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Discriminating Pheochromocytomas from Other Adrenal Lesions: The Dilemma of Elevated Catecholamines

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Abstract

Introduction—Screening tests for pheochromocytoma involve measuring levels of catecholamines in the urine or plasma, which have significant false positive rates. We reviewed patients with adrenal masses and elevated levels of catecholamines to determine the value of different preoperative tests in diagnosing pheochromocytomas.

Methods—A retrospective chart review identified patients who underwent adrenalectomy between 1997 and 2011 with elevation of urine or serum catecholamines. A database of clinicopathologic factors was created including preoperative urine and plasma metanephrines, normetanephrines, vanillylmandelic acid, and fractionated catecholamines, and tumor dimensions on imaging and pathology.

Results—Seventy patients underwent adrenalectomy due to presence of an adrenal mass and elevation of catecholamines or normetanephrines or metanephrines. Forty-six had pathologically confirmed pheochromocytomas. To improve our ability to discriminate between pheochromocytoma and other pathology, we examined different combinations of clinicopathologic factors and catecholamine levels and found the best test was a scoring system. Points are awarded for a hierarchy of elevated NM, norepinephrine, metanephrines, with additional points received for age <50 and size on imaging >3.3 cm. A score of 2 is suggestive of pheochromocytoma, with a positive predictive value of 86–87%, while a score of 4 is diagnostic with positive predictive value of 100%.

Conclusion—We found that urine/serum normetanephrine levels were the most valuable screening tool, however a score examining the size of adrenal mass on preoperative CT, age, and either plasma or urine norepinephrine, metanephrine and normetanephrine values leads to a higher positive predictive value, making this scoring system superior to individual lab tests.

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INTRODUCTION

Pheochromocytomas are tumors derived from the adrenal medulla, with an incidence of 0.8 per 100,000 individuals¹. The classic presentation involves a constellation of clinical features, including hypertension, headaches, sweating, palpitations, and anxiety². Pheochromocytomas, although rare, may account for up to 0.1–0.3% of cases of hypertension^{3,4}. As imaging studies have improved over time, increasing numbers of asymptomatic patients are being found with adrenal masses. Incidentally discovered adrenal masses may be pheochromocytomas in as many as 5% of cases⁵, and therefore a reliable presurgical method for making the diagnosis is important.

The diagnosis of pheochromocytoma has evolved over time. Early on it became clear that the clinical features were due primarily to excess catecholamine secretion. In the 1950s, 24 hour urinary catecholamine excretion became the test of choice due to the episodic nature of secretion^{6,7}. This later included the O-methylated metabolites of norepinephrine and epinephrine, normetanephrine and metanephrine, and vanillylmandelic acid (VMA), their final breakdown product.

Many studies have assessed which screening test is the best. Lenders et al. addressed this in 2002, by assessing 858 patients at risk for pheochromocytoma. Patients were identified due to signs suggestive of a pheochromocytoma in the face of an incidentaloma, or those who had a genetic predisposition to development of a pheochromocytoma. Patients had measurements of plasma and urinary catecholamines, urinary fractionated metanephrines and VMA, as well as plasma values of free metanephrines. Findings in this study confirmed that the plasma free metanephrine was the best individual screening test, with 99% sensitivity and 89% specificity. They noted a very low false negative rate, with only 3 of 214 patients with pheochromocytoma having normal values⁸.

Pheochromocytoma is treated by resection, which was initially associated with poor outcomes, due to crisis brought about by excess catecholamine secretion. The first report of surgical excision of a pheochromocytoma in North America was by Dr. Charles Mayo in 1927⁹. The Mayo Clinic reported decreased operative mortality in the 1950s, with successful removal of 61 pheochromocytomas from 51 patients over 11 years, by using alpha blockade with phenoxybenzamine to treat hypertension and epinephrine to treat hypotension¹⁰. The preoperative and intraoperative treatment of these patients has continued to improve, but many patients suspected of having this tumor undergo unnecessary operation because of false-positive test results. In this study, we set out to evaluate the levels of catecholamines in our cohort of patients undergoing adrenalectomy suspected of having pheochromocytoma, and to develop a method for improving the selection of patients for operation.

