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Case 16-2005: A Nine-Year-Old Girl with Headaches and Hypertension

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PRESENTATION OF CASE

A nine-year-old girl was admitted to this hospital because of headaches, enuresis, recent visual changes, and vomiting.

Intermittent frontal headaches began 18 months before admission, occurring most often during physical activity, but occasionally in the early morning, accompanied by nausea, but without vomiting, visual changes, or facial flushing. The child had been squinting, and she said she had been having difficulty reading; one month before admission, the results of an eye examination were reportedly normal.

Nocturnal enuresis began eight months before admission and did not respond to fluid restriction and voiding before bedtime. The patient was evaluated by an urologist and a nephrologist at another institution six months before admission. A plain radiograph of the abdomen and ultrasonographic studies of the kidneys and the bladder reportedly showed no abnormalities.

Three days before admission, a neurologist examined the child and observed abnormal optic disks and papilledema of the left eye. The next day, magnetic resonance imaging (MRI) of the brain revealed a T_2-weighted hyperintense focus in the right cerebellar white matter; there was a possible slight mass effect that did not show abnormal enhancement after the administration of gadolinium, and there were prominent lateral ventricles. An MRI of the spine showed no abnormalities. The next day, a neuro-ophthalmologist confirmed the presence of papilledema. In the office, the child vomited repeatedly; she was admitted to the hospital.

The patient had had no previous illnesses. Her brother had occasional headaches; her mother and a maternal aunt had had migraines, but rarely. A paternal aunt and cousin had had enuresis. There was no family history of renal, endocrine, or neurologic diseases or of hypertension. She lived with her parents and brother and was an excellent student.

On physical examination, the patient was alert, conversant, and cooperative. The blood pressure was 210/130 mm Hg, measured in both arms and legs. The pulse was 100 beats per minute, the respiratory rate 18 breaths per minute, temperature 37.3°C, height 1.40 m (55 in.), and weight 26 kg (58 lb). Cardiac examination revealed a hyperdynamic precordium, a regular rate and rhythm, and no murmurs. Three café-au-lait

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lesions were present, one that measured 12.5 cm by 7.5 cm on the lower abdomen, and two that were 0.5 cm in diameter on the left thigh. The remainder of the physical examination and a detailed neurologic examination revealed no abnormalities.

Urinalysis showed 2+ protein and was otherwise normal; the hematocrit was 46.7 percent and the hemoglobin level 16.6 g per deciliter; the remainder of the complete blood count was normal. The levels of thyrotropin, thyroxine, and free thyroxine were normal; other laboratory test results on admission are shown in Table 1. Chest radiography showed no abnormalities. An electrocardiogram showed early repolarization with possible left ventricular strain. A 24-hour urine collection to test for catecholamines was unsuccessful because of enuresis. Intravenous hydralazine was administered. Later that day, an episode of respiratory distress occurred, with cramping in the hands and legs, and the patient was transferred to the pediatric intensive care unit. The blood pressure was 190/110 mm Hg. A continuous labetalol infusion was begun and titrated gradually to maintain the systolic blood pressure in the range of 100 to 120 mm Hg.

On the second hospital day, the systolic blood pressure was in the range of 111 to 129 mm Hg and the diastolic pressure was in the range of 52 to 64 mm Hg, but the patient had a sudden deterioration of vision, worse in the left eye than in the right eye. A neuro-ophthalmologic examination confirmed a left afferent pupil defect and bilateral papilledema with macular exudates. An urgent cranial computed tomographic (CT) scan revealed no intracranial hemorrhage or territorial infarct. A lumbar puncture revealed an opening pressure of 28 cm of water and a closing pressure of 11 cm of water after the removal of 25 ml of cerebrospinal fluid. The spinal fluid was clear and colorless, with one red cell and one white cell per high-power field. The cerebrospinal fluid glucose level was 74 mg per deciliter and the protein level was 18 mg per deciliter. A culture of a sample of spinal fluid yielded no growth. Treatment with acetazolamide was begun.

