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Pheochromocytoma — Death of an Axiom

MEDICAL students often learn axioms in order to remember the key features of a disorder. The "rule of 10" used to describe pheochromocytomas is a good example: 10 percent are extraadrenal, and of those, 10 percent are extraabdominal; 10 percent are malignant; 10 percent are found in patients who do not have hypertension; and finally, 10 percent are hereditary.[1] Familial pheochromocytoma is inherited as an autosomal dominant trait alone or as a component of the multiple endocrine neoplasia type 2 syndromes (MEN-2A and MEN-2B), von Hippel–Lindau disease, or, in rare cases, neurofibromatosis type 1.[2] The remaining 90 percent of pheochromocytomas are classified as sporadic or nonsyndromic. In this issue of the *Journal,* a report by Neumann et al.[3] on the screening of a large cohort of patients with sporadic pheochromocytoma and no family history of the disorder has dashed the rule of 10. Approximately 25 percent of the screened population had germ-line mutations of one of four susceptibility genes for pheochromocytoma.[3] Molecular analysis has advanced the knowledge that came from clinical observation.

The adrenal medulla and ganglia of the sympathetic nervous system are derived from the embryonic neural crest. The endocrine cells of this sympathoadrenal system synthesize and secrete catecholamines and exhibit a characteristic histochemical (chromaffin) reaction when treated with oxidizing agents. Pheochromocytomas, rare neoplasms that produce catecholamines, usually arise from the adrenal medulla. If they arise in extraadrenal chromaffin tissue, they are called paragangliomas or extraadrenal pheochromocytomas. Patients with pheochromocytomas may present with sustained hypertension that is resistant to conventional treatment. A classic clinical feature is a paroxysm resulting in the triad of episodic headache, sweating, and palpitations as a result of the release of stored catecholamines from the tumor. An unrecognized pheochromocytoma may lead to death as the result of a hypertensive crisis, arrhythmia, or myocardial infarction.

After biochemical confirmation of catecholamine excess, radiographic imaging of the abdomen reveals an adrenal pheochromocytoma in the majority of cases. Demonstration of normal adrenal glands points toward a diagnosis of paraganglioma, which arises from sympathetic ganglia in the abdomen, chest, head, and neck.[4] Nonchromaffin paragangliomas (chemodectomas) arise from parasympathetic ganglia in the head and neck and include the carotid-body and glomus-jugulare tumors of the 9th and 10th cranial nerves. Paragangliomas below the head and neck are often functional, and patients with these tumors present with signs of catecholamine excess. The predominant clinical manifestation of tumors of the head and neck is a mass effect, such as cranial-nerve palsies and tinnitus, but a small proportion of such tumors may secrete catecholamines.[4]

Recently, the gene encoding succinate dehydrogenase subunit D (*SDHD*) was identified as a susceptibility gene for autosomal dominant familial paraganglioma (glomus tumor).[5] Since pheochromocytomas and glomus tumors are both derived from neural-crest tissue, analysis of *SDHD* as a susceptibility gene for sporadic pheochromocytoma was performed in several small studies, with both positive[6] and negative[7] results. In the report by Neumann et al., a large cohort of patients with nonsyndromic pheochromocytoma from two registries in Freiburg, Germany, and Warsaw, Poland, were screened for germ-line mutations of four pheochromocytoma-susceptibility genes.[3] These included the proto-oncogene *RET* (MEN-2), the tumor-suppressor gene *VHL,* and two novel genes that confer a predisposition to the development of pheochromocytomas and glomus tumors: *SDHD* and the gene encoding succinate dehydrogenase subunit B (*SDHB*). Of 271 patients, 66 (24 percent) had germ-

line mutations. Of these, 30 had mutations of *VHL* (45 percent), 13 of *RET* (20 percent), 11 of *SDHD* (17 percent), and 12 of *SDHB* (18 percent). Retrospective identification of clinical clues to the presence of a hereditary syndrome included multifocal and extraadrenal tumors and a young age. However, these features were noted to be disease-specific. For example, 80 percent of probands with the newly identified mutations of *SDHD* and *SDHB* presented with solitary pheochromocytomas, and 40 percent were older than 30 years of age.