METHODS

Following IRB approval, a retrospective chart review was performed on all patients who underwent adrenalectomy from 1997 to 2011 at the University of Iowa Hospitals and Clinics. Only patients who underwent adrenalectomy for suspected pheochromocytoma were enrolled in this study. Patients were suspected of having a pheochromocytoma if they

had an adrenal mass on imaging with elevated laboratory values of plasma or urine metanephrine, normetanephrine, and/or fractionated catecholamines (epinephrine, norepinephrine, dopamine), with or without symptoms. All patients underwent pre-operative alpha blockade prior to adrenalectomy with an incrementally increasing dose of phenoxybenzamine over 2 weeks (10 mg bid for 4 days, then 10 mg tid for 4 days, 20 mg bid for 4 days, then 20 mg in am/10 mg at noon/20 mg at hs x 4 days; the last dose given the evening prior to surgery). Beta-blockade was begun 3 days prior to surgery, with propranolol at 10 mg tid, with the last dose given the morning of surgery.

A database was created which included clinical, operative, and laboratory variables. Imaging results were recorded by size, scan type (CT or MRI), and laterality, and available scans were reviewed by an attending radiologist and recorded as either consistent with adenoma or indeterminate/not consistent with adenoma (and therefore possibly a pheochromocytoma). On CT, consistent with adenoma was defined as pre-contrast Hounsfield units of <10, or enhancement with contrast with >40% washout after 15 minutes¹¹. On MRI, consistent with adenoma was defined as high T1 signal relative to the liver and spleen with >20% drop out-of-phase, or low T2 signal¹².

Geometric means for lab values and tumor characteristics were used because these variables are log-normally distributed. Lab values were reported as a fold change over the upper limit of normal. Univariate statistical analysis was performed using the Student's *t* test for continuous variables, and Chi-square and Fisher's exact tests were used for frequency association of categorical variables. All tests were two sided and a $p < 0.05$ was defined as significant. Receiver operating characteristic (ROC) analysis was used to assess the diagnostic predictive capability of individual tests. Using this method, empiric cutoffs were determined for each laboratory value that yielded maximum predictive capacity. To determine a composite multivariable scoring system, logistic regression coefficients were utilized to weight individual components and a scoring system was determined and evaluated by ROC analysis. All statistical analyses were performed with Stata 11.2 (StataCorp, College Station, TX).

RESULTS

Seventy patients had adrenalectomy for suspected pheochromocytoma. All patients underwent preoperative alpha blockade and no complications from preoperative blockade were observed. On final pathology, 46 patients (65.7%) were determined to have a histologic diagnosis of pheochromocytoma. The remaining 24 patients (34.3%) had other pathologic diagnoses, including cyst, hyperplasia, cortical adenoma and normal adrenal tissue. Demographic characteristics are listed in Table 1. Of note in the pheochromocytoma group, 6 patients had von Hippel Lindau Syndrome, and 1 patient had Neurofibromatosis Type 1.

All laboratory values are summarized in Table 2. Serum metanephrine and normetanephrine levels were the most commonly ordered tests in our cohort. The pheochromocytoma group had significantly higher mean preoperative levels of normetanephrine, metanephrine, and norepinephrine relative to the non-pheochromocytoma group by both urine and blood levels.

The non-pheochromocytoma group had a significant number of positive results for most urine and plasma tests demonstrating the low positive predictive value of individual tests and highlighting the diagnostic dilemma of elevated catecholamines. Interestingly, for the most commonly ordered tests (metanephrine and normetanephrine) we found that a positive value for the plasma test was more highly associated with the diagnosis of pheochromocytoma than the urine test. Further, of all laboratory values, only positive results for plasma and urine normetanephrine and plasma metanephrine were associated with the diagnosis of pheochromocytoma (Table 2, $p<0.05$).

All patients underwent cross-sectional imaging, with imaging available for re-review in 53 (75.7%) patients, including 36/46 (78.3%) patients found to have pheochromocytoma and 17/24 (70.8%) patients with other adrenal pathology. Thirty-one of thirty-nine patients with CT scans for review had findings not consistent with adenoma (and therefore possibly pheochromocytoma), of which 25 of these 31 (80.6%) were determined to be pheochromocytoma by histology. Of the 26 patients with pheochromocytoma who had CTs, 25 (96.2%) had findings not consistent with adenoma, as compared to 6/13 (46.2%, $p<0.001$) patients found to have other histology after resection. MRI images were reviewed for 20 patients. Imaging that was not consistent with adenoma was found in 17 patients, including 15/16 (93.8%) patients with histologically proven pheochromocytoma and 2/4 (50.0%) patients with other pathology ($p=0.09$). In total, when all imaging modalities were assessed, 43/53 (81.1%) patients were correctly identified, with false positives accounting for 8 of the 10 misidentifications.