On the third hospital day, the patient's systolic blood pressure was in the range of 120 to 130 mm Hg and the diastolic pressure was approximately 70 mm Hg. Several boluses of potassium chloride were administered to treat hypokalemia, and the serum levels of sodium and potassium returned to the normal range without fluid restriction. Visual acuity improved. The results of endocrinologic tests are shown in Table 2. A renal ultrasonographic examination showed that the right kidney was 7.8 cm long and the left kidney 10.2 cm long. The renal parenchyma appeared normal. Spectral Doppler imaging of the renal arteries showed a blunted parvus et tardus waveform (a prolonged systolic acceleration time with decreased peak systolic velocity) on the right, with a slow systolic rise; the left-renal-artery waveform appeared normal. The flow velocities in the intrarenal branches on the right were lower than those on the left. The urinary bladder appeared nor-

Table 1. Blood and Urine Findings on Admission.*

Variable	Value
Sodium (meq/liter)	133
Potassium (meq/liter)	2.6
Chloride (meq/liter)	88
Carbon dioxide (mmol/liter)	28.3
Urea nitrogen (mg/dl)	20
Creatinine (mg/dl)	0.8
Glucose (mg/dl)	109
Calcium (mg/dl)	9.7
Phosphorus (mg/dl)	6.0
Magnesium (meq)	1.9
Bilirubin (mg/dl)	
Total	3.0
Direct	0.5
Protein (g/dl)	7.5
Albumin	4.2
Globulin	3.3
Serum osmolality (mOsm/kg of water)	281
Alanine aminotransferase (U/liter)	25
Aspartate aminotransferase (U/liter)	37
Alkaline phosphatase (U/liter)	177
Creatine kinase (U/liter)	207
Creatine kinase isoenzymes (U/liter)	3
Troponin T (ng/ml)	<0.01
Serum and urine toxicologic screens	Negative
Urine sodium (mmol/liter)	6
Urine potassium (mmol/liter)	27
Urine chloride (mmol/liter)	<10
Urine osmolality (mOsm/kg of water)	273

* To convert the value for urea nitrogen to millimoles per liter, multiply by 0.3569. To convert the value for creatinine to micromoles per liter, multiply by 88.4. To convert the value for glucose to millimoles per liter, multiply by 0.05551. To convert the value for calcium to millimoles per liter, multiply by 0.25. To convert the value for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for total and direct bilirubin to micromoles per liter, multiply by 17.1.

Table 2. Endocrine Test Results.*

Variable	First Hospital Day	Second Hospital Day	Fourth Hospital Day	Fifth Hospital Day	Normal Range
Plasma					
Renin (ng/ml/h)			1.0	11.0	0.65–5.0
Aldosterone (ng/dl)	202		2.3	21.3	1–31
Norepinephrine (pg/ml)		2854			70–1700
Dopamine (pg/ml)		35			<30
Epinephrine (pg/ml)		80			0–140
Normetanephrine (nmol/liter)		5.05			<0.90
Metanephrine (nmol/liter)		0.25			<0.50
Deoxycorticosterone (ng/dl)		9			2–34
17-Hydroxypregnenolone (ng/dl)		10			<100
Urine					
Volume (ml/24 hr)			1150		
Dopamine (μg/24 hr)			325		65–400
Epinephrine (μg/24 hr)			5.5		0.2–10.0
Metanephrine (μg/24 hr)			83		43–122
Norepinephrine (μg/24 hr)			203		13–65
Normetanephrine (μg/24 hr)			1137		55–277
Total metanephrine (μg/24 hr)			1220		107–394

* To convert the values for renin to nanograms per liter·second, multiply by 0.2778. To convert the values for aldosterone to picomoles per liter, multiply by 27.74. To convert the values for norepinephrine to nanomoles per liter, multiply by 0.005911. To convert the values for dopamine to picomoles per liter, multiply by 6.528. To convert the values for epinephrine to picomoles per liter, multiply by 5.458. To convert the values for deoxycorticosterone to nanomoles per liter, multiply by 30.3. To convert the values for urine dopamine to nanomoles per 24 hours, multiply by 6.53. To convert the values for urine epinephrine to nanomoles per 24 hours, multiply by 5.458. To convert the values for urine metanephrine and total metanephrine to nanomoles per 24 hours, multiply by 5.07. To convert the values for urine norepinephrine to nanomoles per 24 hours, multiply by 5.911. To convert the values for urine normetanephrine to nanomoles per 24 hours, multiply by 5.46.

mal. Medial to the middle portion of the right kidney and lateral to the inferior vena cava, there was a well-demarcated solid, round paraspinal mass, 2.9 cm by 2.3 cm by 1.8 cm, which showed prominent vascularity on color Doppler imaging. No mass was identified in either adrenal bed.

On the fourth hospital day, the patient's systolic blood pressure was in the range of 107 to 136 mm Hg and the diastolic pressure was in the range of 53 to 73 mm Hg; the labetalol was discontinued. Oral hydralazine and enalapril were started. Visual acuity was stable at 20/65 in the right eye and 20/100 in the left eye, although the bilateral papilledema and macular exudates persisted; subretinal fluid decreased by 10 percent as compared with earlier examinations. The results of the 24-hour urine collection are shown in Table 2. Systolic blood pressure was maintained at 125 to 150 mm Hg and diastolic pressure at 58 to 86 mm Hg with oral hydralazine and enalapril.

