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Preoperative genetic testing in pheochromocytomas and paragangliomas influences the surgical approach and the extent of adrenal surgery*

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Abstract

Background—Our knowledge of the susceptibility genes for pheochromocytomas/paragangliomas (PCs/PGLs) has increased; however, data on its impact on surgical decision-making has not been described. The aim of this study was to determine the effect of routine preoperative genetic testing on the operative intervention in patients with PCs/PGLs.

Methods—One-hundred-eight patients diagnosed with PCs/PGLs who underwent 118 operations had preoperative genetic testing for nine known PC/PGL susceptibility genes. A retrospective analysis of a prospective database was performed to evaluate clinical factors associated with the surgical approach selected and the outcome of the surgical intervention.

Results—In 51 patients (47%), a germline mutation was detected and one-third had no family history of PC/PGL. In 77 operations (65%), it was the first operative intervention for the disease site (60 laparoscopic, 17 open), and 41 (35%) were reoperative interventions (36 open, 5 laparoscopic). For initial operations, variables associated with whether an open or laparoscopic approach was used were tumor size ($P=0.009$) and presence of germline mutation ($P=0.042$). Sixty-eight adrenal operations were performed (54 total, 14 cortical-sparing). Variables significantly associated with a cortical-sparing adrenalectomy being performed were the presence of germline mutation ($P=0.006$) and tumor size ($P=0.013$).

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Conclusions—Preoperative knowledge of the germline mutation status affects the surgical approach and extent of adrenalectomy.

Keywords

pheochromocytoma; paraganglioma; germline mutation; adrenalectomy; cortical-sparing adrenalectomy

Introduction

Pheochromocytoma (PC) is a tumor that originates from chromaffin cells of the adrenal medulla, while paraganglioma (PGL) arises from the chromaffin cells of sympathetic and parasympathetic ganglia, as defined by the World Health Organization (WHO). PC/PGL is present in 0.1–0.6% of patients with hypertension and is found in 0.05% of patients during autopsy.¹ Most PCs/PGLs hypersecrete catecholamines and their metabolites, which may cause difficult-to-control hypertension, diabetes mellitus, and cardiovascular morbidity.² Patients may also present with an incidentally discovered mass or with vague symptoms, which include diaphoresis, headaches, palpitations, and anxiety.¹

PC/PGL may be sporadic or inherited. Inherited PC/PGL syndromes include neurofibromatosis type 1 (NF1), multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau syndrome (VHL), myc-associated factor X (MAX), and familial PC/PGL with succinate dehydrogenase (SDHx) mutations. There has been considerable progress made in our knowledge of the susceptibility genes that predispose to PCs/PGLs, and there are 12 well-known germline mutations related to these tumors. The germline mutations occur in the following genes: *RET*, *VHL*, *NF1*, *SDHA-D*, *MAX*, *FH*, *KIF1β*, *SDHAF2*, and *TMEM127*.³ The frequency of germline mutation in patients with PC/PGL is up to 40% in patients of all ages and can be as high as 80% in the pediatric population.⁴

There is no data on preoperative genetic testing and its impact on the surgical treatment of PC/PGL. The aim of this study was to determine if routine preoperative genetic testing was associated with the type of operative intervention and the extent of adrenalectomy used in patients with PC/PGL and to determine the rate of clinically unknown inherited PC/PGL.

Methods

One hundred eight patients diagnosed with PC/PGL underwent resection of their tumors at the National Institutes of Health Clinical Center between November 2009 and September 2016. After informed consent was obtained, all patients were enrolled in clinical protocols (NCT00004847, NCT01005654). The study was approved by the institutional review boards of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Cancer Institute. Only patients with a histologic diagnosis of PC/PGL were included in the study. The operations were classified into first-time operations and reoperations. A reoperation was defined as having a previous operation at the same site as the newly diagnosed tumor. Preoperative genetic testing was performed for known PC/PGL susceptibility genes (*RET*, *VHL*, *NF1*, *SDHA-D*, *MAX*, and *FH*) in a Clinical Laboratory Improvement Amendments certified laboratory.

