Adrenal Incidentaloma, Borderline Elevations of Urine or Plasma Metanephrine Levels, and the “Subclinical” Pheochromocytoma

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Objective: To assess the risk of pheochromocytoma in patients with borderline-elevated urine or plasma metanephrine levels.

Design: Retrospective review.

Setting: University tertiary care center.

Patients: Forty-two consecutive patients with adrenal incidentalomas (defined as adrenal tumors identified during routine imaging for another condition) who were treated at the UCSF (University of California, San Francisco) Medical Center between January 1, 1995, and July 31, 2005. Patients with genetic syndromes were excluded.

Intervention: Laparoscopic adrenalectomy for adrenal incidentaloma based on size criteria and preoperative hormonal test results.

Main Outcomes Measures: Urine or plasma metanephrine and catecholamine levels, tumor size, and presence of pheochromocytoma.

Results: Of 42 patients, 14 (33%) had a pheochromocytoma (11 of whom had clear-cut elevations in urine or plasma metanephrine levels defined as greater than 2 times the upper limit of normal) and 28 did not. Ten of the 42 patients (24%) had borderline elevations in urine or plasma metanephrine levels (defined as 1-2 times the upper limit of normal), 3 of whom had a pheochromocytoma (30%). Of patients with borderline elevations, mean±SD tumor size was 5.4±3.1 and 4.8±1.9 cm for patients with and without pheochromocytoma, respectively (P=.37). In these 10 patients, no clinical factors (age, sex, hypertension, presence of symptoms, number of antihypertensive medications, preoperative hemodynamics, or size of tumor on computed tomographic scan) allowed differentiation between those with and without pheochromocytoma.

Conclusions: Thirty percent of patients with adrenal incidentaloma and borderline-elevated urine or plasma metanephrine levels had a pheochromocytoma. Clinical factors cannot distinguish between those with and without pheochromocytoma. In this group of patients, we advocate either routine alpha-blockade preoperatively or further diagnostic tests to better characterize the tumor.

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N ADRENAL INCIDEN-
taloma is an adrenal tu-
mor that is discovered dur-
ing an imaging procedure
done for reasons other than
adrenal disease. Although the true inci-
dence of adrenal tumors is unknown, the
prevalence of incidentalomas disclosed on
computed tomography is approximately
3% to 5%.1,2 Furthermore, the prevalence
increases with age. Autopsy studies have
shown that, while the rate of adrenal in-
cidentaloma is only 1% for those younger
than 30 years, it is as high as 7% for those
older than 70 years.2 Clearly, adrenal in-
cidentalomas represent an important health
care problem that will only increase in mag-
nitude as technology improves and the el-
derly population escalates.