A brain MRI scan on the sixth hospital day showed no change from the scans obtained three days before admission. A renal MRI scan showed a well-demarcated mass, 3.0 cm by 2.4 cm by 2.2 cm, in the hilum of the right kidney, which was isointense with the kidney on T_1-weighted and T_2-weighted images; after the administration of gadolinium there was decreased enhancement as compared with the renal parenchyma. The right kidney had two renal arteries; the upper artery appeared normal, whereas the lower artery appeared to be compressed by the tumor. The upper pole of the right kidney was better perfused than the lower and middle portions. Scintigraphy with iodine-123–labeled metaiodobenzylguanidine (MIBG) on the seventh hospital day showed no abnormal uptake in the area of the renal hilar mass.

During the second week of hospitalization, a clonidine patch and phenoxybenzamine were added to the patient's treatment regimen of hydralazine,

enalapril, and acetazolamide, with adjustments to the drug therapy to maintain her systolic blood pressure at 100 to 140 mm Hg and the diastolic pressure at 55 to 90 mm Hg. Her visual acuity continued to improve.

A diagnostic procedure was performed on the 14th hospital day.

DIFFERENTIAL DIAGNOSIS

Dr. Katherine Nimkin: The initial axial T_2-weighted MRI of the brain shows T_2 hyperintensity in the cerebellar white matter on the right, with a possible slight mass effect (Fig. 1). An axial fast fluid-attenuated inversion recovery (FLAIR) MRI from the same study confirms the presence of a hyperintense lesion in the right-sided cerebellar white matter that was not enhanced after gadolinium administration (Fig.1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). T_2-hyperintense lesions in this location may be seen in patients with neurofibromatosis type 1 and are believed to represent hamartomas or areas of increased fluid within the myelin; the lesions may disappear over time.[1] A postinflammatory demyelinating process is also possible. The presence of a slight mass effect raises the possibility of a tumor, but the absence of contrast enhancement on MRI makes this unlikely — although a low-grade neoplasm might not show enhancement.

Dr. Daniel S. Kohane: This nine-year-old girl had a history of headaches, enuresis, and the new onset of blurred vision, papilledema, and severe hypertension. Her case represented two problems for the physicians in the intensive care unit: managing the hypertension and determining its cause.

MANAGEMENT OF HYPERTENSIVE EMERGENCIES

Identifying the Problem

We first considered whether the hypertension required immediate treatment or whether treatment might be either unnecessary or harmful, as it could be if the hypertension were related to pain, hypoxemia, hypercapnea, or increased intracranial pressure. Second, we needed to identify and treat the physiological variables contributing to the child's condition.

Blood pressure is determined by three variables[2]: functional intravascular volume, cardiac output, and vascular tone, which are interrelated. Blood pressure is proportional to cardiac output and systemic vascular resistance and can be expressed as the product of the two. Autonomic reflexes will act to maintain a normal blood pressure. For example, increases in systemic vascular resistance will be offset by a decrease in cardiac output. Conversely, increases in cardiac output will be counteracted by vasodilation. Furthermore, cardiac output is the product of the stroke volume and heart rate. Changes in vascular tone can increase stroke volume by venoconstriction, which may increase venous return. In contrast to hypotension, volume typically plays a secondary role in causing severe hypertension.

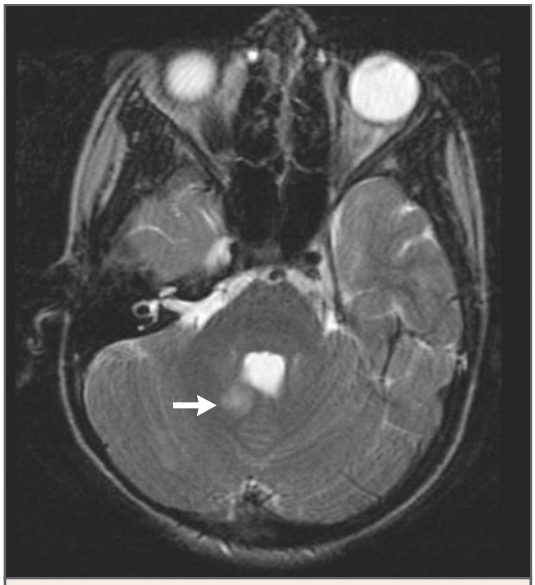

Figure 1. Axial T_2-Weighted MRI of the Brain.
The arrow shows the area of T_2-weighted hyperintensity in the cerebellar white matter on the right, with slight mass effect.