We performed a retrospective analysis of prospectively collected data on demographic characteristics (age, gender, and ethnicity/race), clinical data (body mass index [BMI], operative approach, operative duration, the extent of adrenalectomy, tumor size, and pathologic diagnosis), and genetic testing results, as well as laboratory data including preoperative and postoperative 24-hour urine and plasma dopamine, epinephrine, norepinephrine, free metanephrine, and free normetanephrine. Patients with laboratory values elevated to two times the upper limit of normal or higher were considered to have functional tumors. Biochemical remission was defined as a postoperative laboratory value less than two times the upper limit of normal in patients with a functional tumor on a preoperative evaluation.

Statistical Analysis

Univariate analysis using Spearman's correlation coefficient, Student's t-test, and chi-square tests and multivariate analysis using logistic regression were performed. We analyzed demographic characteristics, clinical factors, and genetic information to evaluate their impact on the surgical approach selected and the extent of adrenalectomy. Two-tailed *P* values were used and reported. A *P* value < 0.05 was considered statistically significant. IBM SPSS Statistics Data Editor (New York, NY) and Microsoft Excel (Redmond, WA) were used for statistical analyses.

Results

The demographic and clinical characteristics of the study cohort are summarized in Table 1. One hundred eight patients underwent 118 operations. Eight patients underwent more than one operation. In 51 patients (47%), a germline mutation was detected. In 17 of the 51 patients (33%) with a germline mutation (1 *VHL*, 1 *FH*, 2 *RET*, 1 *SDHA*, and 11 *SDHB*) there was no family history of PC/PGL or family members with a positive genetic testing result.

In 76 operations (65%), it was the first operative intervention for the disease site, 60 of which were performed with a laparoscopic approach and 17 with an open approach (Figure 1). Forty-one operations (35%) were reoperative interventions, 36 of which were open and 5 were laparoscopic. Twenty-five patients (17 no germline mutation, 5 *SDHB*, 1 *SDHA*, 1 *VHL*, and 1 *RET*) underwent an operation for metastatic disease. In patients with functional tumors, 79% of the operations resulted in biochemical remission. Factors associated with a higher risk of persistent/recurrent disease on biochemical testing were an open surgical approach (*P* < 0.001), presence of metastatic disease (*P* < 0.001), reoperations (*P* < 0.001), and male gender (*P* < 0.05), but not age, BMI, and presence of germline mutation.

Minimally invasive vs. open surgical approaches for initial operative interventions

The demographic and clinical characteristics of 76 patients who underwent PC/PGL resection as their initial operation are summarized in Table 2. A germline mutation in susceptibility genes was present in 39 patients. Twenty-nine patients with a germline mutation (8 *VHL*, 14 *RET*, 4 *SDHB*, 1 *NFI*, 1 *MAX*, and 1 *MEN1*) underwent minimally invasive surgery and 10 (7 *SDHB*, 1 *SDHA*, 1 *SDHD*, 1 *VHL*) underwent an open operation.

The average tumor size in patients who underwent a minimally invasive approach was significantly smaller than those of patients who had an open surgery (3.9 vs. 5.8 cm, $P < 0.01$). Clinical characteristics associated with whether an open or laparoscopic approach was used were tumor size ($P < 0.01$) and presence of germline mutation in known susceptibility genes ($P < 0.05$). Comparing patients with a germline mutation in *RET*, *VHL*, or *NF1* to the rest of the cohort undergoing an initial operation, patients with the aforementioned mutations were more likely to undergo a minimally invasive approach ($P < 0.05$). Comparing patients with a known *SDHB* mutation to the rest of the cohort whose surgery was their initial operative intervention for that site of disease, patients with *SDHB* mutation were more likely to undergo an open surgical approach ($P < 0.01$) on multivariate analysis (Table 2). In patients who had their first-time operation for a PGL (8 *SDHB*, 2 *VHL*, and 4 unknown mutation), all of patients with *VHL* mutation had a laparoscopic approach, whereas 7 out of 8 (87.5%) patients with *SDHB* mutation had an open approach.