Fortunately, most incidentalomas are
small and of little clinical consequence.
The wide variety of adrenal tumors that
may present as an incidentaloma can be
classified as functional (pheochromocy-
toma, Cushing syndrome, aldoster-
onoma, and androgen-secreting tumors),
malignant (metastatic disease and non-
functional adrenocortical cancer), and
nonfunctional, nonmalignant (eg, corti-
cal adenoma, myelolipoma, and cyst).
Given this broad spectrum of potential tu-
mors, appropriate workup is crucial to ef-
fective management. The 2002 National
Institutes of Health State of the Science
Conference on the “Management of the
Clinically Inapparent Adrenal Mass (‘in-
cidentaloma’)” recommended that pa-
tients with an incidentaloma undergo a
1-mg dexamethasone suppression test, plasma aldosterone to renin ratio determination, and plasma metanephrine level measurement.2 If a tumor is hormonally inactive, then the decision to resect the tumor is based on size. Most groups recommend resection of all tumors larger than 5 to 6 cm and resection of tumors between 3 and 6 cm after consideration of the patient’s comorbidities and age.2,4 As with any adrenal tumor, it is critical to rule out pheochromocytoma when dealing with incidentalomas. Pheochromocytoma is a potentially life-threatening disease if left untreated, but it may be cured by surgical resection. Many physicians still rely on 24-hour urine metanephrine levels as the screening test of choice because of the high sensitivity of the plasma metanephrine test yields far too many false-positive results when used as a screening test.5,6 Only 40% of patients with pheochromocytoma present with the classic constellation of episodic hypertension, headaches, diaphoresis, and flushing.7,9 Up to 40% of patients with pheochromocytoma have no symptoms and present with only an adrenal incidentaloma.7,9 This latter group of patients is often referred to as having a “subclinical” pheochromocytoma. Most of these patients have biochemical evidence of catecholamine excess, by either plasma or urine metanephrine screening. The Study Group on Adrenal Tumors of the Italian Society of Endocrinology found that, in more than 1000 patients with incidentaloma, 3.4% had a diagnosis of subclinical pheochromocytoma; of 22 patients with available data, 19 (86%) had a positive urine metanephrine screening test result.3 However, a certain portion of patients with adrenal incidentalomas have borderline elevations of either the urine or plasma metanephrine levels in a range that is 1 to 2 times the upper limit of normal. Patients with borderline elevations represent a diagnostic and therapeutic dilemma because few data are available that estimate a patient’s risk for pheochromocytoma in the setting of borderline-elevated metanephrine levels. As such, it is difficult to determine whether these patients require resection or medical therapy. Our study wanted to determine how many patients with borderline-elevated metanephrine levels will ultimately have a pheochromocytoma and to make a rational recommendation for disease management in this problematic group of patients.

### METHODS

We performed a retrospective cohort study of all patients who underwent adrenalectomy by one surgeon at a tertiary referral center between January 1, 1995, and July 31, 2005. An adrenal incidentaloma was defined as an adrenal tumor identified incidentally during routine imaging for another condition. We excluded patients who underwent imaging for staging of a non-adrenal malignant neoplasm. A computerized database was used to identify 42 patients with adrenal incidentaloma who underwent adrenalectomy. Patients with known multiple endocrine neoplasia syndromes and von Hippel-Lindau disease were excluded because of the high likelihood of coexisting pheochromocytoma. The clinical presentation, indications for surgery, and final pathologic analysis results were recorded for each patient. We collected the following baseline variables as a review of the medical record: age at operation, sex, body mass index, size of tumor, presence of classic symptoms, number of antihypertensive medications, average preoperative hemodynamic values (systolic pressure, diastolic pressure, and heart rate), operative time, complications, final pathologic analysis results, and postoperative length of stay. Differences in these variables between (1) patients with and without pheochromocytoma and (2) patients with elevated, normal, or borderline-elevated metanephrine levels were compared using the unpaired, 2-tailed $t$ test and $\chi^2$ analysis (Stata statistical software, version 9; StataCorp, College Station, Texas). Laboratory data included levels of potassium; cortisol; aldosterone, renin, metanephrines, and vanillylmandelic acid in the plasma; and metanephrines and vanillylmandelic acid in the urine. Elevations in urine or plasma metanephrine levels were calculated as a multiple of the upper limit of normal. Urine or plasma metanephrine levels greater than 2 times the upper limit of normal were considered diagnostic of a pheochromocytoma.10 Urine or plasma metanephrine levels between 1 and 2 times the upper limit of normal were considered equivocal or “borderline-elevated” results. Urine or plasma metanephrine levels less than the upper limit of normal ruled out the presence of a pheochromocytoma. All patients with elevated or borderline-elevated metanephrine values in the urine underwent alpha-blockade preoperatively. In our practice, all of the patients were seen for follow-up 2 to 4 weeks after surgery. If there were no persistent postoperative problems, subsequent follow-up was with the patient’s endocrinologist or primary care physician. This study was approved by the University of California, San Francisco (UCSF) institutional review board and Committee on Human Research.