The vital signs can be helpful in figuring out which variables are causing the increased blood pressure. Bradycardia suggests increased peripheral vascular resistance; tachycardia suggests increased cardiac output; diastolic hypertension suggests elevated vascular tone, whereas systolic hypertension points toward increased cardiac output. Blanched or poorly perfused skin suggests increased vascular tone, whereas a flushed appearance suggests increased cardiac output (perhaps with compensatory vasodilation), as do a hyperdynamic precordium and tachycardia; the last two factors were present in this patient. Measurement of blood pressure in all four extremities should reveal coarctation of the aorta, and abnormalities of the genitalia or skin pigmentation can suggest errors of steroidogenesis.

Hypoxemia, hypercapnea, and pain were ruled out as causes of the patient's hypertension. Papille-

dema indicates increased intracranial pressure. Initially, it was unclear whether the severe hypertension was the cause or the result of increased intracranial pressure, although in the former scenario, one might have expected bradycardia, abnormalities in the respiratory pattern (Cushing's triad), and abnormalities on the neurologic examination. The tachycardia suggested that cardiac output would be a reasonable target for pharmacotherapy. The patient's warm skin, the only moderately elevated diastolic blood pressure, and the lack of success with hydralazine were signs that vascular tone was probably not the principal problem.

The patient's preexisting symptoms suggested a small group of underlying causes of hypertension: pheochromocytoma, thyrotoxicosis, or a carcinoid tumor that was secreting serotonin. In addition, the signs of hypokalemia and alkalosis raised the possibility of hyperaldosteronism. The classic triad of paroxysmal headache, palpitations, and flushing seen in adults with pheochromocytoma is uncommon in the pediatric population (Table 3), and the symptoms are characteristically sustained rather than paroxysmal. Nevertheless, this girl's symptoms were sufficiently evocative of the adult picture that the diagnosis was entertained.

Laboratory tests and imaging were obtained, along with a lumbar puncture to determine the opening pressure.

Table 3. Findings in Childhood Pheochromocytoma.

Cardiovascular	
	Hypertension
	Tachycardia
	Dysrhythmias
	Catecholamine cardiomyopathy
	Cardiac failure
	Orthostatic hypotension
	Acrocyanosis
Neurologic	
	Nausea and vomiting
	Visual disturbances
	Emotional lability
	Headache
	Hypertensive encephalopathy
	Tremor
Hematologic	
	Polycythemia
Constitutional	
	Weight loss
	Growth failure
	Constipation
	Polydipsia
	Sweating
	Hyperglycemia
Renal	
	Polyuria
	Enuresis

Treating the Problem

Functional intravascular volume, cardiac output, and vascular tone are all amenable to pharmacologic manipulation by diuretics, anti-inotropic agents, and vasodilators. Treatment of one variable can be defeated by compensatory reflexes, which may necessitate combination therapy. Treatment can be diagnostic, in that therapeutic failure suggests an incorrect physiological diagnosis.

Prolonged hypertension can shift the autoregulatory curves of organs, so that normalization of blood pressure can result in organ dysfunction[3]; in the central nervous system this can mean alteration in mental status or even stroke. The planned rapidity of correction should depend on the magnitude of the hypertension, the severity of the associated signs and symptoms, and the type of monitoring available. In general, hypertensive emergencies should be treated with drugs that are relatively rapid in onset and cessation of action, starting with small doses and titrating them as aggressively as is safe.

If increased intracranial pressure were the primary problem in this patient, then a slow correction of the blood pressure would be advisable, particularly in the absence of a direct measure of intracranial pressure with which to calculate cerebral perfusion pressure. The relationship between cerebral perfusion pressure and mean arterial pressure is expressed as follows: CPP = MAP − ICP or CVP, whichever is greater, where CPP denotes cerebral perfusion pressure, MAP mean arterial pressure, ICP intracranial pressure, and CVP central venous pressure.

If hypertension were the primary problem, relatively rapid treatment would be indicated to prevent organ injury. We felt that the preponderance of the evidence supported our decision to address the hypertension. We placed an arterial line to facilitate the rapid titration of medications. We brought the blood pressure down aggressively as long as the systolic pressure was greater than 180 mm Hg and more slowly thereafter. We chose a range slightly above normal as the target blood pressure. We followed the patient's mental status closely, as a measure of organ function. Since the opening and closing pressures on lumbar puncture were 28 cm and 11 cm of water, respectively, we maintained the mean arterial pressure above 70 mm Hg to ensure adequate cerebral perfusion pressure.