In 12 patients (31%) with a germline mutation, (6 *SDHB*, 3 *RET*, 1 *NF1*, 1 *VHL*, and 1 *SDHA*), there was no significant family history of PC/PGL. Out of the 6 patients with *SDHB* mutation, 2 patients presented with PC as their first disease manifestation, 2 patients presented with pelvic PGL, and 2 patients had a history of PC/PGL resection. One of the patients with *RET* mutation had a history of thyroidectomy for medullary thyroid carcinoma (MTC) and 2 presented with concurrent MTC. The patient with *NF1* had a history of neurofibromas, while the patient with *VHL* had previous resection of PCs and presented with a PGL. The patient with *SDHA* mutation presented with metastatic PC/PGL. One patient (2%) with no known germline mutation had a family history of PC/PGL.

Cortical-sparing adrenalectomy

Sixty-eight adrenal operations were performed, 12 of which were bilateral adrenalectomy during the same operation. Fifty-four patients (79%) (33 with no known germline mutation, 7 *RET*, and 3 *SDHB*) underwent a total adrenalectomy and 14 patients (21%) underwent a cortical-sparing adrenalectomy (Figure 2). Five out of 14 patients underwent a unilateral total and contralateral cortical-sparing adrenalectomy, 3 patients underwent bilateral cortical-sparing adrenalectomies, and 2 patients had a history of previous contralateral total adrenalectomy and underwent a cortical-sparing adrenalectomy. Four out of 54 patients had bilateral total adrenalectomy. Three patients (1 *RET*, 1 *MAX*, and 1 no known germline mutation) had a history of a contralateral total adrenalectomy and 1 patient (*NF1*) had a history of bilateral partial adrenalectomy. The average tumor size of patients who underwent a total adrenalectomy was 4.47 cm, and 2.36 cm ($P < 0.05$) for patients who underwent a cortical-sparing adrenalectomy. Out of the 54 patients who underwent a total adrenalectomy, 18 had a germline mutation (7 *RET*, 3 *SDHB*, 2 *VHL*, 2 *NF1*, 1 *SDHA*, 1 *SDHD*, 1 *MAX*, and 1 *MEN1*). Out of the 14 patients who underwent a cortical-sparing adrenalectomy, 13 (93%) had a germline mutation (7 *RET*, 5 *VHL*, and 1 *SDHB*). The patient with *SDHB* mutation had bilateral adrenal lesions, the right measuring 1.2 cm and the left measuring 0.7 cm. The patient underwent a left partial adrenalectomy to avoid adrenal insufficiency.

Variables significantly associated with a cortical-sparing adrenalectomy being performed were age ($P < 0.05$), presence of germline mutation (*RET*, *NF1*, and *VHL*, $P < 0.01$), and

tumor size ($P < 0.05$) (Table 3). The presence of a germline mutation and tumor size remained statistically significant on multivariate analysis. Thirteen out of 14 patients undergoing cortical-sparing adrenalectomy had functional tumors and achieved biochemical cure, and one patient had no follow-up information available. In patients who had cortical-sparing adrenalectomy, 80% of the patients had adequate adrenocortical function based on postoperative adrenocorticotrophic hormone (ACTH) stimulation testing (Table 4).

The rate of germline mutation and impact of preoperative genetic testing data on operative intervention in patients without a family history PC/PGL

Although we found an association between the presence of germline mutation and the operative approach and extent of adrenalectomy, we wanted to determine the rate of germline mutation in which patients had no known inherited syndrome until the preoperative genetic testing results and how this impacted our surgical management. Seventeen (15.7%) patients were found to have a germline mutation in a PC/PGL susceptibility gene without any family history or a personal history to suggest an inherited syndrome. In 10 patients (6 *SDHB*, 2 *RET*, 1 *VHL*, 1 *SDHA*), it was their first operation for tumor site and in 7 patients (5 *SDHB*, 1 *FH*, 1 *RET*) it was a reoperation. In three patients, a minimally invasive approach was used even though the PC was large or it was a PGL based on the preoperative germline mutation. Two patients with a germline *RET* mutation had a laparoscopic adrenalectomy even though their tumors measured 9.5 and 8 centimeters in greatest diameter because of the low risk of metastases/malignancy. A patient with a *VHL* germline mutation had laparoscopic resection of a PGL. Five patients had an open surgical approach because they had a germline *SDHB* or *FH* mutation.

