertension,

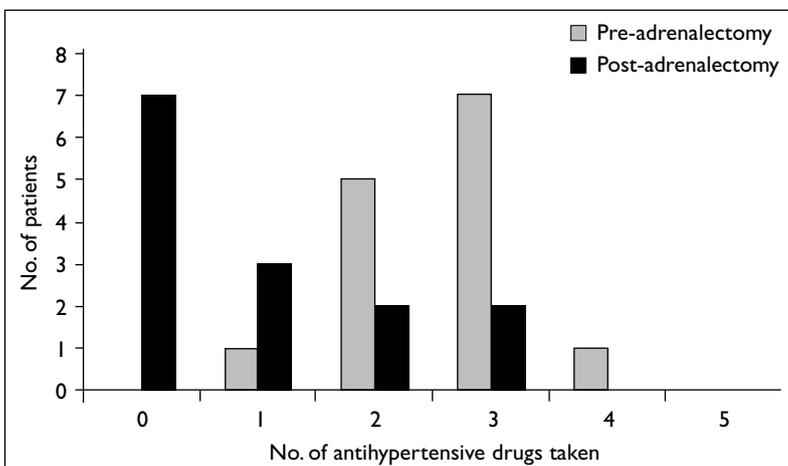


FIG 2. Comparison of antihypertensive drug usage pre- and post-adrenalectomy

those suffering cerebrovascular accidents aged less than 40 years, and hypertension in a first-degree relative of PH patients.¹⁹

To improve the diagnosis rate, screening by ARR is suggested. However, due to cost concerns, limited access to such testing, as well as our own observations, we suggest the following patients be targeted: (1) young age of onset of hypertension, which could be suggestive of a secondary cause; (2) patients deemed to require three or more antihypertensive drugs for blood pressure control; (3) young and/or short-duration hypertensive patients with left ventricular hypertrophy. These suggestions are all compatible with findings from published studies on PH.^{8,9,12,19}

Doctors in GOPC in Hong Kong generally have no access to ARR testing. Primary care doctors should nevertheless act as the gatekeepers and coordinators to pick up high-risk patients and refer them accordingly. We suggest that patients with resistant hypertension and especially those diagnosed when relatively young could be referred to SOPDs for assessment and/or further work-up. To this end, we hope to increase the awareness of the condition among both primary care doctors and other physicians so that appropriate screening can be performed more frequently in high-risk patients. Notably however, an increased ARR is not in itself diagnostic, and PH must be confirmed by aldosterone suppression testing.

About half of our PH patients were eventually found to have adrenal adenomas, which could be surgically cured; successful outcomes being noted after adrenalectomy. Similar outcomes have also been reported in the literature and are believed to be cost-effective in the long-run.^{18,19,22}

Most of our patients enjoyed better blood pressure control with a reduction in the number of antihypertensive drugs they were using; some even ceased taking drugs after successful surgical treatment. Good blood pressure control can reduce cardiovascular complications, ischaemic heart disease, and stroke. Almost all patients with hypokalaemia had their abnormality corrected, which in turn reduced the risk of symptomatic hypokalaemia including muscle paralysis and arrhythmia. From the health care point of view, curative treatment of PH can reduce the long-term health care burden on our society.

Conclusions

Primary hyperaldosteronism was probably significantly underdiagnosed in our locality. Patients with PH are more likely to be younger and more drug-resistant than EH patients. Since PH is potentially surgically curable, instead of screening hypokalaemic hypertensive patients only, we suggest screening all high-risk individuals by ARR, especially those with young age of onset and/or resistant hypertension.

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