We chose to use labetalol, which is both a cardiac depressant (a beta-blocker) and, to a lesser extent, a vasodilator (an alpha-blocker) to lower the patient's blood pressure. Although conventional wisdom holds that beta-blockade is contraindicated in pheochromocytoma, since it can displace excess catecholamines from β- to α-adrenergic receptors,[4] thus worsening hypertension, this patient's physiology suggested that cardiac function was an appropriate target. Furthermore, labetalol has been used with good effect in pheochromocytoma.

Dr. Nimkin: A transverse ultrasonographic image of the right kidney (Fig. 2A) shows a round, solid mass medial to the kidney and lateral to the inferior vena cava. The right kidney is smaller than the left kidney. Color Doppler imaging reveals prominent vascularity of the mass. Doppler imaging of the intrarenal arteries shows a parvus et tardus waveform on the right, which is characterized by a slow systolic upstroke and decreased flow velocity, as compared with that on the left — a finding that usually reflects renal-artery stenosis (Fig. 2 of the Supplementary Appendix).

A coronal fast spin–echo T_2-weighted MRI shows asymmetry in renal size (Fig. 3 of the Supplementary Appendix). An axial fast spin–echo T_2-weighted MRI shows a mass that is isointense to the kidney, adjacent to the renal hilum (Fig. 2B). A gadolinium-enhanced, three-dimensional magnetic resonance angiographic image shows decreased perfusion of the right lower pole and slight narrowing of the lower right renal artery, presumably due to a mass effect from the tumor (Fig. 2C).

Iodine-123-MIBG imaging of the abdomen shows no abnormal uptake in the region of the right renal hilum. MIBG is taken up by storage granules in adrenergic tissue of neural-crest origin.[5] The reported sensitivity of this method for the detection of pheochromocytoma is 83 to 100 percent, with a specificity of 95 to 100 percent.[6] The sensitivity is increased with larger tumors or epinephrine production and when the tumor in question is intraadrenal rather than extraadrenal. Antihypertensive drugs can interfere with MIBG uptake and should be withheld for one to three days before the study. The patient's medications may have interfered with MIBG uptake in the tumor.

Dr. Julie R. Ingelfinger: This child's initial treatment focused on the hypertensive emergency, with consideration given to both safety and probable diagnoses in administering medication. The next step

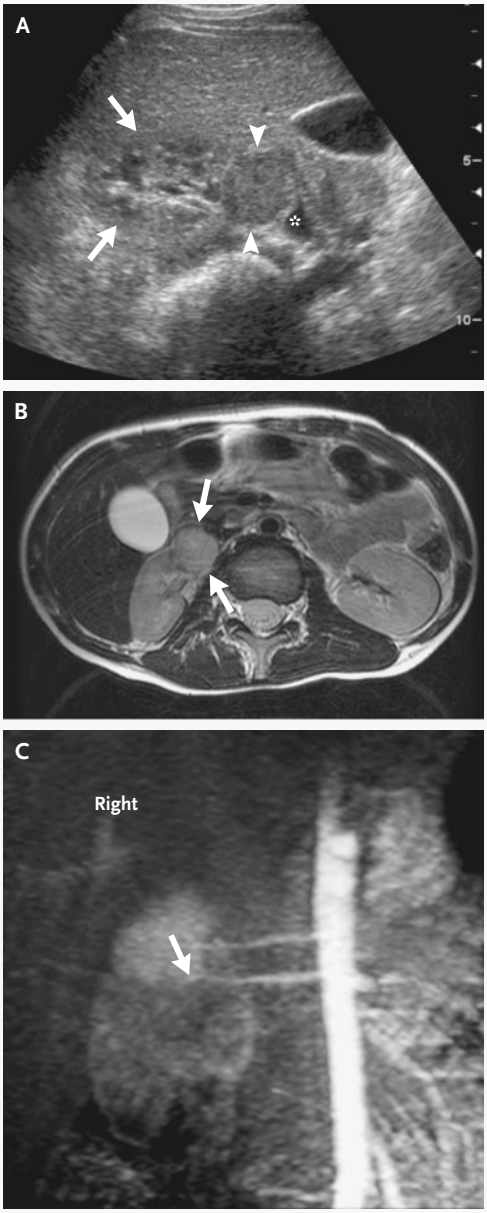

Figure 2. Imaging Studies of the Abdomen.

A transverse ultrasonographic image of the abdomen (Panel A) shows a round, solid mass, 3 cm in diameter (arrowheads) medial to the kidney (arrows) and lateral to the inferior vena cava (asterisk). An axial fast spin–echo T_2-weighted MRI of the abdomen (Panel B) shows a hyperintense mass adjacent to the right renal hilum (arrows); the right kidney is smaller than the left kidney. A gadolinium-enhanced, three-dimensional magnetic resonance angiogram (Panel C) shows two right renal arteries with slight narrowing of the lowermost artery in the region of the mass (arrow).

was to assess potential underlying diagnoses, a process that was easily focused by her presentation.