Receiver operating characteristic (ROC) curves were calculated to assess the association of individual tests and the diagnosis of pheochromocytoma. An area under the ROC curve (AUC) of 50% would indicate chance agreement, with strength of association increasing as AUC approaches 100%. The AUC for individual tests is shown in Table 3, with plasma normetanephrine showing the highest predictive power. To improve univariate predictive power, we developed empiric cutoffs, which improved the predictive power for all individual tests (Table 3).

To further enhance the predictive power of preoperative tests to determine pheochromocytoma, we sought to create a multivariate prediction score. Two tests (plasma normetanephrine, metanephrine) and two clinical variables (age, tumor size) were utilized because they were most highly associated with pheochromocytoma on univariate ROC analysis (Table 3). To design the multivariate pheochromocytoma score, the tests were modeled independently by logistic regression, which is defined in Table 4. Tests for which no results were available were considered negative by this model. The use of this scoring system improved the AUC to 91%, compared to 89% for the best single test (plasma normetanephrine). Based on the results in Figure 1, we suggest a score of 2 as a screening cutoff where patients with a score below 2 are ruled out for pheochromocytoma (89% NPV). A score of 3 or more is diagnostic for pheochromocytoma (92% PPV), which represents a significant improvement over the 80% PPV for the best individual test.

DISCUSSION

Interpretation of elevated catecholamines and their metabolites in the face of an adrenal mass can pose a diagnostic and therapeutic dilemma. The optimal approach has been debated for decades, with evolution from 24 hour urine VMA and catecholamines giving way to plasma catecholamine metabolite levels¹³. Sawka et al. assessed the diagnostic efficacy of various tests in a group of 349 patients (33 with histologically confirmed pheochromocytoma/paraganglioma) who had elevated levels of catecholamines. Sensitivity in this group for plasma metanephrines was 97%, with a specificity of 85%. For urinary values, a sensitivity of 90% was noted, with a specificity of 98%. False negative urinary results were reported in 3 patients, two of whom had MEN2. They concluded that urinary metanephrines and catecholamines were preferred in patients with sporadic pheochromocytoma, but fractionated plasma metanephrines might be favored in patients with a genetic predisposition¹⁴.

Hickman et al. assessed plasma and urine markers in 22 patients with pheochromocytoma. Plasma metanephrine had 100% sensitivity with 98% specificity (using a cutoff of 1.2 fold elevation of upper limit of normal) as compared to their urinary counterparts with 86% sensitivity and 95% specificity. Metanephrine was superior in this study to catecholamines, which showed plasma sensitivity of 79% (specificity 71%), compared to urinary catecholamine sensitivity of 79% (specificity of 88%)¹⁵. In a Danish study of 185 patients suspected to have a pheochromocytoma, 11 patients ultimately had the diagnosis confirmed. Using a cutoff of greater than the upper limit of normal, plasma metanephrines were elevated in 10/11 pheochromocytoma patients (and false positives in 2 patients), with elevation of urinary catecholamines in all (false positive in 12 patients). This group noted the best test to be plasma metanephrines (which includes both metanephrine and normetanephrine) as well, with a sensitivity of 91% (specificity of 99%)¹⁶.

Imaging findings that distinguish between adenoma and other adrenal pathology on imaging have been reported, but this differentiation can be difficult because pheochromocytomas frequently have characteristics that mimic other lesions^{17,18}. We found that when we used accepted criteria for classifying a lesion as possibly being a pheochromocytoma by CT (not consistent with adenoma), that 25/26 pheochromocytomas met these criteria, but so did 6/13 of lesions with non-pheochromocytoma pathology. With MRI, 15/16 pheochromocytoma patients had lesions that met criteria, but so did 2/4 of patients with other adrenal pathology. Similar to biochemical testing, imaging characteristics can be helpful to distinguish pheochromocytomas from other adrenal lesions, but these gave an incorrect result almost 20% of the time in this series, and therefore are not definitive and must be interpreted in the context of other clinical and laboratory data.

These data demonstrate the quandary physicians face regarding the best method to diagnose pheochromocytomas. The problem of false positive results persists. Certain medications are known to interfere with measurements of these lab values. Eisenhofer et al. evaluated tricyclic antidepressants, sympathomimetics, phenoxybenzamine (as well as selective alpha blockers), calcium channel blockers, and β -blockers, and noted that 45% of patients with false positive values of plasma normetanephrine were attributable to tricyclic

antidepressants and phenoxybenzamine¹⁹. Tricyclic antidepressants are thought to increase norepinephrine levels due to the inhibition of the reuptake of monoamines²⁰. Eisenhofer proposed the use of a plasma normetanephrine:norepinephrine ratio of >0.52 or metanephrine:epinephrine >4.2 to tease out patients with low elevation of plasma metanephrines. In our group of 24 false positives, 12 patients were taking β -Blockers (6 atenolol, 6 metoprolol), 2 were taking phenoxybenzamine, and 4 were taking tricyclics (amitriptyline). It has also been recommended to draw blood with the patient supine¹⁵, or use the clonidine suppression test¹⁷, which suppresses catecholamine production in normal patients but not those with pheochromocytoma²¹.

