SUMMARY Childhood familial pheochromocytoma was investigated in four patients by abdominal computed tomographic scan, $[^{131}I]$metaiodobenzylguanidine scan, and vena caval catecholamine sampling. Results conflicted with surgical findings. Computed tomographic scan identified all four adrenal tumors but missed two midline tumors in one patient. $[^{131}I]$metaiodobenzylguanidine scan identified two of three adrenal tumors but also suggested extra-adrenal tumors not confirmed at operation in two of three patients. Vena caval sampling for catecholamines confirmed all adrenal tumors but suggested additional tumors not verified at operation in two of three patients. All patients are asymptomatic and have normal urinary catecholamines 15 to 51 months after operation. Because of the frequency of multiple tumors in familial pheochromocytoma, different diagnostic techniques were employed. False-positive results were more frequent with $[^{131}I]$metaiodobenzylguanidine and vena caval sampling. Reinterpretation of the $[^{131}I]$metaiodobenzylguanidine scans at a later date led to less false-positive interpretation, although the false-negative rate remained unchanged. More pediatric experience with $[^{131}I]$metaiodobenzylguanidine scans and vena caval sampling in familial pheochromocytoma is needed. Confirmation of tumor and its localization rest with meticulous surgical exploration. (Hypertension 8: 851–858, 1986)

KEY WORDS • endocrine hypertension • $[^{131}I]$metaiodobenzylguanidine scan • vena caval sampling • management of pheochromocytoma

PHEOCHROMOCYTOMA is a rare cause of pediatric hypertension.1 Pheochromocytoma may be sporadic or familial. Familial occurrences may or may not be associated with multiple endocrine adenomatosis (MEA) or neurocutaneous abnormalities (NC).2 Because childhood and familial pheochromocytomas are often multiple as well as extra-adrenal, evaluation with sensitive techniques is warranted before operation.

In the present article, we describe a gypsy kindred with known pheochromocytoma in five members and suspected pheochromocytoma in three individuals spanning three generations. The need to localize tumors in four affected children provided an opportunity to compare the sensitivity of computed tomographic (CT) scan, $[^{131}I]$metaiodobenzylguanidine (MIBG) scan, and vena caval sampling (VCS) with surgical findings.

Family History

The kindred is a large gypsy family that was doubly ascertained through V11 and VI17 (Figure 1). There were numerous instances of marriage between this family and another gypsy kindred (i.e., IV2,10), but consanguinity could be established only in one unaffected branch (IV14 and IV15, were allegedly cousins). The first generation definitely affected is IV, in which IV16 had extirpation of an adrenal pheochromocytoma and, 2 years later, an extra-adrenal pheochromocytoma. He has had a thyroid nodule for several years; an unstimulated calcitonin level was normal. IV, had a history of unconfirmed pheochromocytoma. IV14, VI13, and VI1 are described in this report. IV17 had end-stage renal disease associated with hypertension. Two sons V32 and V33 died prematurely of complications of severe hypertension at ages 27 and 31 years, respectively, and pheochromocytoma cannot be excluded.
V6, the father of Patient 1 and Patient 3, also has hypertension but has not been evaluated for pheochromocytoma. Of his unaffected children, one (VI1) has a normal urinary catecholamine level, one (VI6) has a normal plasma catecholamine level, and two (VI4 and VI5) have normal abdominal CT scans. Finally, in addition to the thyroid nodule in IV16, three of his sisters (IV6, IV11, and IV13) and one of his nephews (V13) have goiter. There is no family history of cutaneous stigmata including café-au-lait spots, mucosal or other neuromas, other endocrine adenomas, or unusual habitus.