Though elevated blood pressure was not recorded at the time, the onset of enuresis eight months before admission suggests an inability to form concentrated urine, a sign observed with both catecholamine-secreting tumors and renal parenchymal disease associated with hypertension.[7] A number of conditions can be associated with severe hypertension and increased catecholamine secretion, including primary (essential) hypertension, severe anxiety, hyperthyroidism, ingestion of various substances, diencephalic seizures, and certain lesions of the central nervous system, as well as catecholamine-secreting tumors.[8]

Screening for toxins was negative, and the level of thyrotropin was normal. Although a carcinoid tumor was initially part of the differential diagnosis, one would not expect elevated metanephrine and normetanephrine levels. The presence of a perihilar mass and abnormal catecholamine values indicated that the patient almost certainly had a catecholamine-secreting tumor that was causing her hyperadrenergic state. There was no history of flushing, but a pheochromocytoma causes flushing less often in children than in adults.[9] The location of the mass, despite the negative MIBG scan, suggests that pheochromocytoma (paraganglioma) was more likely than a neuroblastoma.

Does the ipsilateral small kidney indicate the presence of intrinsic parenchymal disease? Renal parenchymal disease accounts for 80 percent of cases of secondary hypertension in children, and renal vascular disease for 10 percent.[10] This child had proteinuria (2+ by dipstick assay) on admission, but proteinuria could be explained by the severe hypertension per se. The negative results of screening of the urine sediment argue against renal parenchymal disease.

The elevated level of plasma renin activity and the patient's initial elevated aldosterone level suggest secondary hyperaldosteronism, which is most often secondary to a renovascular lesion or, sometimes, to hypertension with renal parenchymal disease. The transtubular potassium gradient was inappropriately high. With hypokalemia, one would expect the transtubular potassium gradient to be under 3, but in this case the value was greater than 9.2, suggesting potassium wasting, which is also consistent with secondary hyperaldosteronism.[11]

Could the tumor have contributed to renovascular disease, either by external compression of renal vessels or by hormonal secretion? Renal-artery stenosis in the setting of pheochromocytoma has been recognized since 1958 (Table 4)[12-14] and occurred in 3.7 percent of 269 cases, as reported by Gill et al.[13] In this child, both the imaging studies and the physiological findings suggest that the tumor is responsible for the renovascular changes in the right kidney. Detecting this is important, as it may be feasible to perform resection of a pheochromocytoma and renal revascularization in one procedure.[15]

Table 4. Categorization of Renal Lesions in Patients with Pheochromocytoma.

Spontaneous	Iatrogenic
Direct compression of renal artery	Postarteriography resection
Catecholamine-induced vasospasm	Surgical trauma
Intrinsic renovascular disease	Adhesions after excision

Does this patient have a unifying systemic diagnosis? Certainly, neurofibromatosis comes to mind, as she had three café-au-lait spots, although the diagnostic criteria for neurofibromatosis in a child older than five years of age require six or more café-au-lait spots larger than 1.5 cm.[14] Her cerebral lesions might also be consistent with a diagnosis of neurofibromatosis.

PERIOPERATIVE MANAGEMENT OF PHEOCHROMOCYTOMA

Dr. Kohane: Once the acute issues had been addressed, we needed to reverse sympathetic stimulation and prevent it from recurring in preparation for surgery.[16] Oral phenoxybenzamine (a long-acting α-adrenergic antagonist), which is usually started two weeks or more before surgery, was started on day 4 of the patient's hospital stay, both to prevent the release of catecholamines from the presumed pheochromocytoma and to reverse chronic vasoconstriction so as to allow volume repletion.[17] Volume repletion prevents orthostatic hypotension in the presence of α-adrenergic agents, normalizes the hematocrit, and reduces the odds of hypotension on induction of anesthesia or after tumor removal. Clonidine was also begun in order to minimize sympathetic stimulation. Intravenous phentolamine, a shorter-acting α_1- and α_2-antagonist, was used for intraoperative blood-pressure control. Beta-blocking agents can be used for dysrhythmias, but they were not necessary in this case. A cardiac evaluation

is important if catecholamine cardiomyopathy is suspected, since its presence may warrant more invasive monitoring. In this patient, the results of echocardiography showed no abnormalities.

