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Keeping primary aldosteronism in mind: Deficiencies in screening at-risk hypertensives ☆

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ABSTRACT

Background: Primary aldosteronism is a common but underdiagnosed cause of hypertension. Patients with this disorder have worse morbidity compared with those with essential hypertension, but with timely diagnosis and appropriate intervention these patients are potentially cured and may have reversal of target organ damage. The goal of this study was to determine if hypertensive patients considered high risk were checked for primary aldosteronism.

Methods: We reviewed electronic health records to identify patients age 18 years or older with coexisting hypertension and hypokalemia or hypertension and sleep apnea, then determined if they had been investigated with measurement of aldosterone or renin. We built regression models to identify explanatory variables for screening in these 2 high-risk groups.

Results: Of nearly 37,000 patients with hypertension and hypokalemia, only 2.7% were ever screened for primary aldosteronism. Most opportunities for case detection were during inpatient hospitalizations, yet in this setting, patients were less likely than clinic patients be screened. Similarly, 3.0% of hypertensive patients with sleep apnea were screened since the inclusion of this group in case detection recommendations.

Conclusion: Uptake of practice guidelines by hospital physicians, fueled by support from their specialty societies, may help to identify many more patients with unrecognized primary aldosteronism.

Introduction

Primary aldosteronism is estimated to affect between 5% and 12% of hypertensive patients and has gained recognition as a major public health problem.[1,2] Many physicians are taught in medical school that high blood pressure and hypokalemia are necessary for diagnosis. Although hypertension in primary aldosteronism is associated with lower potassium levels, only a quarter of all cases of primary aldosteronism have hypokalemia at presentation, and these are likely patients with more severe disease.[3] One of the major clinical challenges over the years has been identifying patients with primary aldosteronism from among the many patients with essential hypertension.

The most common subtypes of this disease are aldosterone-producing adenoma and adrenal hyperplasia. In centers where adrenal vein sampling is routinely performed, the prevalence of adrenal adenomas among patients with primary aldosteronism ranges from 28% to 50%.[3] For patients with a unilateral cause of primary aldosteronism, surgery can be curative. However, early diagnosis and appropriate treatment is key. Delays or failures to diagnose primary aldosteronism lead to significant damage to the cardiovascular and renal systems, greater than what is observed in patients with high blood pressure alone.[4] Timely surgical intervention not only produces clinical and biochemical success in the majority of patients, but can reverse target organ injury.[5–8] Despite knowledge that adrenalectomy may cure hyperaldosteronism in patients with some subtypes of primary aldosteronism, it still remains a largely unrecognized and untreated disease.[9,10]

The Endocrine Society recently updated their clinical practice guidelines on the screening, diagnosis, and treatment of primary aldosteronism.[11] Screening tests are recommended for several groups of patients considered high risk for this disease, comprising about half of all patients with high blood pressure.[9] Included in this strategy are hypertensive patients with sleep apnea. Although sleep apnea is a known cause of secondary hypertension, more recent evidence suggests sleep apnea may manifest from primary