Methods

The plasma catecholamines were assayed by a modified radioenzyme method using tritium-labeled tromethamine and rat liver catechol-O-methyltransferase as described by Peuler and Johnson.3 The intra-assay coefficient of variation is 4% (norepinephrine) and 13% (epinephrine), while the interassay coefficient of variation is 7.2% (norepinephrine) and 13.7% (epinephrine). Urinary catecholamines were determined by trihydroxyindole formation from endogenous catecholamines to enable a fluorometric assay as described by Crout.4 The intra-assay coefficient of variation is 4% (norepinephrine) and 10.9% (epinephrine), while the interassay coefficient of variation is 6 to 7% (norepinephrine) and 1.2% (epinephrine). Correction for body size or urinary excretion rate was not performed. A 9800 GE scanner (Schenectady, NY, USA) performed the CT scans, using a slice thickness of 5 mm; all studies were performed with intravenous contrast medium. The [131I]MIBG was obtained from the University of Michigan and had a specific activity of at least 1.8 mCi/mg. A dose of 0.5 mCi/m2 was administered to a maximum dose of 0.5 mCi after blockade of thyroid uptake with Lugol's solution. Scans were performed with a medium energy collimator 24, 48, and 72 hours after injection. Overlapping images from skull to bladder base contained 100,000 counts or were obtained for 10 minutes. Inferior VCS was performed by the same angiographer using a 5F polyethylene catheter with a terminal curve and an end hole. Levels were localized anatomically, without intravenous contrast medium, and blood was withdrawn by gentle aspiration. All operations were performed by one surgeon through a midline incision with exploration from diaphragm to pelvis.

Case Reports

Patient 1

Patient 1 (VI2) is a 13-year-old girl who was admitted to Childrens Hospital of Los Angeles for malignant hypertension associated with a 9 kg weight loss. For 2 months she had experienced easy fatigability and episodic headaches accompanied by dizziness and blurred vision. Blood pressure measured 240/160 mm Hg. Family history was positive for an uncle (IV6) who had had two pheochromocytomas resected.

Physical examination revealed a gaunt adolescent girl with a weight of 34.7 kg, height of 57.5 cm, pulse of 84 beats/min, and blood pressure of 210/140 mm Hg. Funduscopic examination showed Grade 4 hypertensive retinopathy. A Grade 2/6 holosystolic murmur at the lower sternal border and an intermittent S4 were present. Her extremities were cold and clammy with poor perfusion.

Initial blood pressure management, which included diazoxide, hydralazine, and captopril, was not adequate until phenoxybenzamine was added. Blood pressure and pulse control were optimal with a regimen of phenoxybenzamine, 15 mg b.i.d., and propranolol, 10 mg b.i.d.
Diagnostic study results included a negative hypertensive intravenous pyelogram and normal roentgenogram of the chest. An electrocardiogram showed left ventricular hypertrophy. The 24-hour urinary vanillylmandelic acid was 24 mg/g creatinine (normal, <3 mg/g). Plasma norepinephrine was 11,485 ng/L (normal, 148 ± 45 ng/L), and plasma epinephrine was 122 ng/L (normal, 59 ± 63 ng/L). Abdominal CT scan showed a left adrenal mass (Figure 2). An MIBG scan showed increased activity in the region of the left adrenal with questionable activity in the right adrenal. Basal calcitonin level was 7 pg/ml (normal, 2-17 pg/ml; Nichols Laboratory, San Juan Capistrano, CA, USA).

Following discharge from the hospital, blood pressure control was satisfactory and she gained 14 kg. Abdominal cramps persisted. Two months after diagnosis, a 3-cm tumor was removed from the left adrenal near the hilum of the left kidney. Because the tumor was adherent to a 1-cm segment of the left renal vein, vascular reconstruction was required after removal of the tumor. In addition, a 2 × 2-cm tumor was resected from the aortic area just above the level of the inferior mesenteric artery and a 1-cm tumor was resected from under the left renal vein near its origin overlaying the aorta. There was no tumor in any of the resected lymph nodes. A subsequent bone scan was negative and posterior iliac bone biopsy results were normal. The multiple tumors were interpreted as multicentric pheochromocytomas.