Discussion

There have been significant advances in our understanding of the pathobiology and imaging modalities to detect PC/PGL. The rarity of PC/PGL calls for a multidisciplinary approach to each patient involving endocrinologists, surgeons, medical oncologists, and genetic counselors to optimize patient outcome. There is limited data and no prospective study on the impact of preoperative genetic testing information on surgical management of patients with PC/PGL. Thus, we analyzed demographic, clinical, and genetic factors that could influence the surgical management of PC/PGL. We found that the presence of germline mutation and tumor size were significantly associated with the surgical approach used (open versus minimally invasive approaches) and the extent of adrenalectomy (total versus cortical-sparing adrenalectomy). Most importantly, 15.7% of our study cohort had no family history and tested positive for a germline mutation in a susceptibility gene preoperatively. This genetic data did impact the surgical approach and extent of resection in 15 of the 108 patients in our study.

In recent guidelines, genetic testing for common susceptibility genes has been recommended. In the 2014 Endocrine Society Clinical Practice Guidelines, genetic testing is recommended based on a clinical feature driven diagnostic algorithm.⁶ In a more recent practice guideline by the European Society of Endocrinology, genetic testing is also recommended in all patients with PC/PGL.^{5,6} However, in neither clinical practice guideline

is routine preoperative genetic testing clearly addressed or recommended in all patients with PC/PGL. In our study cohort, 33% of the patients with a germline mutation did not have any family history of an inherited syndrome, and 36% of the patients with *SDHB* germline mutations had no family history and had no previous history of PC/PGL on presentation.

Advances in genomic medicine with next-generation sequencing has allowed for rapid, accurate, and more cost-effective testing for cancer susceptibility genes including susceptibility genes for PC/PGL.⁷ Important genotype-phenotype associations in PC/PGL have been characterized and have important implications in the clinical management of PC/PGL. For example, Castinetti and colleagues showed in a multicenter, multinational study that in patients with *RET* germline mutations the rate of malignancy was extremely low, and that 44% of patients presented with bilateral PC at the initial presentation.⁸ Thus, this data would suggest that cortical-sparing adrenalectomy in patients with germline mutations in *RET* would be reasonable if there are no clinical signs of malignancy. In another study by Aufforth and colleagues, who studied VHL-associated PCs/PGLs, 16% of the patients with PC presented with bilateral disease and 20% subsequently developed contralateral PC. Again, this would also suggest that cortical-sparing adrenalectomies are warranted in patients with VHL to preserve cortical function and avoid lifelong steroid replacement and the risk of Addisonian crisis.

A minimally invasive surgical approach and cortical-sparing adrenalectomy is preferred in patients with specific germline mutations (*NFI*, *RET*, and *VHL*) associated with a low risk of malignancy.⁷⁻⁹ In our study, we found that patients with large tumors and preoperative *RET* germline mutation testing result had successful laparoscopic adrenalectomy and a patients with a *VHL* germline mutation had a laparoscopic approach for a PGL because of the low risk of malignancy in these patients. In contrast, germline mutations in *SDHB*, *TMEM127*, or *FH* confer a higher risk of recurrence, presence of extra-adrenal disease, and/or metastatic disease^{5,10-12}. Therefore, an open surgical approach with regional lymphadenectomy is probably preferred in most patients with a high-risk tumor (positive *SDHB*, *TMEM127*, and *FH*), especially those with large primary tumors^{6,10,13}. Although there is no randomized control trial to determine the optimal surgical approach, there is general agreement that large tumors that are potentially malignant should be resected using an open approach.^{5,6} Moreover, there have been reports associated with peritoneal seeding in patients who had laparoscopic resection for what likely were malignant tumors.^{14,15} We found that 4.6% of patients had a germline mutation in *SDHB* or *FH* without a family history and we used an open surgical approach in these patients because of the risk of malignancy.