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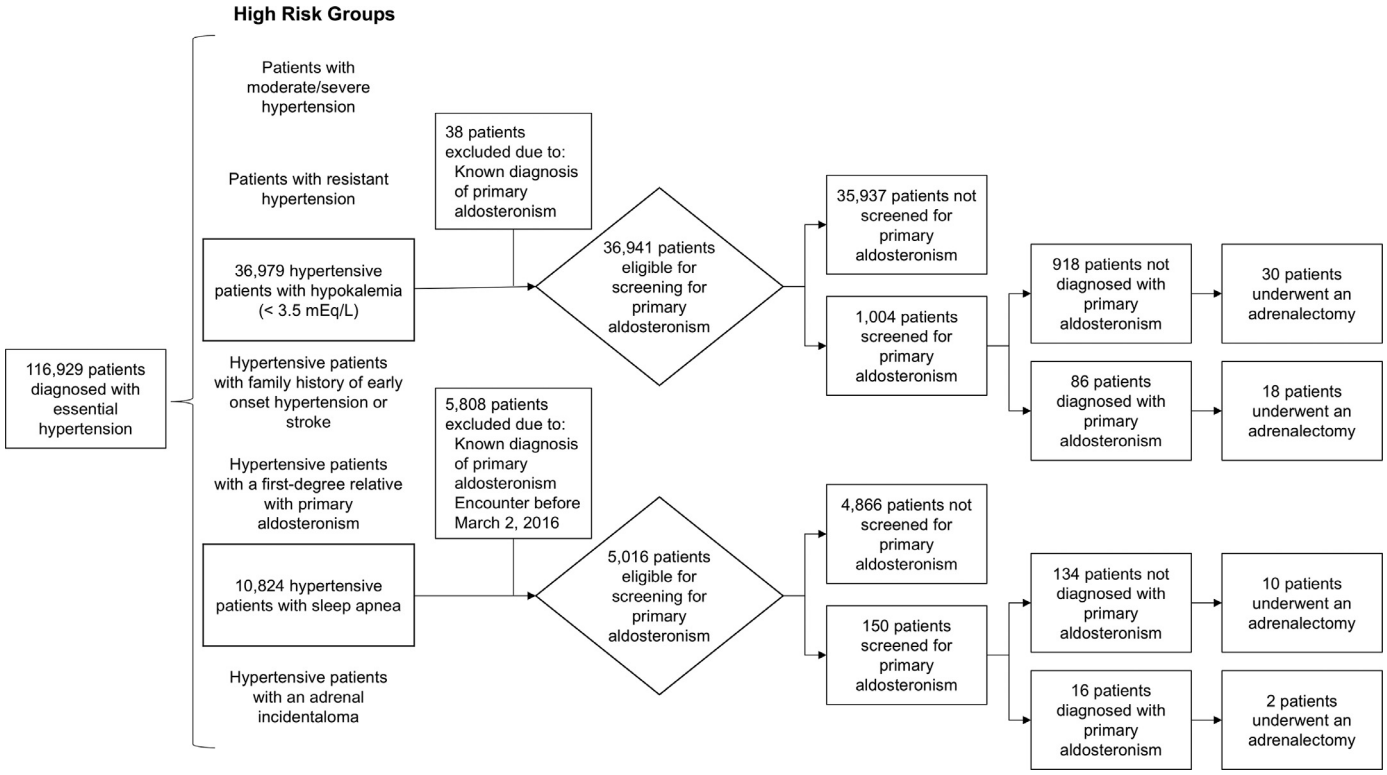

Fig. 1. Overview of study results (flowchart).

aldosteronism, possibly owing to fluid retention in the neck leading to an increase in airway resistance.[12] The principle goal of this study was to determine if physicians were appropriately recognizing those considered to have a higher probability of primary aldosteronism. First, we identified hypertensive patients having hypokalemia and explored screening patterns within this group. Next, we searched for patients with hypertension and sleep apnea and looked at their frequency of screening since the release of these expanded screening guidelines. With both strategies, we discovered a marked deficiency in screening for primary aldosteronism.

Methods

This study was deemed exempt by the University of Chicago Institutional Review Board because all data were deidentified. To identify qualifying patient encounters, we queried electronic health records stored in the clinical research database warehouse using a cohort discovery program. This database contains patient information in electronic health records from our tertiary care center, including outpatient, inpatient, and emergency department encounters. We selected all patients from the age of 18 years and older having *International Classification of Disease*, ninth and tenth editions (ICD-9/10) codes consistent or compatible with the diagnosis of essential hypertension, from 1999 to 2017. We identified qualifying encounters for any patient also having at least 1 serum potassium level less than 3.5 mEq/L or ICD-9/10 codes for obstructive sleep apnea. Of note, only encounters after March 1, 2016 were considered when evaluating patients with hypertension and sleep apnea to reflect the timing of the updated Endocrine Society guidelines.

Patient demographics, including age, gender, race or ethnicity, and weight, along with laboratory values, diagnosis codes, medications, and encounter details were collected for all groups. Probable outliers were removed from statistical analysis. Only the index encounter, that is the first qualifying encounter of every patient, was considered in our analysis. Although health information for additional qualifying encounters was not collected, the total number of qualifying encounters was measured. Both high-risk groups were matched against a list of all patients who had either an aldosterone or renin level measured at this center, and any matched patient was considered screened for primary aldosteronism. Within both subgroups, we assessed independent association of patient and encounter characteristics with screening using 2-tailed *t*-tests for comparisons of continuous data and chi-squared for comparisons of categorical data. We then built univariable and multivariable logistic regression models to identify explanatory variables for screening. The 95% confidence interval around reported estimates reflects a P value $<.05$. Analyses were performed in Stata software, version 15.0 (StataCorp, College Station, TX). Finally, we matched screened patients against a list of all patients who had an adrenalectomy at this center.

