Diagnosis and Localization of Pheochromocytoma

David S. Goldstein, Graeme Eisenhofer, John A. Flynn, Gary Wand, Karel Pacak

Abstract—This Hypertension Grand Rounds shows how applying new clinical laboratory techniques helped to diagnose pheochromocytoma in a difficult case. In the setting of long-standing, sustained hypertension, the patient had a hypertensive paroxysm during anesthesia induction for surgery, leading to suspicion of a pheochromocytoma. Conventional testing, including CT scanning and fractionated urinary metanephrine test, was not diagnostic. The patient had another hypertensive paroxysm during subsequent anesthesia induction, requiring intensive care. Consistently elevated plasma levels of free normetanephrine provided the first and only biochemical evidence for a pheochromocytoma in this case. 6-\[\text{F}\]Fluorodopamine positron emission tomography and 131I-metaiodobenzylguanidine scintigraphy subsequently agreed on the existence of a small left adrenal mass, which when removed surgically proved to be a pheochromocytoma. Postoperatively, plasma levels of normetanephrine normalized, and there were no further hypertensive paroxysms, although the patient remained hypertensive. This case illustrates the superiority of plasma levels of free (unconjugated) metanephrines, compared with other biochemical tests, to detect pheochromocytoma. It also confirms that functional imaging by 6-\[\text{F}\]fluorodopamine or 131I-metaiodobenzylguanidine scanning can localize pheochromocytoma in difficult cases in which other imaging tests are not diagnostic. (Hypertension. 2004;43:907-910.)

Key Words: pheochromocytoma  norepinephrine

Pheochromocytomas are rare but clinically important tumors of chromaffin cells that take up, produce, store, release, and metabolize catecholamines. Pheochromocytomas usually—but not always—manifest clinically as hypertension, which can be sustained or paroxysmal. Because most pheochromocytomas are benign adrenal tumors, pheochromocytoma constitutes a potentially surgically curable cause of hypertension. Failure to diagnose the tumor can result in sudden, unexpected, and potentially lethal complications. Because of these considerations, clinicians often wish to test for pheochromocytoma in patients who have hypertension and symptoms or signs suggesting catecholamine excess.

The diagnosis and treatment of pheochromocytoma depend on demonstrating increased catecholamine production and identifying the location of the tumor. In most cases, conventional clinical laboratory tests suffice. Urinary excretion of catecholamines or their metabolites can indicate a hypercatecholaminergic state, and computed tomography or MRI, coupled with 131I-metaiodobenzylguanidine scintigraphy, can detect an adrenal tumor of chromaffin tissue.1,2

Computed tomography and MRI are essentially anatomic modalities that offer high spatial resolution but limited specificity. This is a potentially important weakness, because not uncommonly patients have incidental adrenal masses that are not pheochromocytomas. In contrast, 131I-metaiodobenzylguanidine scintigraphy3 exploits 2 important functional characteristics of chromaffin cells—uptake of catecholamines and sympathomimetic amines, via a specific cell membrane norepinephrine transporter, and vesicular sequestration of these compounds, via a vesicular monoamine transporter. 131I-metaiodobenzylguanidine scintigraphy offers high specificity for identifying chromaffin tissue but has limited sensitivity. Clinicians therefore usually order a battery of tests, including levels of catecholamines or their metabolites, computed tomography or MRI, and 131I-metaiodobenzylguanidine scintigraphy. When the results of these tests are positive and consistent with each other, pheochromocytoma can be diagnosed, and the patient can be submitted to surgery.

In discussing the patient presented here, we provide an update and guidance to help clinicians diagnose pheochromocytoma efficiently and cost-effectively using an algorithmic approach. We believe that adoption of such an approach minimizes the likelihood of false-positive results, an inherent risk of the “shotgun” tactic of performing multiple imperfect tests concurrently, while using sufficiently sensitive means to detect pheochromocytoma when the patient actually harbors the tumor.

Case Summary
A 70-year-old white man was referred to the National Institutes of Health for clinical evaluation of possible pheochromocytoma. He had high blood pressure for many years.