Current methods of diagnosis still leave something to be desired. Of 70 patients suspected to have a pheochromocytoma in our study, only 46 were confirmed by histologic diagnosis. Our practice has been to operate on those with an adrenal mass and elevation of urine/serum catecholamines or their metabolites, because it is difficult to disprove that these patients have a pheochromocytoma. Using these broad criteria, we had a 34% false positive rate for the diagnosis of pheochromocytoma. Had we utilized other suggested schemes our false positive rate would range from 8%-88%. For example, using a cutoff of 2–4 fold elevation we would have missed 4 patients (8.5%) with pheochromocytoma while only potentially excluding 13/24 non-pheo patients. Using Sawka's criteria of elevated plasma metanephrine for familial cases would have correctly identified 4/7 cases, but an additional 3/14 would have been false positives. For non-familial patients, use of elevated urinary metanephrine would have correctly identified 21/24 pheochromocytoma patients, but with 12/14 false-positives. Using Eisenhofer's values, a ratio of NM:NE >0.52 was found in 1/11 of those with pheochromocytomas and 1/7 (14%) of those with benign pathology. For the M:E ratio, 2/10 patients with pheochromocytomas fit the criteria of >4.2 , with an additional 2/6 without pheochromocytoma also falling into this category. The best test belonged to Lenders et al.¹¹, where in our group 23/32 pheochromocytoma patients were found to have elevation of NM >2.19 nmol/L; only 1/12 non-pheochromocytoma patients had values above this level. A M >1.2 nmol/L was found in 13/30 pheochromocytoma patients, with no false-positives.

High sensitivity can be achieved using a variety of these different tests, but the more difficult issue is specificity. To improve upon this, we developed a scoring system taking into account multiple factors, including age, normetanephrine, metanephrine, and tumor size. With this scoring system, a score ≥ 2 had a positive predictive value of 87%. Only seven non-pheochromocytoma patients had a score ≥ 2 which led to a false positive rate of 10%, which was an improvement from our baseline of 34% when using any elevation of catecholamines or their metabolites. However, a score of 4 or higher improves the positive predictive value to 100%. We would have improved our negative exploration rate for this group of patients had we had instituted this scoring system.

One limitation of our study is not including patients without suspected pheochromocytomas as a control population. Overall however, the use of this scoring system would have led to a reduced false positive rate and thereby reduced the number of patients undergoing unnecessary preoperative alpha-blockade and adrenalectomy. This score needs to be validated in a prospective study, however. We conclude that this simple score be calculated

to facilitate deciding whether patients are selected for exploration, or observation and retesting after cessation of potentially interfering medications.

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SYNOPSIS

Biochemical tests for the detection of pheochromocytoma are marked by high false positive rates complicating the presurgical diagnosis. We found that elevated urine/serum normetanephrines were the most sensitive screening tool, and that using a score examining the size of adrenal mass on preoperative CT scan, and either plasma or urine norepinephrine, metanephrine and normetanephrine values lead to a much higher positive predictive value than individual tests alone.

Figure 1. Multivariable Score Enhances Identification of Patients with Pheochromocytoma in This High Risk Patient Population

Sample Score Distribution by Pheochromocytoma Diagnosis

Patients were assigned a score based on the system described in Table 4. A score of 3 was considered diagnostic of pheochromocytoma, as 34/47 patients with pheochromocytoma had this score or above, while only 3/24 without pheochromocytoma reached this score. A score 1–2 suggested that further screening was necessary, while that of 0 essentially ruled out pheochromocytoma.