Results

From February 16, 1999 to December 15, 2017, there were 116,929 patients at least 18 years of age with a diagnosis of essential hypertension based on ICD-9/10 codes at this institution. Within this cohort, 36,979 patients (32%) had laboratory evidence of hypokalemia with documentation of a onetime serum potassium level less than 3.5 mEq/L (Fig. 1). This included 64,858 separate clinical encounters, comprising outpatient, inpatient, and emergency department visits. Similar to all patients with hypertension, the majority of hypokalemic patients were non-Hispanic black women (Table 1). However, although most hypertensive patients were seen in an outpatient clinic, 54.2% of the clinical encounters for hypertensive hypokalemic patients were inpatient (Table 1). Although hypokalemia is common in both settings, in this study more cases were identified during an inpatient hospitalization.

For this group of hypertensive patients with hypokalemia, 38 patients had previously been diagnosed with hyperaldosteronism

Table 1
Patient demographics and encounter type.

Characteristic	Hypertension	Hypertension and hypokalemia	Hypertension and sleep apnea*
Total no. of patients	116,929	36,979	5,018
Sex			
Female	65,119 (55.7%)	23,485 (63.5%)	2,709 (54.0%)
Male	51,808 (44.3%)	13,493 (36.5%)	2,309 (46.0%)
Race			
White	40,847 (38.9%)	10,985 (31.7%)	1,732 (35.1%)
Black	60,696 (57.9%)	22,819 (65.8%)	3,079 (62.5%)
Other†	3,335 (3.1%)	861 (2.5%)	119 (2.4%)
Ethnicity			
Hispanic	4,126 (4.6%)	1,123 (4.0%)	177 (3.6%)
Non-Hispanic	85,650 (95.4%)	26,941 (96.0%)	4,764 (96.4%)
Total no. of qualifying encounters	736,192	64,858	12,628
Type of encounter‡			
Outpatient	607,747	23,385	10,562
Inpatient	87,708	36,630	2,324
Emergency Department	31,543	7,581	289

Data are expressed as no. (%).
* Includes only encounters after March 1, 2016
† Includes Asian or Middle Eastern, American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, and patients identifying as having more than 1 race
‡ Some encounters are assigned to more than 1 type

Table 2
Demographics for hypertensive patients with hypokalemia or sleep apnea.

Variable	Hypokalemia			Sleep apnea		
	Not screened $n = 35,937$	Screened $n = 1,004$	*P* value	Not screened $n = 4,866$	Screened $n = 150$	*P* value
Age in years (mean ± SD)	63.0 ± 14.9	55.8 ± 15.4	<.001	57.7 ± 12.6	55.2 ± 12.5	.016
Age in groups			<.001			.283
18–35 y	1,570 (4.4%)	110 (11.0%)		221 (4.5%)	11 (7.3%)	
36–50 y	5,572 (15.5%)	252 (25.1%)		1,144 (23.5%)	40 (26.7%)	
51–65 y	11,463 (31.2%)	329 (32.8%)		1,953 (40.1%)	56 (37.3%)	
>65 y	17,332 (48.2%)	313 (31.1%)		1,548 (31.8%)	43 (28.7%)	
Sex			.180			.002
Female	22,810 (63.5%)	658 (65.5%)		2,609 (53.6%)	100 (66.7%)	
Male	13,126 (36.5%)	346 (34.5%)		2,257 (46.4%)	50 (33.3%)	
Race			<.001			<.001
White	10,755 (32.0%)	215 (21.9%)		1,706 (35.7%)	26 (17.7%)	
Black	22,063 (65.6%)	738 (75.3%)		2,964 (62.0%)	114 (77.6%)	
Other	834 (2.5%)	27 (2.8%)		112 (2.3%)	7 (4.8%)	
Ethnicity			.023			.754
Hispanic	1,098 (4.0%)	22 (2.5%)		171 (3.6%)	6 (4.1%)	
Non-Hispanic	26,067 (96.0%)	852 (97.5%)		4,621 (96.4%)	142 (95.9%)	

Data are expressed as no. (%), except where indicated; *P* values were calculated using chi-squared test for categorical variables and *t*-test for continuous variables

and were excluded from further analysis. Among the remaining 36,941 hypertensive hypokalemic patients, only 1,004 ever had an aldosterone or renin checked at this medical center. In other words, only 2.7% of patients who should be considered for screening for primary aldosteronism had their aldosterone or renin level measured. Comparatively, patients who were appropriately screened had a lower mean age (55.8 vs 63.0 years) than those who were not screened ($P < .001$; Table 2).