Received January 7, 2004; accepted February 20, 2004.
From the Clinical Neurocardiology Section (D.S.G., G.E.), National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Md; the Johns Hopkins University School of Medicine (J.A.F., G.W.), Baltimore, Md; and Pediatric and Reproductive Endocrinology Branch (K.P.), National Institute of Child Health and Development, National Institutes of Health, Bethesda, Md.
Correspondence to Dr David S. Goldstein, Building 10, Room 6N252 NINDS, NIH 10 Center Drive, MSC-1620, Bethesda, MD 20892-1620. E-mail goldstein@ninds.nih.gov
© 2004 American Heart Association, Inc.
Hypertension is available at http://www.hypertensionaha.org

DOI: 10.1161/01.HYP.0000125014.56023.b8

907
Biochemical Tests (Chronological Order) in a Patient With Pheochromocytoma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Date</th>
<th>Finding</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ur NMN</td>
<td>July 1, 2002</td>
<td>458</td>
<td>44–540</td>
</tr>
<tr>
<td>Ur MN</td>
<td>July 1, 2002</td>
<td>185</td>
<td>26–230</td>
</tr>
<tr>
<td>Ur NE</td>
<td>January 13, 2003</td>
<td>58</td>
<td>15–100</td>
</tr>
<tr>
<td>Ur EPI</td>
<td>January 13, 2003</td>
<td>13</td>
<td>2–24</td>
</tr>
<tr>
<td>Ur NMN</td>
<td>March 9, 2003</td>
<td>422</td>
<td>44–540</td>
</tr>
<tr>
<td>Ur MN</td>
<td>March 9, 2003</td>
<td>167</td>
<td>26–230</td>
</tr>
<tr>
<td>NIH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pl NE</td>
<td>March 10, 2003</td>
<td>273</td>
<td>80–498</td>
</tr>
<tr>
<td>Pl EPI</td>
<td>March 10, 2003</td>
<td>20</td>
<td>4–83</td>
</tr>
<tr>
<td>Pl NMN</td>
<td>March 10, 2003</td>
<td>131</td>
<td>18–112</td>
</tr>
<tr>
<td>Pl MN</td>
<td>March 10, 2003</td>
<td>51</td>
<td>12–61</td>
</tr>
<tr>
<td>Ur NE</td>
<td>March 24, 2003</td>
<td>49</td>
<td>15–80</td>
</tr>
<tr>
<td>Ur EPI</td>
<td>March 24, 2003</td>
<td>6.3</td>
<td>0–20</td>
</tr>
<tr>
<td>Ur NMN</td>
<td>March 24, 2003</td>
<td>644</td>
<td>148–560 (900*)</td>
</tr>
<tr>
<td>Ur MN</td>
<td>March 24, 2003</td>
<td>346</td>
<td>44–261 (400*)</td>
</tr>
<tr>
<td>Pl NE</td>
<td>March 31, 2003</td>
<td>222</td>
<td>80–498</td>
</tr>
<tr>
<td>Pl EPI</td>
<td>March 31, 2003</td>
<td>30</td>
<td>4–83</td>
</tr>
<tr>
<td>Pl NMN</td>
<td>March 31, 2003</td>
<td>153</td>
<td>18–112</td>
</tr>
<tr>
<td>Pl MN</td>
<td>March 31, 2003</td>
<td>58</td>
<td>12–61</td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pl NE</td>
<td>June 23, 2003</td>
<td>255</td>
<td>80–498</td>
</tr>
<tr>
<td>Pl EPI</td>
<td>June 23, 2003</td>
<td>7</td>
<td>4–83</td>
</tr>
<tr>
<td>Pl NMN</td>
<td>June 23, 2003</td>
<td>44</td>
<td>18–112</td>
</tr>
<tr>
<td>Pl NE</td>
<td>November 24, 2003</td>
<td>434</td>
<td>80–498</td>
</tr>
<tr>
<td>Pl EPI</td>
<td>November 24, 2003</td>
<td>14</td>
<td>4–83</td>
</tr>
<tr>
<td>Pl NMN</td>
<td>November 24, 2003</td>
<td>38</td>
<td>18–112</td>
</tr>
<tr>
<td>Pl MN</td>
<td>November 24, 2003</td>
<td>21</td>
<td>12–61</td>
</tr>
</tbody>
</table>

Ur indicates urinary excretion, μg/24 h; NMN, normetanephrine; MN, metanephrine; NE, norepinephrine; EPI, epinephrine; Pl, plasma, pg/mL.
*Upper reference limit for patients with hypertension.

During general anesthesia before planned surgery for a right parotid gland mass, he had wide-complex tachycardia and extreme hypertension, followed by bradycardia and hypotension. The surgery was aborted. MRI and magnetic resonance angiography suggested hemangioma of the spleen and duplicated left renal arteries, without renal artery stenosis. There was no indication of an adrenal mass. Urinary excretion rates of normetanephrine and metanephrine were normal (Table).