Table 1**Pheochromocytoma Demographic and Clinical Characteristics**

Characteristic	Pheochromocytoma	Non-Pheochromocytoma	P value
N	46	24	
Age (mean, [Range])	50.3 [12–79]	58.0 [24–82]	0.034
Gender			0.701
Male	17 (37%)	14 (58%)	
Female	29 (63%)	10 (42%)	
Associated Disorders			0.068
Sporadic	39 (85%)	23 (96%)	
VHL	6 (13%)	0	
NF1	1 (2%)	0	
MEN2A	0 (0%)	1 (4%)	0.061
Method of Operation			
Open	20 (43%)	5 (21%)	
Lap	26 (57%)	19 (79%)	0.066
Size on Imaging (median, cm [Range])	4.0 [1.5–11.5]	3.1 [1.0–7.0]	
Pathology Size (median, cm [Range])	7.8 [3.9–13.0]	7.6 [4.0–19.9]	0.536
Tumor Weight (median, g [Range])	39.0 [11.6–870.0]	24.0 [2.5–225.0]	0.002
Location			0.423
Right	21 (46%)	8 (33%)	
Left	21 (46%)	15 (63%)	
Bilateral	4 (9%)	1 (4%)	
MIBG +	2/3 (67%)	4/7 (57%)	0.78
Pathologic Diagnosis			NA
Cortical adenoma	NA	14 (58%)	
Normal adrenal		2 (8%)	
Cyst		3 (13%)	
Hyperplasia		5 (21%)	

NA=Not Applicable

Table 2

Distribution of catecholamine lab values

Catecholamines	Sample	Measure	Pheochromocytoma	Non-pheo	P value
Normetanephrine	Urine	R	5.58±5.31	1.24±1.22	0.005
		Positive	17/17 (100%)	6/9 (67%)	0.032
	Plasma	R	10.68±12.44	0.99±0.96	<0.001
		Positive	32/33 (97%)	8/13 (62%)	0.005
Metanephrine	Urine	R	5.85±8.73	3.68±4.79	0.352
		Positive	17/19 (89%)	11/12 (92%)	1.000
	Plasma	R	4.18±5.73	0.32±0.66	0.002
		Positive	21/33 (64%)	3/14 (21%)	0.011
Epinephrine	Urine	R	7.52±25.57	0.24±0.57	0.211
		Positive	6/18 (33%)	2/12 (17%)	0.419
	Plasma	R	1.43±4.24	0±0	0.215
		Positive	2/11 (18%)	1/9 (11%)	1.000
Norepinephrine	Urine	R	4.77±5.43	0.93±0.99	0.013
		Positive	15/18 (84%)	6/11 (55%)	0.197
	Plasma	R	21.26±59.25	1.21±1.21	0.041
		Positive	12/14 (86%)	6/9 (67%)	0.343
Dopamine	Urine	R	1.08±2.11	1.61±1.61	0.230
		Positive	6/13 (46%)	4/6 (67%)	0.628
	Plasma	R	10.45±27.30	0.96±1.49	0.456
		Positive	7/10 (70 %)	2/6 (33%)	0.302

R: Ratio of laboratory value divided by the upper limit of normal. Positive: Positive value higher than the upper limit of normal over the total number of patients having had that test. P values are χ^2 or Fisher's exact test for categorical frequencies and Wilcoxon rank sum test for ratios.

Table 3

Area under the ROC curve (AUC) of individual catecholamine tests to predict pheochromocytoma

Test	Urine	Plasma
Positive above upper limit of normal		
Metanephrine	49%	71%
Normetanephrine	67%	68%
Epinephrine	58%	54%
Norepinephrine	65%	60%
Dopamine	40%	68%
Positive above empirical cutoff		
Metanephrine	63% (1.34)	76% (1.34)
Normetanephrine	80% (1.63)	89% (1.70)
Epinephrine	63% (1.32)	NA
Norepinephrine	79% (1.62)	78% (2.18)
Dopamine	NA	NA
Other Variables		
Age<50	66%	
Size on imaging >3.3 cm	63%	

The number in parenthesis indicates the value used as an empirical cutoff to yield the highest predictive value. For example, for urine metanephrine, we found that using a cutoff value of 1.34 times the upper limit of normal as defined by the laboratory performing the test yielded a higher predictive value than any other definition of a positive test.

Table 4

Proposed scoring system

Test	Points assigned
Normetanephrine positive ¹	2
Metanephrine positive ²	1
Age<50	1
Image Size>3.3	1
AUC	91%

Total Score Interpretation	Sensitivity	Specificity	PPV	NPV
1	100%	42%	77%	100%
2 (Screen)	96%	71%	86%	89%
3 (Diagnostic)	74%	88%	92%	64%
4	46%	100%	100%	49%
5	11%	100%	100%	37%

¹ Plasma or urine value greater than 1.34 times normal

² Plasma value greater than 1.70 times normal or urine value greater than 1.63 times normal