Resistant hypertension, that is, uncontrolled blood pressure despite treatment with 3 different antihypertensive medications, is another indication for screening for primary aldosteronism. There was a significant difference in the number of antihypertensive agents prescribed between the screened and not screened group (Table 3). In a logistic regression analysis, the odds of screening did not differ when patients were placed on three or even four antihypertensive agents. However, when a patient was prescribed at least 5 different agents, the odds of screening increased by approximately 50%. About half of the patients in both groups were prescribed a potassium-wasting diuretic, such as furosemide. The odds of screening were not significantly different for patients taking a potassium-wasting diuretic, (adjusted OR 1.16, $P = .133$), suggesting this did not influence the provider's decision to screen for primary aldosteronism. We also considered whether being on a potassium-sparing diuretic, including spironolactone, affected screening rates. Surprisingly, the odds of screening were 2.4-fold greater for patients on a potassium-sparing diuretic (adjusted OR 2.44, $P < .001$), suggesting that being on a mineralocorticoid receptor antagonist was not a barrier for screening.

The diagnosis of primary aldosteronism should be considered in patients with hypertension and hypokalemia, regardless of plasma potassium level. Not surprisingly, patients admitted to the hospital had many more potassium measurements, with an average of 8.4 ± 7.4 tests compared to 1.2 ± 0.8 and 1.4 ± 1.0 tests for outpatient and emergency department encounters, respectively. Patients with moderate to severe hypokalemia (less than 3.0 mEq/L) were more likely to be screened compared to patients with mild hypokalemia (3.0–3.5 mEq/L; OR 1.79, $P < .001$). Only 10% of patients with hypokalemia on a lab value had this captured by the correct ICD-9/10 code. However, coding a diagnosis of hypokalemia appeared to almost double the odds of screening (OR 1.86, $P < .001$). As mentioned, the majority of patients with hypertension and hypokalemia were identified during an inpatient hospitalization.

Table 3
Logistic regression analysis of explanatory variables for screening for primary aldosteronism in patients with both hypertension and hypokalemia.

Variable	Not Screened No. (%)	Screened No. (%)	Unadjusted OR (95% CI)	*p* value	Adjusted OR* (95% CI)	*p* value
Total antihypertensive agents						
0-2 agents	9,673 (49.6)	175 (40.7)	.84 (.63, 1.13)	.261	.78 (.58, 1.04)	.095
3 agents	2,650 (13.7)	57 (13.3)	1.00		1.00	
4 agents	2,085 (10.7)	35 (8.1)	.78 (.52, 1.19)	.253	.84 (.56, 1.28)	.426
5 or more agents	4,995 (25.7)	163 (37.9)	1.50 (1.11, 2.02)	.008	1.48 (1.10, 2.00)	.010
Potassium-sparing diuretic						
Yes	1,426 (7.3)	69 (16.0)	2.34 (1.82, 3.01)	<.001	2.44 (1.89, 3.14)	<.001
No	17,977 (92.7)	361 (84.0)	1.00		1.00	
Potassium-wasting diuretic						
Yes	9,891 (49.0)	225 (47.7)	1.05 (.87, 1.27)	.580	1.16 (.96, 1.40)	.133
No	9,512 (51.0)	205 (52.3)	1.00		1.00	
Median potassium level*						
<3.0 mEq/L	652 (1.8)	56 (5.6)	1.96 (1.51, 2.56)	<.001	1.79 (1.35, 2.37)	<.001
3.0 – 3.5 mEq/L	12,661 (35.3)	532 (53.1)	1.00		1.00	
>3.5 mEq/L	22,621 (63)	414 (41.3)	.45 (.39, .51)	<.001	.49 (.42, .56)	<.001
Hypokalemia coded						
Yes	3,568 (9.9)	178 (17.8)	1.91 (1.62, 2.24)	<.001	1.86 (1.56, 2.20)	<.001
No	32,369 (90.1)	826 (82.3)	1.00		1.00	
Type of index encounter						
Outpatient	6,387 (21.6)	382 (43.4)	1.00		1.00	
Inpatient	22,012 (74.5)	458 (52.1)	.36 (.32, .41)	<.001	.40 (.35, .46)	<.001
Emergency Department	1,142 (3.9)	39 (4.4)	.59 (.42, .81)	.001	.48 (.34, .67)	<.001
Number of qualifying encounters						
1	24,587 (68.4)	406 (40.4)	1.00		1.00	
More than 1	11,250 (31.6)	598 (59.6)	3.08 (2.72, 3.49)	<.001	2.44 (2.12, 2.82)	<.001

* Adjusted for age, sex, race, ethnicity.