Because of continuing complaints of abdominal cramps, a repeat MIBG scan after operation showed a suspicious area of activity in the liver. However, during the 29 months since operation, blood pressure has remained normal and 24-hour urinary catecholamine determinations 5 and 10 months after operation were also normal. Plasma catecholamine level 9 months postoperatively was 386 ng/L (normal, 280 ± 104 ng/L).

Patient 2

Patient 2 (VI 3), the 14-year-old brother of Patient 1, experienced increased sweating and cramping abdominal pain several times per week for 2 months soon after his sister was diagnosed. Physical examination revealed a healthy appearing boy. The only abnormal finding of the examination was a blood pressure of 130/90 mm Hg; pulse was 72 beats/min. His plasma norepinephrine level was 9000 ng/L. Chest roentgenogram was normal. Abdominal CT scan showed a left adrenal mass approximately 2 cm in diameter. A suspicious 6-mm mass to the left of the aorta, at the level of the kidneys, also was identified by CT scan. Subsequently, an MIBG scan revealed increased activity in the area of the right adrenal with some increase in uptake in the midabdomen as well as in the pelvis. He underwent VCS (Table 1); the results were interpreted as consistent with a left adrenal tumor, possible right

<table>
<thead>
<tr>
<th>Table 1. Results of Inferior Vena Caval Sampling</th>
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<tbody>
<tr>
<td>Location of sample</td>
</tr>
<tr>
<td>Right internal jugular</td>
</tr>
<tr>
<td>Left internal jugular</td>
</tr>
<tr>
<td>Right atrium</td>
</tr>
<tr>
<td>High IVC</td>
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<tr>
<td>Left renal vein</td>
</tr>
<tr>
<td>Left adrenal vein</td>
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<tr>
<td>Right adrenal vein</td>
</tr>
<tr>
<td>Low IVC</td>
</tr>
<tr>
<td>Left iliac vein</td>
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<tr>
<td>Right iliac vein</td>
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</tbody>
</table>

NE = norepinephrine; E = epinephrine; IVC = inferior vena cava.
adrenal tumor, and possible pelvic tumor. He was begun on a regimen of phenoxybenzamine, 5 mg b.i.d., 2 weeks before operation. His blood pressure returned to normal, and he gained 0.7 kg during that period.

One month after evaluation, a 3-cm left adrenal tumor was removed. No other tumors were identified during intraoperative exploration. Because of the preoperative identification of plasma catecholamine elevations from various sites, plasma catecholamines were drawn at the level of the left iliac, right iliac, and right adrenal veins during operation after the tumor was removed (see Table 1).

Postoperative recovery was uneventful. He remains asymptomatic with a normal blood pressure. Twenty-four-hour urinary catecholamine excretion determined 4 and 9 months after operation was normal. He is asymptomatic with a normal blood pressure 23 months after operation.

**Patient 3**

Patient 3 (VIII), first cousin of Patients 1 and 2, was a 6-year-old boy evaluated because of a 1-month history of night sweats associated with pallor and tachycardia, episodic headaches, increased tremulousness, and anxiety. His father (IV (6) had had two pheochromocytomas resected. Initial examination revealed a thin, tired-looking child whose weight was 16 kg, with a blood pressure of 150/100 mm Hg and a pulse of 120 beats/min. Other results of the examination were unremarkable. His blood pressure was controlled with phenoxybenzamine, 5 mg b.i.d. Subsequently, propranolol, 5 mg b.i.d., was added in a partially successful attempt to control persistent sweating and tachycardia. He gained 1.5 kg before operative intervention.

Two 24-hour urine catecholamine determinations contained 44 and 77 μg/hr/g creatinine, respectively (normal, 2.6 ± 1.3 μg/hr/g). Chest roentgenograms were normal, while CT scan of the abdomen showed a 3-cm left adrenal tumor. An MIBG scan confirmed the presence of a left adrenal tumor (Figure 3). Results of VCS were interpreted as compatible with a left adrenal tumor and suggested the possibility of right adrenal involvement (see Table 1). Basal calcitonin level was 46 pg/ml (normal, 25–150 pg/ml; Endocrine Science, Tarzana, CA, USA).