We found that 80% of patients who had cortical-sparing adrenalectomy had adequate adrenocortical function and did not require steroid replacement. There are several factors that contribute to the decision and the ability to perform a cortical-sparing adrenalectomy. In our study cohort, the only factors that were statistically significant on univariate and multivariate analyses were the size of the tumor and germline mutation status in known susceptibility genes. The rate of adrenal insufficiency after cortical-sparing bilateral adrenalectomy reported in the literature is approximately 20%¹⁶, which is similar to our study results. We performed partial adrenalectomy, leaving at least 30% of normal adrenal

gland *in-situ*, which was not feasible in 11 patients with large or centrally located tumors, or tumors in close proximity to the adrenal vein, but that had germline mutations in *RET*, *VHL*, and *NFI*. Brauckhoff and colleagues evaluated patients undergoing bilateral partial adrenalectomy and found that a remnant size of 15–30% of two normal adrenal glands was necessary to prevent adrenal insufficiency.¹⁶

There are several limitations to our study. Although it was based on prospectively collected data, being a tertiary referral center may have created a selection bias for more patients having inherited syndromes. However, 60% of our cohort had no known germline mutation and 33% of the patients with germline mutation had no family history to suggest that referral of patients with a high predisposition to inherited PC/PGL accounts for our study findings. While we found the type of surgical approach and extent of resection was impacted by the preoperative genetic testing result and a significant number of patients without a family history had a germline mutation found, we cannot determine if this data impacts patient outcome.

In conclusion, approximately half of patients with PC/PGL have a germline mutation and preoperative knowledge of the type of germline mutation, in addition to other clinical variables, affects the surgical approach and extent of adrenalectomy. Therefore, surgeons should request genetic testing information to make an informed surgical intervention.

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Figure 1.

Mutation status, tumor size and outcome by type of operative intervention in those who had an initial surgical intervention.

Figure 2.

Mutation status, tumor size and outcome in patients having total versus cortical-sparing (partial) adrenalectomy.

Table 1

Demographic, clinical, and biochemical data in study cohort.

Variables		108 patients
Median age in years (range)		42 (5–76)
Median BMI (range)		26.41 (14.08–45.13)
Gender (female/male)		60/48
Type of operation		
Initial videoscopic transabdominal/redo videoscopic transabdominal		58/2
Initial open/redo open		17/36
Initial videoscopic retroperitoneal/redo videoscopic retroperitoneal		2/3
Mean surgery duration (min) (range)		209 (65–615)
Genetic mutation		
Present		51
Not present		57
Adrenalectomies		
Partial		14
Total		54
Functional status of tumor (2 times the upper limit of normal) at the time of the operation		
Functional		100
Non-functional		18 ^
Biochemical Remission (2 times upper limit of normal)		
Remission/no remission		80/17
No information available		21
Plasma biochemistries		
Preoperative values (normal range)	Median	Range
Dopamine (5–23)	18	0–3112
Epinephrine (4–58)	27	0–2418
Norepinephrine (84–794)	879.5	72–14861
Metanephrine (12–61)	49	0–5996
Normetanephrine (18–112)	493.5	16–23350
Postoperative values	Median	Range
Dopamine	10	0–507
Epinephrine	6	0–185
Norepinephrine	260	89–3338
Metanephrine	18	0–357
Normetanephrine	67.5	0–2282
Urinary biochemistries		
Preoperative values	Median	Range
Dopamine (65–400)	289	20–9704
Epinephrine (0–20)	6.65	0–789
Norepinephrine (15–80)	134	19–4287

Variables		108 patients
Metanephrine (0–261)	169	0–22920
Normetanephrine (0–451)	1617.5	155–31175
Postoperative values	Median	Range
Dopamine	195	0–683
Epinephrine	2.5	0–51
Norepinephrine	41	4–1837
Metanephrine	72	0–1558
Normetanephrine	318	92–15374

[^] Number more than 108 patients because based on the number of operations.

Table 2

Comparison of variables and surgical approach in patient having their initial operations.