Table 4
Fraction of screened patients with elevated aldosterone and/or suppressed renin levels.

Variable	Percentage of patients with an abnormal laboratory value	Total number of patients on which specific test was performed
Serum aldosterone concentration		
≥10 ng/dL	43.6%	935
≥15 ng/dL	28.0%	935
≥25 ng/dL	14.0%	935
Renin measurement		
PRA ≤ 1.0 ng/mL/hr	61.1%	776
DRC ≤ 10 mcU/mL	44.8%	96
Urine aldosterone excretion		
≥12 mcg/24hrs	69.9%	103
≥30 mcg/24hrs	26.2%	103

PRA = plasma renin activity; DRC = direct renin concentration

Nevertheless, hypertensive patients found to have hypokalemia at an outpatient clinic were more likely to undergo screening compared with patients diagnosed either in the inpatient ward or in the emergency department (Table 3). For patients not screened, two-thirds had hypokalemia at only 1 encounter. By comparison, in the screened group, 60% were hypokalemic on multiple encounters.

Determination of the aldosterone-to-renin ratio is the most reliable method of initial screening for primary aldosteronism, as it is more specific than renin measurement and more sensitive than plasma aldosterone alone. In this study, 80% of patients screened had both labs measured simultaneously, indicating that the aldosterone-to-renin ratio was used by the majority of providers for screening for primary aldosteronism. There were 10% of screened patients having 24-hour urinary aldosterone level (Table 4). For patients with serum aldosterone checked, 14% had levels greater than 25 ng/dL, consistent with an aldosterone-producing adenoma. Further, 60% of patients who had renin measured, either with evaluation of plasma renin activity or direct renin concentration, had low or undetectable levels. A total of 8.6% of screened patients were diagnosed with hyperaldosteronism and 20.9% of these patients required an adrenalectomy (Fig. 1).

The Endocrine Society published its new guidelines for primary aldosteronism online on March 2, 2016 when they recommended case detection for patients with hypertension and sleep apnea for the first time. Between May 2, 2016 and December 15, 2017, there were 5,016 patients seen at this institution carrying both diagnoses, and only 150 patients (2.9%) were screened for primary aldosteronism. The majority of patients having sleep apnea were non-Hispanic black women (Table 1). For those who underwent screening, there were significantly more black women. However, when adjusting for these differences, there was no discernible difference in the odds of screening based on body mass index or number of antihypertensive agents, suggesting screening for primary aldosteronism in this group was largely random (Table 5). Only 421 patients (8.3%) also had hypokalemia at their index encounter, but this was not a significant predictor for screening ($P = 0.344$). Finally, patients with obstructive sleep apnea were far less likely to be screened for primary aldosteronism if the sleep apnea was diagnosed during an in patient hospitalization.

Discussion

Screening for primary aldosteronism is recommended for hypertensive patients with hypokalemia and other high-risk hypertensive patients, including those with severe or resistant hypertension, an incidental adrenal mass, or obstructive sleep apnea.[11] We discovered that screening tests were not performed on 97% of patients with hypertension and hypokalemia. These findings are dramatic but parallel results from similar studies. In 1 recent cross-sectional study, less than 10% of general practitioners ordered renin and aldosterone levels for patients at diagnosis of hypertension.[10] Primary care physicians are likely the first contact for hypertensive patients and principle screeners of primary aldosteronism. However, we found that the majority of patients with hypertension and hypokalemia presented during inpatient hospitalization, and here, were 2.5 times less likely than clinic patients to be screened. In general, hospitalized patients receive care by specialists who may be less familiar with screening practices for primary aldosteronism. Therefore, efforts to increase awareness among hospital physicians could lead to improved screening rates of all patients at risk.

Table 5
Characteristics for hypertensive patients with sleep apnea between May 2, 2016 and December 15, 2017.