A 3-cm left adrenal tumor was removed 1½ months after diagnosis. A brief rise in blood pressure to 160/100 mm Hg during removal of the tumor was treated with phentolamine. No other tumors were identified. His immediate postoperative course was complicated by pulmonary edema, which responded to furosemide and fluid restriction.

Twenty months after operation, he is asymptomatic and normotensive. The 24-hour urinary catecholamine determinations obtained 1 and 6 months postoperative-ly were in the normal range.

**Patient 4**

Patient 4 (IV), a 12-year-old boy who was initially evaluated elsewhere for a 3-month history of malaise, 1 month of episodic sweating, and 3 days of headache, vomiting, and scotomata. His blood pressure was 240/180 mm Hg; physical examination revealed Grade 4 hypertensive retinopathy with no other physical findings. Initial blood pressure control was achieved with a regimen of nitroprusside and then minoxidil. A hypertensive intravenous pyelogram was negative. Abdominal aortography with selective renal arterial studies did not reveal an anatomical abnormality. Results of VCS showed elevated norepinephrine levels from the level of the superior vena cava to the level of L3. Repeat VCS showed elevated norepinephrine levels from the inferior jugular veins to the right femoral vein. A thoracic aortogram and selective carotid angiograms failed to reveal a tumor. Medications were changed from minoxidil to phenoxybenzamine and propranolol. Additional study results included normal levels of calcitonin and parathyrome.

During evaluation at our institution, he was asymptomatic and had a blood pressure of 98/62 mm Hg with a pulse of 68 beats/min. Abdominal CT scan revealed a mass lesion situated inferior to the left adrenal gland, lateral to the aorta, and ventral to the kidney. Repeat VCS was performed and confirmed the presence of a left-sided tumor (see Table 1). Bilateral adrenal venograms were also performed and were normal. At operation, a 6 × 5-cm tumor adherent to the aorta below the left renal artery and vein was resected. Blood supply and drainage were through the left renal artery and vein.

His intraoperative and postoperative course were uncomplicated. He was seen approximately 6 weeks after operation and was asymptomatic with a normal blood pressure. He subsequently returned to the care of his previous physicians.

**Discussion**

Pheochromocytoma usually presents as a sporadic mutation. Sporadic pheochromocytoma may occur at any time in life, although the tendency to multiplicity and extra-adrenal occurrence is increased in childhood. Stackpole et al. compiled a series of 100 children with 140 tumors, of which 68 were single and 19 were extra-adrenal. Twenty children had bilateral intra-adrenal tumors, whereas only four had extra-adrenal tumors and eight had both intra-adrenal and extra-adrenal tumors.

The relationship of uncomplicated familial pheochromocytoma to familial pheochromocytoma as a component of MEA-NC syndrome is unknown. Few reports exist of kindreds with uncomplicated familial pheochromocytoma who have had adequate follow-up. A 7-year follow-up of one kindred did not show syndrome overlap. Another series of three kindreds, one of which was observed for a 19-year period, also confirms this finding. Usually, MEA-NC-associated pheochromocytomas are diagnosed in adulthood when an affected person is discovered to have thyroid medullary cancer or another MEA-NC condition and is screened for abnormal catecholamine metabolism. MEA-NC-affected children are often identified by ab
FIGURE 3. Posterior $^{[131I]}$iodobenzylguanidine scintiphotograph demonstrating the left adrenal tumor in Patient 3.

normal results of chemical tests, such as elevated serum calcitonin or elevated urinary catecholamines, although results of physical examination may be normal. Pheochromocytomas tend to be bilateral in as many as 63% with MEA-NC pheochromocytomas. Long-term follow-up of affected kindreds with or without associated MEA-NC is essential due to the tendency for recurrent tumor.

