Doing Away with the Rule of 10 %

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Pheochromocytomas (PCC) and paragangliomas (PGL) are rare tumors that require definitive surgical resection for management. Depending on the location of the tumor, the patient may present to any number of surgical specialists, including endocrine surgery, urology, surgical oncology, thoracic surgery, otolaryngology, and general surgery. Traditionally, PCC has been associated with the so-called Rule of 10 %, but over the last 10–15 years, this rule has been challenged as more and more data have accrued demonstrating much higher rates of germ line mutations.^{1–3}

Fishbein et al. reviewed their experience with both neuroendocrine tumor types and found an overall rate of associated mutations of 41 %.⁴ They further break down the specifics of the tumors and their associated germ line mutations. They conclude that, given the high rate of mutations, all patients with PCC or PGL should be referred for genetic counseling and/or testing.

They propose an extremely helpful algorithm in how to approach the PCC/PGL patient, and which genetic mutations would be most likely involved and therefore should be the first to investigate. In our current health care environment, where the rising cost of health care is constantly under scrutiny, this provides a means to a more methodical and systematic way to perform focused genetic testing instead of blanket testing each patient for all known possible mutations. Given the complexity of the factors involved, it also demonstrates the importance of our medical genetics colleagues in helping navigate this continually evolving area. They can best educate both the patient and provider on the utility of genetic testing, including its interpretation and implications for patients and their families.

The setting of this study is in a medical genetics clinic associated with a dedicated neuroendocrine tumor center, where all patients with PCC or PGL are at least offered referral to the medical genetics clinic.⁴ Because only 14 (10 %) of the initial 139 patients within the study cohort declined the referral, the study captured an overwhelming majority of the PCC and PGL patients managed at their institution. Although the diagnosis of PCC or PGL is generally made on the basis of a biochemical evaluation before surgery, for the purposes of this study, final pathology was required for the definitive diagnosis. Because of this, patients were referred for genetic testing in the postoperative period. Because the *SDHB* mutation is often found in tumors with the highest propensity for malignancy, would preoperative genetic testing for patients with PGL change management? Or because immunohistochemistry allows for the detection of *SDHB* on pathology specimens, would staining of all PGL specimens for *SDHB* exclude the need for genetic testing for this particular mutation if testing is only to be done in the postoperative setting, and would this approach be more cost-effective?

Although the inheritance pattern of the *SDHB* mutation is autosomal dominant, it has been shown to have a penetrance of only 25–40 %.² *SDHD* is also autosomal dominant but is affected by maternal imprinting, where the gene is only potentially active if inherited from the father.^{3,5} In both instances, this can result in multiple generations of carriers without evidence of disease, making analysis of family history much more complicated.

The best-known syndromes associated with PCC and PGL are von Hippel Lindau, neurofibromatosis type 1, and multiple endocrine neoplasia (MEN) type 2.¹ The PCC and/or PGL are just one aspect of the clinical presentation for these syndromes, and affected patients will often have additional characteristics of the syndrome at time of presentation for the PCC/PGL. Interestingly, in the study by Fishbein et al., the patients who tested positive for von Hippel Lindau, neurofibromatosis type 1, and MEN type 2

did not have a known family history before presentation 30–70 % of the time.⁴ This reinforces the importance of testing for these mutations as well, when the clinical scenario indicates.

Fishbein et al. conclude that all patients with PCC or PGL should be offered genetic testing.⁴ Given the complexity of the possible mutations causing the tumor, it is reasonable to refer patients to the medical genetics department to assist in counseling of the patient and determining which mutation to test for first. Moving forward, on the basis of the findings of Fishbein et al., the standard of care should include a referral to the medical genetics department for all patients with PCC or PGL. Appropriate long-term follow-up for both patients and their families can then be planned accordingly.

Further study is need to determine whether genetic testing of both patients and their family members will positively impact long-term outcomes. RET testing has resulted in significant improvements in the management of medullary thyroid cancer associated with MEN types 2A and 2B, as well as familial medullary thyroid cancer.¹ Only time will tell if similar improvements in patient care will result in the uniform genetic counseling and testing of all PCC/PGL patients. We encourage Fishbein and colleagues

to continue prospective assessment of their testing protocols so we may be able to learn whether outcomes are affected by this practice.

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