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Pheochromocytoma—*quo vadis*?

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Pheochromocytomas have many unusual manifestations aside from the classic symptoms of catecholamine excess. Initial screening involves measurement of catecholamines and fractionated metanephrines in plasma and/or urine. Levels are generally at least 2–3-times the normal upper limit in patients with tumors. Conversely, two serial negative catecholamine and metanephrine screens exclude the diagnosis with 99% certainty. False positives can result from catecholamine excess due to tricyclic antidepressants or phenoxybenzamine ingestion,[1] or benign incidentalomas.

Tumor localization should follow biochemical confirmation. ^{123}I-labeled or ^{131}I-labeled metaiodobenzylguanidine is generally favored for initial imaging, and is followed by contrast-enhanced CT or MRI. Hypertensive crisis must be avoided before contrast-enhanced CT. Recently, 6-[^{18}F]-fluorodopamine PET (combined with CT) showed utility in tumor localization, but a comprehensive evaluation is needed.

Preoperative preparation has been well described, but evidence-based studies are still lacking. Blockade of α-adrenoreceptors with phenoxybenzamine, doxazosin and prazosin or combined blockade of α-adrenoreceptors and β-adrenoreceptors with labetalol, or vasodilatation with calcium-channel blockers, is essential. Reflex tachycardia might necessitate delayed introduction of a β-adrenoreceptor blocker. Metyrosine reduces catecholamine synthesis, but is rarely needed. Careful anesthetic preparation and intraoperative monitoring are vital.

Laparoscopic removal is ideal for adrenal pheochromocytomas, and even large tumors can be removed in this manner.[2] For multiple primary or secondary tumors, debulking is desirable, and increases the efficacy of systemic therapy with ^{131}I-labeled metaiodobenzylguanidine. New therapies await evaluation in clinical trials.

The identification of pheochromocytomas as a component of familial tumor syndromes, and identification of germ line mutations in ~24% of patients with nonsyndromic pheochromocytomas[3] led to the recommendation that all patients with apparently sporadic pheochromocytomas should be offered genetic counseling and germ line screening for mutations in *RET* (a proto-oncogene), *VHL* (von Hippel–Lindau tumor suppressor), *SDHD* and *SDHB* (subunits D and B of the succinate dehydrogenase complex).[3,4] Others recommend a conservative approach; they screen only those who present before 20 years of age, have a family history or features of familial disease, or have sympathetic paragangliomas—screening of other individuals is deemed optional.[5] We disagree with that approach and favor selective genetic screening of all patients with apparently sporadic pheochromocytomas, because of differences in presentation and penetrance,[6] the low penetrance of some *SDHB* mutations, imprinting of *SDHD* and the presence of *de novo VHL* mutations. Not all patients need to be tested for all genes associated with pheochromocytomas; however, specific features of an individual's disease allow prioritization.[7]

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The observation that *SDHD* is mutated in families with head and neck paragangliomas also linked this gene to hypoxia responses.[8] VHL protein, RET, the succinate dehydrogenase subunits and neurofibromin (the *NF1* gene is also associated with pheochromocytomas) might be involved in a pathway that regulates neuronal survival during development; this pathway includes prolyl hydroxylase and mediates destruction of hypoxia-inducible factor 1α.[9] Succinate might be involved in intracellular signals that inhibit prolyl hydroxylase in tumors with *SDHD* or *SDHB* mutations.[10,11] Knowledge of these pathways and elucidation of the mechanisms of tumorigenesis will inevitably identify targets for new therapies.

Supplementary information, in the form of a list of references cited in this article, is available on the *Nature Clinical Practice Endocrinology & Metabolism* website.

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Competing interests
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