### RESULTS

Between January 1, 1995, and July 31, 2005, 42 patients underwent adrenalectomy for adrenal incidentaloma at the UCSF Medical Center. All underwent laparoscopic adrenalectomy with no conversions to an open or hand-assisted technique. Results of the final pathologic analysis for this cohort are shown in the following tabulation.

#### Table. Urine or Plasma Metanephrine Levels in All 42 Patients

<table>
<thead>
<tr>
<th>Urine or Serum Metanephrine Levels</th>
<th>Pheochromocytoma, No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated (&gt;2× upper limit of normal)</td>
<td>Yes</td>
</tr>
<tr>
<td>Borderline (1-2× upper limit of normal)</td>
<td>3</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
</tbody>
</table>

Of the 14 patients with a pheochromocytoma on final pathologic analysis, 11 had diagnostic elevations in urine or plasma metanephrine levels and 3 had only borderline elevations (Table). No patient with a final pathologic diagnosis of pheochromocytoma had normal urine or plasma metanephrine levels. There was no statistically significant
difference in average age, sex distribution, presence of preoperative hypertension, number of preoperative antihypertensive medications, average systolic or diastolic pressure, or postoperative length of stay between patients with and without a pheochromocytoma. However, patients with a pheochromocytoma tended to have higher preoperative heart rates (mean±SD, 81.5±11.6 vs 72.3±11.1 beats/min; P = .01), larger tumors (4.6±1.7 vs 3.7±0.9 cm; P = .02), and longer operative times (200.5±20.8 vs 143.5±13.7 minutes; P = .02) than patients without one. On retrospective questioning of patients with pheochromocytoma, 7 (50%) were found to have symptoms classically associated with this disease (ie, hypertension, headaches, palpitations, and/or diaphoresis).

Ten of the 42 patients with adrenal incidentaloma (24%) had borderline-elevated metanephrine levels in the urine or plasma on at least 2 occasions. All 10 patients had borderline-elevated metanephrine levels in the urine, except for 1 patient who had normal levels in the urine and borderline-elevated levels in the plasma. Three of the 10 patients with borderline-elevated metanephrine levels in the urine (30%) had a pheochromocytoma according to the final pathologic analysis, as shown in the following tabulation.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfunctional cortical adenoma</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Cyst</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>

In patients with borderline elevations, the mean±SD tumor size was 5.4±3.1 cm and 4.8±1.9 cm for patients with and without pheochromocytoma, respectively (P = .37). In these 10 patients, there were no statistically significant clinical factors (average age, sex distribution, presence of preoperative hypertension, presence of symptoms, number of preoperative antihypertensive medications, average preoperative systolic or diastolic pressure, average preoperative heart rate, or average tumor size on computed tomographic scan) or perioperative factors (average operative time or postoperative length of stay) that allowed differentiation between those with and without pheochromocytoma. The only major complication in the cohort was death in a patient with a 2-cm adrenal mass and borderline-elevated metanephrine levels in the urine who had a respiratory decompensation following aspiration in the perioperative period.

**COMMENT**

In this study, we reviewed the clinical presentations and outcomes for 42 patients who underwent adrenalectomy for adrenal incidentaloma during a 10-year period. Ten patients with an incidentaloma (24%) had borderline elevations (ie, only 1–2 times the upper limit of normal) in urine or plasma metanephrine levels on multiple occasions, and 3 of those patients (30%) had an asymptomatic or subclinical pheochromocytoma. Urine and plasma metanephrine levels continue to be the mainstays when diagnosing pheochromocytoma. There was a 100% positive predictive value for pheochromocytoma when the urine or plasma metanephrine levels were greater than 2 times the upper limit of normal (ie, all of these patients had a pheochromocytoma). There was a 100% negative predictive value for pheochromocytoma when the metanephrine levels were less than the upper limit of normal (ie, none of these patients had a pheochromocytoma). There was a 30% positive predictive value for pheochromocytoma when the metanephrine levels were 1 to 2 times the upper limit of normal (ie, almost 1 of every 3 of these patients had a pheochromocytoma). With such a potentially lethal and morbid disease, a positive predictive value of 30% warrants intervention. Unfortunately, we could not identify any reliable clinical factors that accurately predicted which patients with borderline elevations ultimately had a pheochromocytoma. In fact, up to 40% of patients with pheochromocytoma are completely asymptomatic.7,8