Analgesia and anxiolytic treatment should be provided. Drugs that cause the release of histamine, which is a sympathetic stimulant, should be avoided (examples are morphine, succinylcholine, atracurium, cisatracurium [but to a lesser extent], and mivacurium). Abdominal examination can cause catecholamine release, presumably by direct palpation of the pheochromocytoma. Succinylcholine can trigger secretion from pheochromocytomas by inducing abdominal-wall fasciculations. Droperidol and metoclopramide can increase secretion of catecholamine from pheochromocytomas.

On day 14, a laparotomy with removal of the retroperitoneal mass was performed. The intraoperative course was uneventful.

CLINICAL DIAGNOSIS

Pheochromocytoma.

PATHOLOGICAL DISCUSSION

Dr. Chin-Lee Wu: The mass was well circumscribed, 2.8 cm in maximal diameter, with a homogeneous tan cut surface. Microscopical examination revealed anastomosing trabeculae and nests of tumor cells with indistinct cell borders and abundant amphophilic cytoplasm (Fig. 3A). The tumor cells were positive by immunohistochemical staining for neuroendocrine markers, chromogranin, synaptophysin, and neuron-specific enolase (Fig. 3B). Electron-microscopical examination revealed numerous electron-dense neuroendocrine granules (Fig. 4 of the Supplementary Appendix). The morphologic, immunologic, and ultrastructural features of this mass are diagnostic of an extraadrenal paraganglioma (pheochromocytoma).

Paragangliomas are named according to their anatomical sites of origin: adrenal medullary paraganglioma is referred to as pheochromocytoma. Extraadrenal paragangliomas or pheochromocytomas occur more frequently in children than in adults.[9,18] The biologic behavior of pheochromocytomas cannot be reliably predicted by macroscopic or microscopic features. Features associated with distant metastasis include vascular invasion, capsular invasion, diffuse architecture, mitoses, high cellularity, and necrosis.[19,20] In this patient's tumor, focal small-vessel invasion was present, but the significance of this finding is unclear. Other features suggesting malignancy were not seen.

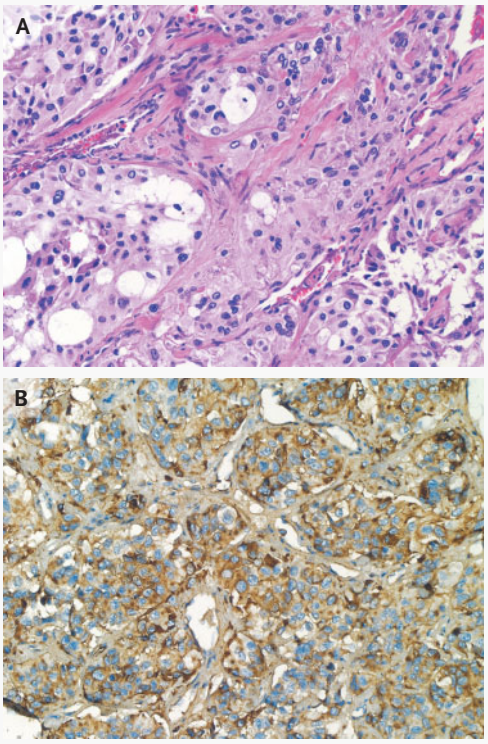

Figure 3. Histologic Sections of the Resected Tumor.
The tumor consists of cells with indistinct cell borders and abundant amphophilic cytoplasm, arranged in nests and trabecular patterns (Panel A, hematoxylin and eosin). Staining for chromogranin showed dense cytoplasmic staining in the tumor cells (Panel B, immunoperoxidase stain).

Dr. Ingelfinger: Several issues should be considered in the long-term management of this patient. First, recent reports suggest that many apparently sporadic pheochromocytomas are associated with germ-line mutations.[21,22] Periodic evaluations of her catecholamine status will be required to detect recurrent or new tumors. Although some advocate periodic urinary collections for measurement of catecholamines,[8] recent data pooled from four centers[23] suggest that measurement of free metanephrines in plasma is more sensitive and specific and should be performed six weeks after surgery, at six months, and then yearly.

A second issue is the renal vasculature in this patient. Will the disparity in renal size diminish after the removal of the tumor? Radioangiography with technetium-99m mercaptoacetyltriglycine performed one week after the operation showed that

the smaller kidney was contributing only an estimated 10 percent of total renal function. Complete recovery of function in the right kidney would seem unlikely.

Dr. Harris: Dr. Daouk, can you tell us how the child is doing?