The mode of inheritance and the penetrance of the pheochromocytoma gene are similar in instances in which differentiation between uncomplicated familial pheochromocytoma and pheochromocytoma with MEA-NC has been made. Both are autosomal dominants with a high degree of penetrance (98%). The findings in our kindred are consistent with uncomplicated familial pheochromocytoma, most likely caused by an autosomal dominant. However, the available family history demonstrates reduced penetrance compared with previous reports. Although the frequency of thyroid goiter and nodules is impressive in this kindred, goiter usually does not precede the development of medullary carcinoma of the thyroid. Additionally, Van Dyke et al. has reported three unrelated MEA kindreds in whom a similar deletion of chromosome 20 [del (20) (pter→p12.2::p11.4→qter)] was demonstrable with high resolution cytogenetic techniques. Prophase analysis of Giemsa-banded karyotypes of peripheral blood lymphocytes from Patient 3 revealed no abnormality.

In Patient 1, the occurrence of renal vein invasion and the presence of tumor in multiple sites suggested that the pheochromocytoma may have been malignant. Wilson and Ibanez described the presence of blood vessel invasion in six of 14 cases of pheochromocytoma; of the six cases, two were associated with MEA while the remaining four were sporadic pheochromocytomas. Only one of six with vascular invasion was a malignant pheochromocytoma. Neville proposed that the absolute criterion for the diagnosis of malignant pheochromocytoma is the presence of chromaffin tissue in abnormal locations. The midline location of the nonadrenal tumors in Patient 1 was in the sympathetic chain, and evaluation revealed no metastasis. An additional indication that a pheochromocytoma might be
Urinary homovanillic acid excretion was not elevated in Patient 1. However, she persistently complained of abdominal cramps after operation despite normal physical examination results. An area in the liver was regarded as suspicious on repeat MIBG scan, although urinary and plasma catecholamine determinations were in the normal range. Criteria to investigate the possibility of malignancy or recurrent pheochromocytoma for Patient 1 would include recurrence of hypertension, weight loss, severe symptoms, or measurable catecholamine abnormality.

Vena caval sampling for determination of the location of catecholamine secretion was utilized as early as 1955 to identify the tumor site. Subsequently, ultrasound localization preceded the use of CT scan. The MIBG scan may serve as a complementary function to CT scan, because MIBG scans can identify adrenal hyperplasia and pheochromocytoma as well as tumors in sites inaccessible to CT scan. The sensitivity of all localizing techniques is validated by surgical findings that normal adrenal glands retain MIBG caused us to reinterpret the data (Table 3). Thus, with current interpretive skills, MIBG scans would have correctly identified the lack of extra-adrenal tumors in two of three patients (no false positives), whereas the presence of two extra-adrenal midline tumors and one intra-adrenal tumor would still have been missed. Because of the persistence of abdominal symptoms in Patient 1, a follow-up MIBG scan was performed. Findings were interpreted as showing a normal right adrenal, but there was a questionable lesion in the liver. Confirmation of the existence of this lesion by repeat CT scan, VCS, or biopsy has not been necessary because of the continued health of the patient.

### Table 2. Results of Diagnostic Imaging Techniques

<table>
<thead>
<tr>
<th>Diagnostic technique</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left adrenal tumor; 2 midline tumors</td>
<td>Positive; false negative</td>
<td>Positive; false positive</td>
<td>Not done</td>
<td>Positive; false positive</td>
</tr>
<tr>
<td>Positive; false positive</td>
<td>Positive; false positive</td>
<td>Positive; false negative</td>
<td>Positive; false negative</td>
<td></td>
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<tr>
<td>Positive; false positive</td>
<td>Positive; false positive</td>
<td>Positive; false negative</td>
<td>Positive; false negative</td>
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</tr>
<tr>
<td>Positive; false positive; false negative</td>
<td>Positive; false positive; false positive</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CT = computed tomographic; MIBG = \(^{131}\)I-metaiodobenzylguanidine.
TABLE 3. Results of Diagnostic Imaging Techniques Using “Experienced” Interpretation of Metaiodobenzylguanidine Scan

<table>
<thead>
<tr>
<th>Diagnostic technique</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation</td>
<td>Left adrenal</td>
<td>Left adrenal</td>
<td>Left adrenal</td>
<td>Left adrenal</td>
</tr>
<tr>
<td>MIBG scan</td>
<td>Positive; negative</td>
<td>Negative; negative</td>
<td>Positive; negative</td>
<td>Negative; positive</td>
</tr>
</tbody>
</table>

MIBG = [131]Imetaiodobenzylguanidine.