It is crucial to treat patients with borderline elevations of metanephrine levels as if they have a pheochromocytoma. For this reason, we recommend either alpha-blockade prior to resection for all patients with borderline elevations in metanephrine levels or further workup, perhaps with MIBG (iodine I 123 or I 131 [123ai or 131ai]–metaiodobenzylguanidine) scanning or the repetition of biochemical studies. A positive MIBG scanning result supports the diagnosis, but a negative result does not rule out a pheochromocytoma because the sensitivity is only 80% to 90% and it tends to miss small tumors. In addition, pheochromocytomas will often demonstrate a characteristic brightness on T2-weighted magnetic resonance imaging, which can be helpful diagnostically. If the tumor does not meet the size criteria for resection, then a repetition of the imaging, hormonal testing, and/or the clonidine suppression test is indicated. Although the clonidine suppression test is not routinely indicated for patients with clear-cut elevations in urine or plasma metanephrine levels, it may serve as a good confirmatory test for patients with borderline elevations.11 We also recommend the same genetic screening protocol for these patients as for those with clear-cut elevations—ie, genetic screening is recommended if family history or other clinical findings suggest syndromic disease.

There are a few limitations to this study. First, the number of patients in this study was small. Clearly, a larger cohort is needed to confirm these results. Second, selection bias may have affected our results. Our particular database is skewed toward patients with larger tumors because it includes only patients with an incidentaloma who ultimately underwent adrenalectomy. One of the main criteria for resection of an incidentaloma is size; smaller incidentalomas typically are observed and not referred to our practice. This bias is likely the reason that the average tumor size in our study tended to be larger than that in most series, in which the majority of tumors were less than 3 cm.12 This factor may also explain why the rate of pheochromocytoma was so high in our study (33%) compared with other large series of incidentalomas with a rate of approximately 11%.3,7,13 Presumably, the smaller the tumor, the less likely it is to secrete a detectable amount of catecholamines. Finally, there were fewer patients with subclinical Cushing syndrome in our sample (3%) compared with most other large series that found rates of approximately 10%.3,7,13,14
Another confounding factor in the analysis of patients with borderline-elevated metanephrine levels is that a number of conditions will cause false-positive biochemical test results. Major physical or psychological stress, heart disease, and anxiety disorders can increase catecholamine release. In addition, certain drugs such as tricyclic antidepressants, buspirone hydrochloride, clozapine, sympathomimetic drugs, and β-blockers can cause false-positive results.10,11-17 We typically recommend that patients undergo a 24-hour urine metanephrine test at least 2 weeks after cessation of any confounding medications and after optimal treatment of any confounding conditions. If metanephrine levels are borderline elevated, we recommend repetition of the testing. Of course, it may not be safe to stop certain medications (eg, antidepressants), and other modalities may be needed to assess disease in these patients. Because plasma metanephrine levels have a specificity of only 80% to 85%, the high false-positive rate makes this a less useful screening test. With a sensitivity of approximately 90% and a specificity of 97% to 100%, 24-hour urine metanephrine testing makes an excellent screening tool.5,6

In conclusion, 10 patients (24%) with adrenal incidentaloma had borderline-elevated urine or plasma metanephrine levels on screening and 14 patients (33%) had a pheochromocytoma on final pathologic analysis. We found no reliable way to predict which of these patients had a pheochromocytoma. Clearly, these data require validation in a larger series before determining whether all patients with borderline-elevated metanephrine levels should undergo adrenalectomy irrespective of tumor size. For patients with tumors that meet the size criteria for surgical resection, it is imperative to pursue other diagnostic modalities or to institute preoperative alpha-blockade in all patients with incidentaloma and borderline-elevated metanephrine levels prior to adrenalectomy.