Several months later, the patient had another episode of wide-complex tachycardia and extreme hypertension during anesthesia induction, followed by bradycardia and circulatory collapse. While the patient received high-dose epinephrine intravenously, left ventricular ejection fraction was decreased at 20% to 25%, and systemic vascular resistance was low. After treatment in the intensive care unit for 4 days and discontinuation of intravenous epinephrine, the echocardiogram showed normal left ventricular function.

Subsequent biochemical testing indicated normal urinary excretion of catecholamines and fractionated metanephrines (Table). \(^{123}\text{I}-\text{metaiodobenzylguanidine scintigraphy showed nondiagnostic “mild focal uptake in the left region of the left adrenal gland.” Abdominal computed tomography showed a 1.5×1.5-cm nodule in the inferior pole of the left adrenal gland; and MRI of the adrenals showed a 1.5-cm nodule in the lateral limb of the left adrenal gland. The patient was referred to the NIH for further evaluation. At the NIH, the patient’s plasma catecholamine levels were normal, as were 24-hour urinary excretion rates of catecholamines and fractionated metanephrines (Table). Serum chemistries and complete blood count were also normal or noncontributory, and aldosterone and plasma renin concentrations were normal.

The concentration of free (unconjugated) normetanephrine, however, was elevated over a 2-week period. Because of the entirely normal plasma norepinephrine levels, the plasma normetanephrine/norepinephrine ratio (0.69) was also increased above the range previously established for patients with false-positive increases in plasma normetanephrine (0.09 to 0.52). The concentration of metanephrine was within normal limits. The elevated plasma normetanephrine concentration and increased plasma normetanephrine/norepinephrine ratio were the first and only biochemical findings supporting a diagnosis of pheochromocytoma in this case. Clonidine suppression testing was not performed because of the patient’s concerns about possible side effects. \(^{6-\text{[18F]}}\text{Fluorodopamine positron emission tomography indicated a left adrenal mass (Figure 1). After }^{123}\text{I}-\text{metaiodobenzylguanidine scintigraphy confirmed the existence of a focus of radioactivity in the left adrenal gland, the patient was submitted to surgery. An approximately 1.5-cm mass was removed from the left adrenal gland. Surgical pathology was diagnostic of pheochromocytoma. Postoperatively and at 5-month follow-up, the patient continued to have hypertension, which was controlled with medication, but plasma levels of metanephrines were normal.}

Approximately 6 months after removal of the pheochromocytoma, and ~1.5 years after the initial episode, which anesthesia induction for elective surgery had evoked, the patient underwent the planned surgery under general anesthesia without incident.

**Discussion**

This case illustrates several scientific and practical points related to the diagnosis, localization, and management of pheochromocytoma.
First, the finding of a high plasma level of free (unconjugated) normetanephrine constituted the initial and only biochemical indication of a pheochromocytoma. Repeated measurements of plasma levels of catecholamines and urinary excretion rates of catecholamines and “fractionated metanephrines” (normetanephrine and metanephrine quantified separately) yielded false-negative results. The finding of normal plasma levels and urinary excretion rates of catecholamines, with elevated plasma free normetanephrine levels, can be explained by episodic release of catecholamines, whereas metanephrines are produced continuously from leakage of catecholamines from storage vesicles into the cytoplasm of pheochromocytoma tumor cells.5,6

Usually, elevated plasma levels of normetanephrine and metanephrine are accompanied by a similar pattern of increased urinary excretion of “fractionated” metanephrines. During testing at the NIH, the patient did have a slightly elevated urinary excretion of normetanephrine compared with the reference range in normotensives; however, the patient was hypertensive, and the urinary excretion of normetanephrine was within the reference range for hypertensives.

Second, our usual approach at the NIH for patients with slight to moderate elevations of plasma normetanephrine is to confirm the finding as a true-positive or a false-positive result using the clonidine suppression test. This test is used for distinguishing high plasma catecholamine levels caused by increased sympathetic nervous system outflows from high levels caused by a high rate of secretion by a pheochromocytoma;7,8 however, the test has limited value in patients with normal or mildly elevated plasma catecholamine levels.9 Measurement of effects of clonidine treatment on plasma levels of normetanephrine overcomes this limitation.4 In the event that clonidine suppression testing is not performed, a high ratio of plasma metanephrines to the corresponding catecholamines during follow-up testing can provide a confirmatory biochemical test result,4 as was the case here.