Vena caval sampling was performed in three patients in an attempt to clarify the disparate CT and MIBG findings in Patient 2 and as confirmation of lack of other tumors in Patients 3 and 4. Although VCS accurately identifies the level of tumor in 97% of adult patients, a comparable series in children does not exist. This technique confirmed the presence of a left adrenal tumor in Patient 2. The possibility of a second tumor medial to the left adrenal as suggested by CT and MIBG scans could not be confirmed nor disproved by VCS because drainage from the medial tumor may have been confluent with left adrenal venous drainage. The presence of a lower pelvic lesion previously suggested by MIBG scan was also suspected because of the elevated norepinephrine level in the left iliac vein. Even had the “experienced” MIBG interpretation been available, VCS would not have clarified the issue. Surgical exploration as well as intraoperative venous sampling for catecholamines did not confirm multiple tumors (see Table 2). The elevated norepinephrine levels may reflect accidental switching of the left iliac and left renal samples during collection or analysis, or perhaps the location of the catheter was not as accurate as desired. In Patient 3, the slight possibility of a right adrenal tumor was suggested by the elevated right adrenal norepinephrine level unaccompanied by a norepinephrine level increase in the renal veins. A tumor was not confirmed at surgical exploration. In retrospect, the right adrenal sample may have included venous blood from the inferior vena cava. In Patient 4, persistently high nonlocalizing norepinephrine levels in the initial VCS were inexplicable and repeat study was required. The third study showed elevated norepinephrine levels from the left renal and adrenal vein, which indicated the presence of left-sided tumor as defined by the CT scan and confirmed at operation. The presence of the elevated epinephrine level from the right adrenal represented actual catheterization of the adrenal vein itself with secretion of catecholamines from a normal gland.

In our hands, the use of multiple localizing techniques led to conflicting results. The importance of the discrepant observations is not clear and may be clarified with prolonged follow-up. The CT scan was the most sensitive test for identification of tumor in our children. The original MIBG scan interpretations were misleading, but retrospective review of the scans eliminated the false-positive readings. However, three tumors found at operation were not identified by MIBG scan. Recent series suggest that 3 to 10% of tumors that are not diagnosed by MIBG scan may be missed because of the tumor’s low storage capacity or the tumor’s inability to uptake MIBG. Although our series is small, three of five tumors were not identified by MIBG scan, suggesting the possibility of differential handling of the radioisotope in children or a fundamental difference in tumor biology in childhood. Although VCS did not clarify the disparate CT and MIBG scan findings, it did suggest other sites of involvement that were not confirmed surgically. The lack of confirmation of level of tumor by VCS may reflect a technical problem in children. Venous mixing and inaccurate location of the catheter because of small patient size may account for some observed discrepancies. Current recommendations for evaluation of childhood pheochromocytoma include chest roentgenographic examination and a CT scan. Further experience with MIBG scans in the pediatric age group is needed to define the true false-negative rate in sporadic or familial pheochromocytoma with or without MEN-NC, and MIBG scan should be included in the initial evaluation of childhood pheochromocytoma. If more reliable and sensitive MIBG scan results are defined in a larger pediatric series, it might become possible to reserve the invasive technique of VCS for the atypical patient. Until more experience with both techniques is acquired and results are compared, VCS will remain an important tool for localization of childhood pheochromocytoma. Despite recent recommendations to the contrary, surgical exploration through a midline incision is indicated for the management of childhood pheochromocytoma. In our series, tumors not localized preoperatively were identified intraoperatively and tumors thought to have been present according to preoperative evaluation were in fact not present. There is no substitute for palpation of the adrenals or other organs, as well as examination of nodes and sympathetic ganglia.

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