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REFERENCES


DISCUSSION

Brett C. Sheppard, MD, Portland, Oregon: The authors have given us new, important information for a problem that, while simple, we continue to wrestle with. I have no doubt this study will often be considered in the future as we try to strike the delicate balance between operating too frequently and losing the chance to cure. Pheochromocytoma is indeed a vexing tumor when up to 40% of our patients will be asymptomatic when first encountered. It is important then to look for other cues that may be helpful to arrive at the correct conclusion. As you stated, patients with “pheos” can be normotensive in our office. This may be because continuous exposure to catecholamines will desensitize their receptors over time. In extreme cases this may induce orthostatic hypotension, but more often desensitization may lead to a loss of the normal circadian variation in blood pressure. So patients will not have a normal nocturnal decrease in their blood pressure and will also usually demonstrate an elevated heart rate without circadian variation. Your data have nicely shown the elevated heart rate in your group of patients. I am wondering if you have any information on the diurnal blood pressure variation in your borderline patients.
Pheochromocytomas usually have an attenuation of greater than 10 and, more often, greater than 25 Hounsfield units on unenhanced computed tomographic (CT) scans. How many patients did you have with borderline biochemistry who had CT scans that fulfilled this criterion? Did any have an attenuation of less than 10 Hounsfield units? Was there a difference between those patients with clearly elevated biochemistries and those who were borderline?

A few questions regarding further workup in this borderline group. Is your approach different when the initial test is a plasma result rather than a 24-hour urine? Should we always repeat the biochemical studies? Should all borderline patients be asked to have an MIBG or similar study? Or will these patients be offered surgery in light of a negative scan due to the importance of not missing a pheo in an otherwise appropriate surgical candidate?

In regard to follow-up, have you found a difference in the biology of patients with clear-cut biochemistries vs those diagnosed as part of the incidentaloma workup? Although the numbers are small, could you comment on the biology of the borderline patients? Do they recur less frequently? Do you follow all pheochromocytoma patients the same? Do you offer your patients with borderline biochemistry found to have a pheochromocytoma the same genetic testing as those more classically diagnosed? One final question: of those patients who had borderline biochemistry and were found not to have a pheochromocytoma, did you reexamine their biochemistry? What was their outcome?

Dr Duh: No, we do not have information regarding diurnal variation of the blood pressure in these patients. Hounsfield units on CT scan is a great question, since those less than 10 [Hounsfield units] on precontrast scan are less likely to bepheos. Unfortunately, most of the CT scans from which the incidentalomas were discovered were with contrast. For the few that had precontrast scans, none had less than 10 Hounsfield units. Regarding plasma vs urinary metanephrine studies, plasma levels are more sensitive and urinary levels more specific for pheochromocytoma. In this situation, although plasma metanephrines would be expected to have a higher false-positive rate, we do not have enough patients to compare them. For practical purposes, we would treat the incidentaloma as a possible pheo if either the plasma or the urine test is positive. If the patient is taking medications that could interfere with the testing or if the validity of the test is questioned, such as very high or low concurrent creatinine clearance, we would repeat the test. For patients in whom the suspicion for pheochromocytoma is very high, if the urinary test is negative, we may do the plasma test because it is more sensitive. We do not routinely do MIBG as a diagnostic test in patients with incidentaloma. We don't do it, either, for patients with a routine adrenal pheochromocytoma. We use MIBG to search for extra-adrenal phosos, for recurrences, for metastasis in those with malignant phosos, and in patients with known familial disease. We do not have a simple explanation for the patients with borderline metabolites who did not have a pheo. They are followed long-term by their primary physician and the endocrinologist, and I don't know whether how their metanephrine levels change after the adrenalectomy. For patients with pheochromocytomas, we consider genetic testing if the patient is young or has a family history, if the tumor is extra-adrenal or multiple, or if there are other manifestations of the syndromes (such as medullary thyroid cancer or renal cell cancer). Interestingly, some patients, who we screen because of genetic predispositions, have only borderline elevation in metabolites because the phoses are small. Of course, since we scan these at-risk patients to look for phosos, if we find them they would not be considered to be incidentalomas.

