Pheochromocytoma
Sadiqa Edmonds, Daniel M. Fein and Alison Gurtman
_Pediatrics in Review_ 2011;32;308
DOI: 10.1542/pir.32-7-308

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pedsinreview.aappublications.org/content/32/7/308
high likelihood of spontaneous regression. In other words, most of the tumors found would have disappeared without ever becoming symptomatic, but their identification leads to the enormous anxiety associated with cancer and often to treatment that is more likely to be toxic than beneficial. The ability to screen does not mean that all screening should be undertaken, an issue raising controversy for our colleagues in adult medicine about the use, for example, of prostate-specific antigen as a screen for prostate cancer.

Henry M. Adam, MD
Editor, In Brief

In Brief

Pheochromocytoma

Sadiqa Edmonds, MD
Daniel M. Fein, MD
Alison Gurtman, MD
Children’s Hospital at Montefiore
Bronx, NY

Pheochromocytoma, a rare disease occurring more often in adults than in children, accounts for only about 1% of pediatric hypertension and often is associated with a variety of genetic syndromes. The National Registry of Childhood Cancers reports an incidence of 0.11 benign and 0.02 malignant pheochromocytomas per 1 million children. Eighty-five percent of pheochromocytomas are located in the adrenal glands; the rest develop in the extra-adrenal parasympathetic and sympathetic paraganglia. Most tumors are less than 5 cm in size, and 25% to 33% are bilateral. Approximately 10% of intra-adrenal and 40% of extra-adrenal pheochromocytomas are malignant. In childhood, these tumors are more prevalent in boys than girls, but during adolescence this trend reverses, possibly because of hormonal influences.

In children 18 years of age and younger, about 60% of pheochromocytomas have an associated germline mutation, and in children younger than 10 years, this number increases to 70%. Familial genetic syndromes predispose to the development of pheochromocytoma by altering sympathetic neuronal cell precursor apoptosis. A family history of genetic syndromes is common but not equivocal in affected children. Many associated syndromes are autosomal dominant, but spontaneous mutations occur.

The Table summarizes four familial syndromes commonly associated with pheochromocytoma. Von Hippel-Lindau syndrome (VHL), a neurocutaneous syndrome associated with 20% of all pheochromocytomas, carries a 10% to 20% risk of developing pheochromocytoma. The tumors can be bilateral or extra-adrenal, but only 5% associated with VHL are malignant.

Multiple endocrine neoplasia (MEN) types IIA and IIB are associated with pheochromocytoma. MEN IIA manifests with parathyroid hyperplasia, adrenal medullary hyperplasia or pheochromocytoma, and medullary thyroid carcinoma. MEN IIB is characterized by neuromas, medullary carcinoma, and pheochromocytoma. The risk of pheochromocytoma in MEN IIA is about 50% and in MEN IIB is higher.

Neurofibromatosis type 1, an autosomal dominant syndrome associated with café au lait macules, Lisch nodules, neurofibromas, optic gliomas, and axillary or inguinal freckling, carries a 1% risk of pheochromocytoma. In familial paraganglioma syndrome, which is also autosomal dominant, paragangliomas develop in the head, neck, chest, abdomen, and pelvis; about 20% of affected patients develop a pheochromocytoma.

Pheochromocytomas become symptomatic from the increased secretion of norepinephrine (predominant in chil-
Table. Familial Syndromes Associated With Pheochromocytoma

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Risk of Pheochromocytoma</th>
<th>Genetic Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Hippel-Lindau syndrome</td>
<td>10% to 20%</td>
<td>Chromosome 3p25.5</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia</td>
<td>≥50%</td>
<td>RET gene on 10q11.2</td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>1%</td>
<td>NF1 gene on 17q11.2</td>
</tr>
<tr>
<td>Familial paraganglioma syndrome</td>
<td>20%</td>
<td>SDHB/SDHD gene on 11q23</td>
</tr>
</tbody>
</table>

Children, epinephrine, and dopamine. Children often have sustained hypertension as their primary sign, which may be severe enough to cause encephalopathy or cardiac failure. Children are less likely than adults to present with the classic triad of tachycardia, headache, and diaphoresis. Associated findings can include visual changes, nausea, vomiting, constipation, diaphoresis, orthostatic hypotension, urinary symptoms, psychiatric disturbances, and weight loss. Although patients have presented with symptomatic pheochromocytomas after glucocorticoid therapy, this outcome is uncommon in pediatrics. All reported cases have been adults. The mechanism is still being debated.