Variables	Minimally invasive surgical approach (n = 60)	Open (n = 17)	<i>P-value</i> [^]
Age in years, median (range)	42 (5–76)	43.5 (12–75)	0.56
Gender			0.28
Female	34	7	
Male	26	10	
BMI mean (range)	26.955 (14.08–45.13)	24.14(21.1–42.46)	0.16
Duration of the operation (minutes) [*]	193 (65–440)	194.5 (73–384)	
Metastatic disease	0	7	
Multiple primary lesions	0	9	
Mean tumor size in cm (range)	3.95 (0.8–9.5)	5.77 (2.2–15)	0.009
Genetic testing results			
No germline mutation	31	7	0.58
Germline mutation	29	10	
No <i>SDHB</i>	56	10	0.0016
<i>SDHB</i>	4	7	
<i>SDHA</i>	0	1	0.18
<i>SDHD</i>	0	1	0.18
<i>VHL</i>	8	1	1
<i>RET</i>	14	0	0.17
<i>MAX</i>	1	0	1
<i>NFI</i>	1	0	1
<i>MEN1</i>	1	0	1
<i>RET, NFI, VHL</i>	23	1	0.0154
No <i>RET, NFI, VHL</i>	37	16	
Biochemical remission ^{***}	48/50 (96%)	12/14 (86%)	0.21
Not remission	2 (4%) [§]	2 (14%) ^{§§}	

^{*} Operative time was from skin incision to skin closure.

^{**} No biochemical information was available in 13 patients (10 laparoscopic and 3 open).

^{***} Twelve patients (8 laparoscopic and 4 open) did not cross the threshold of biochemical positivity.

[§] One patient had elevated plasma epinephrine and dopamine while urinary studies were within normal limits. The other patient underwent bilateral adrenalectomy, and one month later continued to have elevated urinary norepinephrine and normetanephrine; two months later, plasma norepinephrine remained elevated with no evidence of recurrent disease noted on FDG PET/CT.

^{§§} Both patients underwent a palliative resection in a setting of skeletal metastatic disease.

[^] P value adjusted for multiple comparison.

Table 3

Evaluation of variables associated with the extent of adrenalectomy.

Variables	Total = 54 (79%)	Partial = 14 (21%)	<i>P-value</i> [^]
Age median (range) in years	43 (11–76)	42 (5–60)	0.040
Gender			1.000
Female	29	8	
Male	25	6	
Bilateral adrenal tumors	4	8	
Tumor size mean (range) in centimeters	4.47 (1.1–15)	2.36 (0.7–5.8)	0.004
Genetic background			
No germline mutation	36(61%)	1	
Germline mutation	18 (39%)	13	0.0012
<i>RET</i>	7	7	0.0024
<i>SDHB</i>	3	1	0.18
<i>VHL</i>	2	5	0.0012
<i>NFI</i>	2		
<i>SDHA</i>	1		
<i>SDHD</i>	1		
<i>MAX</i>	1		
<i>MEN1</i>	1		
<i>VHL, RET, NFI</i>	11	12	0.0012

[^] P value adjusted for multiple comparison.

Table 4

ACTH stimulation responses in patients undergoing cortical sparing adrenalectomy.

Patient	POD * of ACTH ** stimulation test	Cortisol 0 min	Cortisol 30 min	Cortisol 60 min	Notes:	Hydrocortisone	
						On discharge	Long term
1	Not done				POD3 cortisol 17.9	No	No
2	2	5.8	15.2	17.7		No	No
3	1	2.1	6.3	7.1		Yes	Yes
4	5	15.4	20.4	24.8		No	No
5	2	4.5	12.9	15.4		No	No
	5	16.6	19.9	21.8			
6	Not done					Yes	No
7	2	13.6	18	18.7		No	No
8	60	11.5	14.9	15.8	Repeat ACTH stimulation test outside normal	Yes	No
9	2	7.2	8.9	10.3			
	5	14.3	17.4	17.9		No	No
10	60	6.9	12.5	13.1		Yes	Yes

Patient were given 250 micrograms of ACTH and cortisol measured at baseline (before administration of ACTH, 0 minutes) and at 30 and 60 minutes.

Seven patients underwent a unilateral cortical-sparing adrenalectomy and contralateral total adrenalectomy, while 3 patients underwent a bilateral cortical-sparing adrenalectomy. Four out of 10 patients had adrenal insufficiency in the immediate post-operative period, while only 2/10 (20%) had persistent adrenal insufficiency. Two patients did not undergo an ACTH stimulation test prior to discharge, one of whom had normal cortisol level while the other patient was discharged with empiric hydrocortisone replacement and was successfully weaned off the medication.

* Post-operative day.

** Adrenocorticotrophic hormone.