Dr. Ghaleb H. Daouk (Pediatric Nephrology): After the patient was discharged, her mother monitored her blood pressure at home. Within six months, the child no longer needed to take the enalapril, and I stopped the labetalol treatment after nine months. Six months after the operation, her catecholamine levels were normal, and the right kidney was providing 25 percent of the renal function. A follow-up ultrasonographic examination showed that the right kidney had increased in size by 0.7 cm. Her most recent urinalysis showed no proteinuria, and her creatinine level was 0.5 mg per deciliter. One year after the operation, her blood pressure was normal without antihypertensive medications and the optic fundi were normal. We have suggested to the family that the patient be tested for mutations in the *VHL*, *SDHA*, *SDHB*, *SDHD*, and *RET* genes.

Dr. Harris: Did the enuresis stop?

Dr. Daouk: It improved but did not stop completely.

ANATOMICAL DIAGNOSIS

Pheochromocytoma.

REFERENCES

1. Feldmann R, Denecke J, Grenzebach M, Schuierer G, Weglage J. Neurofibromatosis type I: motor and cognitive function and T2-weighted MRI hyperintensities. Neurology 2003;61:1725-8.
2. Guyton AC, Hall JE. Textbook of medical physiology. 9th ed. Philadelphia: W.B. Saunders, 1996.
3. Reed G, Devous M. Cerebral blood flow autoregulation and hypertension. Am J Med Sci 1985;289:37-44.
4. Sloand EM, Thompson BT. Propranolol-induced pulmonary edema and shock in a patient with pheochromocytoma. Arch Intern Med 1984;144:173-4.
5. Ilias I, Pacak K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. J Clin Endocrinol Metab 2004;89:479-91.
6. van der Harst E, de Herder WW, Bruining HA, et al. [(123)I]metaiodobenzylguanidine and [(111)In]octreotide uptake in benign and malignant pheochromocytomas. J Clin Endocrinol Metab 2001;86:685-93.
7. Galvez OG, Roberts BW, Mishkind MH, Bay WH, Ferris TF. Studies of the mechanism of contralateral polyuria after renal artery stenosis. J Clin Invest 1977;59:609-15.
8. Case Records of the Massachusetts General Hospital (Case 13-2001). N Engl J Med 2001;344:1314-20.
9. Stackpole RH, Melicow MM, Uson AC. Pheochromocytoma in children: report of 9 cases and review of the first 100 published cases with follow-up studies. J Pediatr 1963; 63:314-30.
10. Londe S. Causes of hypertension in the young. Pediatr Clin North Am 1978;25:55-65.
11. West ML, Marsden PA, Richardson RM, Zettle RM, Halperin ML. New clinical approach to evaluate disorders of potassium excretion. Miner Electrolyte Metab 1986;12: 234-8.
12. Harrison JH, Gardner FH, Dammin GJ. A note on pheochromocytoma and renal hypertension. J Urol 1958;79:173-8.
13. Gill IS, Meraney AM, Bravo EL, Novick AC. Pheochromocytoma coexisting with renal artery lesions. J Urol 2000;164:296-301.
14. Camberos A, Bautista N, Rubenzik M, Applebaum H. Renal artery stenosis and pheochromocytoma: coexistence and treatment. J Pediatr Surg 2000;35:714-6.
15. Pickard JL, Ross G, Silver D. Co-existing extraadrenal pheochromocytoma and renal artery stenosis: report and review of the pathophysiology. J Pediatr Surg 1885; 30:1613-5.
16. Kohane DS, Tobin T, Kohane I. Endocrine, mineral and metabolic disease in pediatric intensive care. In: Rogers MC, Nichols DG, eds. Textbook of pediatric intensive care. Baltimore: Williams & Wilkins, 1996: 1247-314.
17. Williams DT, Dann S, Wheeler MH. Phaeochromocytoma — views on current management. Eur J Surg Oncol 2003;29: 483-90. [Erratum, Eur J Surg Oncol 2003; 29:933.]
18. Reddy VS, O'Neill JA Jr, Holcomb GW III, et al. Twenty-five-year surgical experience with pheochromocytoma in children. Am Surg 2000;66:1085-91.
19. Linnoila RI, Keiser HR, Steinberg SM, Lack EE. Histopathology of benign versus malignant sympathoadrenal paragangliomas: clinicopathologic study of 120 cases including unusual histologic features. Hum Pathol 1990;21:1168-80.
20. Thompson LD. Pheochromocytoma of the Adrenal gland Scaled Score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. Am J Surg Pathol 2002; 26:551-66.
21. Neumann HPH, Bausch B, McWhinney SR, et al. Germ-line mutations in nonsyndromic pheochromocytomas. N Engl J Med 2002;346:1459-66.
22. Dluhy RG. Pheochromocytoma — death of an axiom. N Engl J Med 2002;346:1486-8.
23. Lenders JWM, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 2002;287: 1427-34.