Variable	Not Screened No. (%)	Screened No. (%)	Unadjusted OR (95% CI)	*p* value	Adjusted OR* (95% CI)	*p* value
BMI in kg/m^2 (mean ±SD)	38.1 ±9.5	40.7 ±10.4	1.03 (1.99, 1.06)	.177	1.03 (.98, 1.07)	.244
Total antihypertensive agents						
0-2 agents	1,405 (71.0)	18 (64.3)	.80 (.24, 2.71)	.726	.61 (.18, 2.07)	.426
3 agents	188 (9.5)	3 (10.7)	1.00		1.00	
4 agents	141 (7.1)	0 (0)				
5 or more agents	245 (12.4)	7 (25)	1.77 (.46, 6.75)	.404	1.41 (.36, 5.58)	.620
Type of Index Encounter						
Outpatient	3,504 (72.7)	124 (83.8)	1.00		1.00	
Inpatient	1,258 (26.1)	22 (14.9)	.55 (.32, .79)	.003	.56 (.28, .89)	.015
Emergency Department	55 (1.1)	2 (1.4)	1.03 (.26, 4.05)	.970	.87 (.22, 3.44)	.843
Hypokalemia						
Yes	406 (8.3)	15 (10.0)	1.21 (.72, 2.05)	.471	1.29 (.76, 2.17)	.344
No	4,460 (91.7)	135 (90.0)	1.00		1.00	

* Adjusted for age, sex, race, ethnicity.

Patients develop hypokalemia in the hospital for a variety of reasons, either because of the physiology of their acute illness or as a byproduct of the interventions they are receiving, as is seen in many postoperative patients. On the other hand, hypokalemia in an ambulatory setting more likely represents a chronic state. We do not know the true prevalence of primary aldosteronism among the 97% patients who were not screened. However, as 1 in 10 people with unselected hypertension are thought to have hyperaldosteronism, we speculate that some of the patients identified in this study have aldosterone overproduction that appears unrecognized. Our study has several other limitations. This was a single-center study, and some patients may have been referred for screening to another tertiary referral hospital or hypertension center in the region. Further, as a retrospective chart review, inaccuracies in diagnosis coding along with incomplete and missing data are both causes for potential bias. In fact, we demonstrated significant deficiencies in coding for hypokalemia, particularly toward patients not screened. Coding can affect both billing and risk stratification of patients. In an effort to better capture billing and patient complexity, hospitals, including this one, have employed coders to scan through medical records and remind providers to document accurate codes. This may partially explain why coding is predictive of screening for primary aldosteronism, at least for hypertensive patients with hypokalemia.

We suspected screening for primary aldosteronism in hypertensive patients already managed with spironolactone may have been avoided because these agents can make interpretation of the aldosterone-to-renin ratio unreliable.[11] However, stopping or substituting such agents before screening is not always necessary. First, mineralocorticoid receptor antagonists are more likely to cause a false-negative result, so if aldosterone is elevated and renin low in these patients then the diagnosis can still be convincingly made. In addition, a reasonable alternative to screening is a therapeutic trial of spironolactone, which has been demonstrated to substantially reduce blood pressure in patients with resistant hypertension.[13] In our study, we found that taking a mineralocorticoid receptor antagonist was not a barrier to screening. Furthermore, our findings dispel the notion that potassium-wasting diuretics impose a barrier for screening. This was a surprising result. For these patients, we suspected primary aldosteronism would be overlooked because hypokalemia is readily attributable to the medication. On the other hand, thiazide-induced hypokalemia, particularly with a low dose, serves as a valuable clue to an underlying primary aldosteronism, as such abnormalities are not typical for most hypertensive patients.

Most providers may be unfamiliar with the association of obstructive sleep apnea and primary aldosteronism. Only recently has primary aldosteronism been realized to be highly prevalent in this subgroup, especially among men. Aldosterone in excess is thought to contribute to the development of sleep apnea, most likely from fluid accumulation in the neck leading to an increase in airway resistance.[14] There has also been shown an association between hyperaldosteronism and obesity.[15] In our study, we saw a very low rate of screening for patients with hypertension and sleep apnea after the Endocrine Society endorsed screening for this at-risk group, reflecting poor compliance with national guidelines. Perhaps only a minority of practitioners treating hypertension are aware of the Endocrine Society guidelines, and there is also difficulty for providers recognizing when such guidelines are updated. Therefore, it is prudent that we find a way to improve the system of disseminating such important information to the clinicians who need it most. Just recently, the American College of Cardiology and the American Heart Association released their guidelines on the prevention, detection, evaluation, and management of hypertension, in which they also endorse screening hypertensive patients with obstructive sleep apnea.[16] Hopefully this endorsement will give more leverage and attention to the risk of primary aldosteronism in these patients.