Dr Sheppard: Dr Duh, I have 2 more questions for you. First, Dr Lee did allude to the referral bias. I am just wondering, in 10 years there were only 42 patients, and I am sure UCSF [Medical Center] does about a million scans a year. Do you think the endocrinologists are seeing a bunch of patients with inciden-

talomas? They do the metanephrines; [the results] are 1.1 or 1.2 times normal, and [the endocrinologists] just don't even send them to you?

Dr Duh: You are right. In fact, that is a very important question because it may affect one of our conclusions. In the current study, no patient with an incidentaloma and normal metanephrine had a pheochromocytoma. But there is a selection bias; many patients with small incidentalomas are not referred to us. We have followed a few patients with von Hippel-Lindau syndrome and small pheochromocytomas over the years, and, as the tumors grow to a certain size, they cross the threshold to have a positive plasma or urine metanephrine test. I believe there are a number of patients with small pheochromocytomas who are not referred because they have borderline or normal metabolites.

Philip Haigh, MD, Los Angeles, California: I have 2 questions. The first is regarding referral bias, which was alluded to by Dr Lee in his presentation. I think that your quoted percentage of 30%, the number of patients with an incidentaloma and borderline elevations in metabolites who have a pheochromocytoma, is quite high. I think that may be explained by referral bias. Can you give me some information about the referral patterns at UCSF to your clinic? Surely there are millions of CT scans performed at UCSF, but in a 10-year time period you have only identified 42 patients with an incidentaloma. I would bet that many patients are seen by endocrinologists and never end up seeing you in the clinic. So the denominator is probably very much higher than 42.

Dr Duh: You are absolutely right; the denominator number ought to be much higher since we would expect to find an incidentaloma in at least 1% of our CT scans. Most of the incidentalomas are evaluated by the physician who ordered the scan; some are evaluated by the endocrinologists. Only a fraction of these patients are sent to our clinic, usually because [the tumors] are larger than 3 cm. In addition, in this series we did not include patients who were evaluated by us but did not have an adrenalectomy. However, we have recommended adrenalectomy for almost all patients we see with incidentaloma who have borderline elevation of metabolites. So the borderline-elevated patients in the endocrine surgery clinic are included. What do we not know are the number of patients who were never referred to the endocrine surgery clinic who may or may not have had metanephrine evaluation. The retrospective Italian and prospective Swedish databases showed that about one-third of the patients with incidentaloma had adrenalectomy and about 5% of the tumors are phosos, not 30%. I agree that we do not want to overestimate the probability of having a pheochromocytoma in these patients. On the other hand, from autopsy data we can surmise that only a quarter of pheochromocytomas were identified before death. Certainly, we are missing the majority of phosos now.

Dr Haigh: I am very curious to know, in the lesions that were removed with borderline elevations that ended up pathologically nonpheochromocytomas, did they still have borderline elevations in metabolites 6 months later or a year later? I am guessing that they probably had no change in their metanephrine level, which would signify a false-positive result. There are probably some normal patients who have an incidentaloma that is nonfunctioning without a pheochromocytoma, but who happen to have laboratory values outside the normal range.

Dr Duh: I don't know the answer to that question. I don't know whether or not the endocrinologists have repeated the metanephrine studies for those who don't have pheochromocytomas since there is no clinical indication for it, but that's a great question.

Dr Sheppard: I think that would help with the false-positive, false-negative issue.

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