In addition to the effects of hormones released by the pheochromocytoma, the mass effect of the tumor may cause abdominal pain and distention or back pain. Laboratory abnormalities can include increased erythrocyte sedimentation rate, polycythemia, leukocytosis, and hyperglycemia. Panic attacks, thyrotoxicosis, intracranial lesions, renovascular disease, and sympathomimetic drug use are in the differential diagnosis.

The diagnosis depends on demonstrating both catecholamine excess and evidence of a tumor on imaging. Measuring fractionated metanephrines, the metabolites of catecholamines, in urine or plasma is the most sensitive test. However, no consensus has established which of these tests is superior. For children who have episodic symptoms, the best time to assess concentrations is during or immediately after an episode, when hormone values are highest. Borderline elevations typically are false-positive findings.

Diagnostic imaging can start with ultrasonography in symptomatic patients. Computed tomography (CT) scan and magnetic resonance imaging (MRI) with contrast both have high sensitivity. Iodinated contrast media can contribute to a hypertensive crisis, so it is prudent to avoid using contrast in patients who have significant hypertension. MRI is a better choice for locating extra-adrenal tumors. A less sensitive but more specific method of diagnosis is a \(^{131}I\) or \(^{123}I\)-metaiodobenzylguanidine (MIBG) scan. MIBG is a radiodine-labeled norepinephrine analog that is taken up by tumor cells but not by healthy adrenal medullary cells. The test is useful for discovering multiple tumors if CT scan or MRI is positive. Functional positron emission tomography is another diagnostic tool that is especially useful when the diagnosis is equivocal.

Although surgery is the preferred treatment option, tumor resection should not be attempted without preoperative medical preparation to oppose catecholamine-induced cardiovascular effects (immediate and anticipated physiologic changes during surgery) as well as to assure volume expansion. Universal consensus about the pharmacologic agent of choice has not been reached, but the preferred method is alpha-adrenergic blockade with the nonselective irreversible medication phenoxybenzamine. Administration should begin 2 weeks before surgery to allow for correction of hypertension, starting at a low dose and titrating upward, while monitoring for adverse effects such as abdominal pain, nasal congestion, and orthostasis. Selective alpha-1-adrenergic blockers are typically avoided preoperatively because they often result in incomplete alpha-adrenergic blockade.

Once alpha-adrenergic blockade has been obtained, beta-adrenergic blockade is instituted to blunt reflex tachycardia. Beta-adrenergic antagonists never should be started alone because blockage of the vasodilatory effects of beta-adrenergic receptors leads to unopposed alpha-adrenergic activity and worsening hypertension. Increased salt intake and intravenous fluids for volume expansion complete the typical preoperative regimen.

Alternative regimens for preoperative management include administration of calcium channel blockers, such as nicardipine, and inhibition of catecholamine synthesis using the tyrosine hydroxylase inhibitor alpha-methyl-para-tyrosine (metyrosine). These agents typically are reserved for patients who have refractory hypertension despite combined alpha- and beta-adrenergic blockade or for those experiencing intolerable adverse effects.

Laparoscopy often is used for resection of both benign and malignant tumors smaller than 10 cm. Total adrenalectomy is performed for unilateral tumors located in the adrenal gland. Patients who have bilateral pheochromocytomas more frequently undergo bilateral cortical-sparing adrenalectomies to prevent the need for lifelong corticosteroid replacement. Monitoring is required during surgery because hypertension can occur from manipulation of...
the tumor and immediately after tumor removal. Adjunctive therapy, such as high-dose $^{131}$I-MIBG, may be used in patients who develop metastatic disease.

Removal of a benign pheochromocytoma should result in resolution of symptoms. Hypertension beyond 24 hours after resection raises concern for retained tumor. Initial follow-up consists of monthly blood pressure and urinary catecholamine measurements. In patients who have no underlying genetic condition, annual follow-up is likely to be sufficient after the first 6 months. However, lifelong follow-up is required because tumors can recur, particularly with familial pheochromocytomas that are part of a genetic syndrome.

Comment: When I was in medical school (granted, a long time ago), we actually spent more time in physiology and pathology classes hearing about pheochromocytoma than essential hypertension. Although pheochromocytoma is in the differential diagnosis, we hope that in the midst of an epidemic of childhood obesity and associated hypertension, it is not still topping the list.

Henry M. Adam, MD
Editor, In Brief