The optimal screening strategy for primary aldosteronism is not clear. The Japan Endocrine Society employs a wider screening strategy, recommending measurement of aldosterone and renin for all patients with newly diagnosed hypertension, despite having a similar prevalence of primary aldosteronism.[17,18] Critics of this approach argue that a broad screening strategy offers a low yield, a high number of false positives, and a high cost when patients unnecessarily undergo complete diagnostic evaluation. However, 1 reason primary aldosteronism is underdiagnosed is because not all patients with this condition have an obvious clinical syndrome, including absence of low potassium or even high blood pressure.[19,20] Still, we find that even patients with the classic phenotype do not undergo the appropriate investigations for detecting primary aldosteronism. Systematic screening could bring about a substantial increase in the diagnostic rate of primary aldosteronism and, in turn, identify more patients with a surgically curable disease. While clinical judgment needs to supersede rote application of guidelines, it should help physicians to keep primary aldosteronism in mind.

Conflicts of interest

Funding for this study was provided by the Department of Surgery at the University of Chicago.

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References

1. Douma S, Petidis K, Doumas M, Papaefthimiou P, Triantafyllou A, Kartali N, et al. Prevalence of primary hyperaldosteronism in resistant hypertension: a retrospective observational study. *Lancet*. 2008;371:1921–1926.
2. Rossi GP, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol*. 2006;48:2293–2300.
3. Mulatero P, Stowasser M, Loh KC, Fardella CE, Gordon RD, Mosso L, et al. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. *J Clin Endocrinol Metab*. 2004;89:1045–1050.
4. Monticone S, D'Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2018;6:41–50.
5. Williams TA, Lenders JWM, Mulatero P, Burrello J, Rottenkolber M, Adolf C, et al. Outcomes after adrenalectomy for unilateral primary aldosteronism: an international consensus on outcome measures and analysis of remission rates in an international cohort. *Lancet Diabetes Endocrinol*. 2017;5:689–699.
6. Sechi LA, Novello M, Lapenna R, Baroselli S, Nadalini E, Colussi GL, et al. Long-term renal outcomes in patients with primary aldosteronism. *JAMA*. 2006;295:2638–2645.
7. Gaddam K, Corros C, Pimenta E, Ahmed M, Denney T, Aban I, et al. Rapid reversal of left ventricular hypertrophy and intracardiac volume overload in patients with resistant hypertension and hyperaldosteronism: a prospective clinical study. *Hypertens (Dallas, Tex 1979)*. 2010;55:1137–1142.
8. Catena C, Colussi G, Nadalini E, Chiuch A, Baroselli S, Lapenna R, et al. Cardiovascular outcomes in patients with primary aldosteronism after treatment. *Arch Intern Med*. 2008;168:80–85.
9. Buffolo F, Monticone S, Burrello J, Tetti M, Veglio F, Williams TA, et al. Is primary aldosteronism still largely unrecognized. *Horm Metab Res*. 2017;49:908–914.
10. Mulatero P, Monticone S, Burrello J, Veglio F, Williams TA, Funder J. Guidelines for primary aldosteronism: uptake by primary care physicians in Europe. *J Hypertens*. 2016;34:2253–2257.
11. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101:1889–1916.
12. Wolley MJ, Pimenta E, Calhoun D, Gordon RD, Cowley D, Stowasser M. Treatment of primary aldosteronism is associated with a reduction in the severity of obstructive sleep apnoea. *J Hum Hypertens*. 2017;31:561–567.
13. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet (London, England)*. 2015;386:2059–2068.
14. Di Murro A, Petramala L, Cotesta D, Zinnamosca L, Crescenzi E, Marinelli C, et al. Renin-angiotensin-aldosterone system in patients with sleep apnoea: prevalence of primary aldosteronism. *J Renin Angiotensin Aldosterone Syst*. 2010;11:165–172.
15. Goodfriend TL, Calhoun DA. Resistant hypertension, obesity, sleep apnea, and aldosterone: theory and therapy. *Hypertens (Dallas, Texas)*. 2004;43:518–524.
16. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2018;71:e13–115283.
17. Nishikawa T, Omura M, Satoh F, Shibata H, Takahashi K, Tamura N, et al. Guidelines for the diagnosis and treatment of primary aldosteronism—the Japan Endocrine Society 2009. *Endocr J*. 2011;58:711–721.
18. Omura M, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. *Hypertens Res*. 2004;27:193–202.
19. Rossi GP. A comprehensive review of the clinical aspects of primary aldosteronism. *Nat Rev Endocrinol*. 2011;7:485–495.
20. Brown JM, Robinson-Cohen C, Luque-Fernandez MA, Allison MA, Baudrand R, Ix JH, et al. The spectrum of subclinical primary aldosteronism and incident hypertension: a cohort study. *Ann Intern Med*. 2017;167:630–641.