Previously identified germ-line mutations that confer a predisposition to pheochromocytoma involve both proto-oncogenes and tumor-suppressor genes (Table 1). Activating mutations of the *RET* proto-oncogene in the MEN-2 syndromes act as gain-of-function mutations, causing constitutive activation of the receptor tyrosine kinase.[8] As a result of tissue-specific expression, calcitonin-producing parafollicular cells and adrenomedullary chromaffin cells initially undergo hyperplasia, with a high rate of subsequent neoplastic transformation. In contrast, von Hippel–Lindau disease results from loss-of-function (i.e., inactivating) mutations of the *VHL* suppressor gene. The VHL protein regulates the normal degradation of proteins such as hypoxia-inducible factor, which is implicated in the response to low oxygen tension.[9] *SDHD* and *SDHB* are part of mitochondrial complex II, which regulates oxygen sensing and signaling.[10,11] Therefore, patients with a predisposition to pheochromocytoma or paraganglioma due to mutated *VHL, SDHD,* or *SDHB* may share a defect in the oxygen-sensing system. It is postulated that this abnormality would result in activation of hypoxic signaling pathways that may be associated in some way with malignant proliferation. Finally, these same genes with germ-line mutations have also been found to be somatically mutated (i.e., in the tumor only) in sporadic cases of pheochromocytoma.[2]

The clinical implications of the germ-line mutations described by Neumann et al. in cases of pheochromocytoma that were thought to be sporadic are clear-cut for both the proband and the family. For the proband, there may be a lifelong risk of component tumors (Table 1). For example, in patients who had mutations of *SDHD* or *SDHB,* there was a 20 to 30 percent likelihood of the subsequent development of a glomus tumor. Periodic physical and ultrasonographic examinations of the neck should be performed in affected patients, since these neoplasms are difficult to treat surgically when they are advanced. In the case of von Hippel–Lindau disease and MEN-2, some of the component tumors are clearly life-threatening, such as hemangioblastoma of the central nervous system and medullary carcinoma of the thyroid, respectively. In addition, since all four of these disorders are inherited in an autosomal dominant fashion, it is important to screen first-degree relatives in order to detect new cases and identify patients who should undergo biochemical and radiographic monitoring for the development of component tumors.

On the basis of the finding that 25 percent of screened patients had germ-line mutations, Neumann et al. conclude that routine analysis for mutations of *RET, VHL, SDHD,* and *SDHB* in apparently sporadic cases of pheochromocytoma should be consid-

TABLE 1. HEREDITARY SYNDROMES ASSOCIATED WITH PHEOCHROMOCYTOMA.*

SYNDROME	CLINICAL PHENOTYPE	RISK OF PHEOCHROMOCYTOMA	MUTATED GERM-LINE GENE
		%	
MEN-2A	Medullary carcinoma of the thyroid, hyperparathyroidism	50	*RET* (proto-oncogene)
MEN-2B	Medullary carcinoma of the thyroid, multiple mucosal neuromas, marfanoid habitus, hyperparathyroidism	50	*RET* (proto-oncogene)
Neurofibromatosis type 1	Neurofibromas of peripheral nerves, café au lait spots	1	*NF1*
Von Hippel–Lindau disease (retinal cerebellar hemangioblastosis)	Retinal angioma, CNS hemangioblastoma, renal-cell carcinoma, pancreatic and renal cysts	10–20	*VHL*
Familial paraganglioma syndrome	Carotid-body tumor (chemodectoma)	20 (estimated)	*SDHD, SDHB*

*MEN-2A denotes multiple endocrine neoplasia type 2A, MEN-2B multiple endocrine neoplasia type 2B, CNS central nervous system, *SDHD* the gene for succinate dehydrogenase subunit D, and *SDHB* the gene for succinate dehydrogenase subunit B.

ered as the clinical standard of care. One cautionary note is the limited geographic area of this study; whether the results can be extended to populations in other regions is unknown. For example, in a previous study in Germany, performed by some of the same authors, a high proportion (20 percent) of patients with von Hippel–Lindau disease were found to have pheochromocytomas.[12] There is considerable genetic variability among kindreds with von Hippel–Lindau disease, and certain mutations lead to a high frequency of pheochromocytoma. Thus, it is possible that specific pheochromocytoma-predisposing mutations were predominant in the two registry populations studied by Neumann et al. On the other hand, it is possible that additional pheochromocytoma-predisposing genes will be found, further reducing the percentage of pheochromocytomas currently classified as sporadic.

What is a reasonable strategy for the diagnosis of these hereditary syndromes in a patient with a newly discovered pheochromocytoma? Although clinicians can screen for the *RET* mutation, screening is not easily available for the other three mutations. However, clinicians should now have a higher index of suspicion for familial syndromes in patients with apparently sporadic pheochromocytoma. A young age and multiple extraadrenal neoplasms are diagnostic clues that should prompt clinicians to obtain a complete family history, particularly a history of component tumors in first-degree relatives. Moreover, a careful physical examination may be diagnostic. The presence of cutaneous or mucosal neurofibromas, a thyroid mass or carotid-body tumor, or a retinal angioma provides strong clinical evidence of a hereditary syndrome. Until genetic testing for *SDHD* becomes commercially available, a high index of suspicion and clinical evaluation are appropriate.

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