Third, 131I-metaiodobenzylguanidine scintigraphy was nondiagnostic. Although positive results of 131I-metaiodobenzylguanidine scintigraphy do indicate the existence of a tumor of chromaffin cells, negative or nondiagnostic results, as in this case, do not exclude pheochromocytoma. In contrast, both 6-[18F]fluorodopamine positron emission tomographic scanning and 123I-metaiodobenzylguanidine scintigraphy correctly demonstrated the tumor. These imaging modalities work by the same general mechanism—uptake by chromaffin cells via the cell membrane norepinephrine transporter, followed by sequestration by and radiolabeling of intracellular vesicles via the vesicular monoamine transporter. As imaging agents, both 123I-metaiodobenzylguanidine and 6-[18F]fluorodopamine have greater sensitivity than does 131I-metaiodobenzylguanidine scintigraphy.10–13

The shorter physical half-life of 123I than of 131I enables administration of a higher dose of radioactivity and more rapid imaging, at equivalent radioactive absorbed doses to body organs. 123I-metaiodobenzylguanidine and 6-[18F]fluorodopamine are also amenable to computed tomography, with better spatial resolution. Unfortunately, availability of these superior tests remains limited in the United States.14

Fourth, sustained hypertension and normal plasma catecholamine levels occurred independently of pheochromocytoma. Therefore, the finding of normal plasma catecholamine levels in a patient with hypertension should not be taken as excluding pheochromocytoma.

Fifth, and probably most important, even a small pheochromocytoma, if left undiagnosed, can cause unexpected, catastrophic consequences. In our patient, a seemingly minor manipulation, anesthesia induction, evoked paroxysmal hypertension, followed by bradycardia and circulatory shock. Chronically, patients with pheochromocytoma can have a severe and potentially lethal form of dilated cardiomyopathy.15–17 The pathological picture includes myofibrillar disruption, high intracellular ionized calcium concentrations, and contraction band necrosis, reflecting direct toxic effects of catecholamines via adrenoceptor occupation on myocardial cells, rather than indirect effects via coronary ischemia. The chronic cardiomyopathy seems to depend on persistently high circulating levels of catecholamines, because after surgical removal of the tumor, the cardiomyopathy can resolve rapidly.16,18 Our patient had cardiomyopathy acutely, probably from intravenous epinephrine administered in an attempt to treat bradycardia and hypotension. Discontinuation of the infusion normalized the patient’s decreased left ventricular ejection fraction, despite the continued presence of the pheochromocytoma. Perhaps catecholamine secretion by the pheochromocytoma interacted with the exogenous catecholamine to produce toxic cardiac effects.

The results confirm the value of an algorithmic approach to the diagnosis of pheochromocytoma (Figure 2). Briefly, the initial diagnostic test of choice is plasma levels of free (unconjugated) metanephrines. This is an extraordinarily sensitive test, and if negative, as the results usually are, pheochromocytoma is excluded, and the workup can end.19 If plasma levels of free (unconjugated) normetanephrine are moderately increased (to approximately <4-times the upper reference limit), then confirmatory biochemical testing is indicated. We recommend a clonidine suppression test, with measurements of plasma norepinephrine and normetanephrine.4 If the results are consistent with pheochromocytoma, then conventional anatomic tests, coupled with functional

**Figure 2.** Algorithm for diagnostic evaluation of a norepinephrine-producing pheochromocytoma (red line indicates route in the present case).
imaging, should be performed. Expensive and time-consuming imaging tests therefore are kept to a minimum.

Because of poor sensitivity, $^{131}$I-metaiodobenzylguanidine scintigraphy should be supplanted by $^{123}$I-metaiodobenzylguanidine scintigraphy, 6-[$^{18}$F]fluorodopamine positron emission tomography, or other functional positron emission scanning modalities, if available. The recent introduction of combined positron emission tomography/CT scanning holds promise for streamlining the diagnostic testing sequence.

We hope that, in the future, routine application of multiple conventional tests simultaneously will be replaced by newer superior biochemical and imaging modalities applied in an algorithmic manner.

Acknowledgments
The authors thank Patricia Sullivan, Beverly McElroy, the Nuclear Medicine and PET Departments of the NIH Clinical Center, and the Surgery and Pathology Departments of the Johns Hopkins Hospital.

References
Diagnosis and Localization of Pheochromocytoma
David S. Goldstein, Graeme Eisenhofer, John A. Flynn, Gary Wand and Karel Pacak

Hypertension. 2004;43:907-910; originally published online March 15, 2004;
doi: 10.1161/01.HYP.0000125014.56023.b8

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/43/5/907

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/