Discussion

Dr Christopher R McHenry (Cleveland, OH): Brian, excellent presentation.

I think the data from many of our centers in Europe where all patients with hypertension are screened for hyperaldosteronism have shown that up to 10% of these patients have potential hyperaldosteronism. I just want to ask you to comment if you think we can simplify the guidelines. Perhaps a recommendation should be that all patients with hypertension, as part of their initial evaluation, should get a serum aldosterone level and a plasma renin activity.

The second question is about the relationship between hyperaldosteronism and sleep apnea. I heard the rationale for the guidelines from the Endocrine Society about why these patients should be a group that we test. But is there really an association? Do patients with hypertension and known obstructive sleep apnea actually have a higher incidence of hyperaldosteronism?

Dr Brian C Ruhle: To answer your first question, I think it's probably somewhere in between. In Japan, their guidelines recommend screening all hypertensive patients for primary aldosteronism versus the more selective strategies that we utilize here in the United States.

I guess the answer is that we are missing patients with hyperaldosteronism, but you have to consider the cost of screening all hypertensives. The answer is probably somewhere in between.

For patients with hypertension and sleep apnea, the initial research on it showed an association between sleep apnea and resistant hypertension. There is actually a recent paper that came out in *Nature* that showed patients with primary aldosteronism and sleep apnea could see a decrease in the severity of their sleep apnea or even a cure, if you treat their primary aldosteronism.

So there is some evidence emerging that there is an association, and that treating these patients benefits both conditions. I think it's a new thought, so it's work that's still ongoing.

Dr Richard Hodin (Boston, MA): I certainly agree that we should make efforts to increase awareness. We have been trying to do that at our institution. It's been a terrible failure for a number of years. So I am wondering if you have any ideas about how to use your electronic medical record perhaps to alert primary care doctors and other physicians to test their patients.

Dr Brian C Ruhle: There's been some research recently on patients with primary hyperparathyroidism and using the electronic health record to flag calcium levels, to identify these patients to prompt screening. We can envision something similar where patients who have a diagnosis of hypertension and who have a potassium measurement of less than 3.5 would have the EMR flagging them to alert the clinician that maybe primary aldosteronism should be considered. Screening in the hospital is difficult and not really recommended for patients who are in bed all day, but I think the part that we are missing is when patients leave the hospital and follow up in clinic.

Dr Cortney Lee (Lexington, KY): When these patients are worked up as inpatients, they tend to have labs to rule out other treatable causes of hypertension, which is going to include hyperaldosteronism. We don't want to get extra tests that are going to cause everybody to get worried about things that are not pertinent. What kind of ideas do you have to get the patient to understand the association and need for follow-up?

Dr Brian C Ruhle: I guess ideally the patient would follow up with their primary care physician, and alert them about the course of their hospital stay and how primary aldosteronism came to mind because their blood pressure in the hospital was difficult

to control and their potassium dropped. I think 1 of the issues that we have at the University of Chicago is that most of these patients only had 1 encounter, and we lose patients to follow-up as well. That's going to be another barrier to address.

Dr Jose Gustavo Olijnyk (Porto Alegre, Brazil): Congratulations on your presentation. I would like to know if you have any information in your data bank about the body mass index. It seems this comorbidity and sleep apnea are common for patients who undergo bariatric surgery. And I would like to know if you think these patients could be screened for this disease.

Dr Brian C Ruhle: Do you mean screening for the disease because of obesity as well as hypertension? Yes, the association between obesity and sleep apnea is well demonstrated, so I definitely think it's something to think about. We did look at BMI in the sleep apnea group and we didn't see a difference in the decision to screen based on BMI. But what we did find was that patients in this group tended to have a higher BMI (close to 40), which is a little skewed in our data.