CHANGING PATTERN OF PHEOCHROMOCYTOMA AND PARAGANGLIOMA IN A STABLE UK POPULATION

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Abstract

Context. Pheochromocytomas and paragangliomas (PCC/PGLs) are diagnosed variously with increasing incidence and changing clinical and pathology pattern.

Objective. The aim was to further characterize PCC/PGLs in a stable population.

Methods. A retrospective, single institution study analysed adrenalectomies for PCC/PGLs between January 2010 - January 2019. Demographics, symptoms, blood pressure, preoperative hormones, imaging, histology, hospital stay, complications and three subgroups [based on the modality of diagnosis - incidentaloma group (IG), genetic group (GG) and symptomatic group (SG)] were noted.

Results. 86 patients included IG 51 (59.3%), GG 10 (11.62%) and SG 25 patients (29.06%). Incidence was 5.30 cases/1 million population. 33.34% of the IG had a delayed diagnosis with a mean interval of 22.95 months (4-120 months). Females presented more often with paroxysmal symptoms (PS) ($p=0.011$). Patients with PS and classic symptoms were younger ($p=0.0087$, $p=0.0004$) and those with PS required more inotropes postoperatively ($p=0.014$). SG had higher preoperative hormone levels ($p=0.0048$), larger tumors ($p=0.0169$) and more likely females. GG are younger compared with those from the IG ($p=0.0001$) or SG ($p=0.178$).

Conclusion. Majority of patients had an incidental and delayed diagnosis. If symptomatic, patients are more likely to be young females with higher hormone levels and larger tumors.

Key words: pheochromocytoma, paraganglioma, clinical pattern, incidence, PCC, PGL.

INTRODUCTION

Pheochromocytoma and paragangliomas (PCC/PGL's) are rare tumors with an approximate annual incidence of 0.004-0.21 per 100000 persons per annum (a nationwide pathology study from Netherlands including 1493 patients with PCC/PGL's) (1), and

an overall incidence of 1-8 per million (2,3). Recent studies showed similar age of diagnosis but different data regarding gender distribution. Average age of presentation is 40-50 years with no differences between women and men (4) *versus* mean age of diagnosis which varies between 43 ± 17 and 56 ± 18 years and PCC/PGL are more frequent in females than in males (55% vs. 45%) (1). Incidence has increased over the last 20 years possibly due to earlier detection of these tumors, with a positive impact on outcome as earlier treatment might reduce future cardiovascular risk (1). Stolk *et al.* demonstrated a 14-fold higher rate of cardiovascular events among patients with a PCC compared to patients with essential hypertension (5). According to the 2017 World Health Organization (WHO) classification of endocrine tumors, PCCs are tumors of the chromaffin cells that arise from the adrenal medulla (6), whereas PGLs are neural crest-derived neuroendocrine tumors (NETs) that can originate at any level of extra-adrenal paraganglia (from the skull base to the pelvis) (7). In the past PCC were characterized by the "10% rule" including rate of malignancy, bilaterality, genetic mutation, extra-adrenal location, and occurrence in children (8, 9). In 10% to 30% of patients, the tumor is discovered incidentally during imaging studies for unrelated symptoms (3). Over the past 2 decades the widespread use of computed tomography (CT), magnetic resonance imaging (MRI), PET-CT and other imaging modalities has increased the detection of adrenal incidentalomas which now may account for up to 40% of PCC (10, 11). Around 4%-5% of abdominal CT scans performed for other indications show an adrenal tumor (12, 13). Majority are sporadic but recent studies showed that up to 40% patients have a germline mutation in one of the 16 susceptibility genes: RET, NF1, VHL, succinate dehydrogenases (SDHA, SDHB, SDHC, SDHD, and SDHAF2), TMEM127, PHD1, PHD2, HIF2A, FH, Myc-associated factor (MAX),

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and KIF1B (12,13). PCC/PGLs are most frequently associated with 4 syndromes – neurofibromatosis type 1 (NF1) (14) Von Hippel-Lindau syndrome (VHL) (15), multiple endocrine neoplasia type 2 (MEN 2) (16) and familial PCC-PGL (succinate dehydrogenase B, C, D, Carney-Stratakis dyad) (17). Patients with genetic background compared with those being sporadic are typically younger at the time of presentation and are more likely to be asymptomatic when diagnosed (18). PCC/PGLs can manifest in the form of three different clinical scenarios: 1. patients with symptoms or signs of catecholamine excess; 2. an adrenal tumor discovered incidentally on a radiological study in an asymptomatic patient or one with minimal symptoms or signs of excess catecholamines; or 3. based on a genetic test performed due to a significant family history of PCC/PGLs endocrine tumor syndrome (17,19). Headache is a common clinical symptom, present in up to 90% of symptomatic patients, and paroxysmal sweating is seen in about 70% (20). One in five patients are supposed to be asymptomatic and normotensive (3,21). Catecholamine release is extremely variable with some PCCs having low or non-secretory activity and some present with a solitary dopamine-secreting pattern (17). PCC/PGLs associated with NF1, MEN 2A, and VHL disease may have different catecholamine biochemical phenotypes if compared to sporadic cases (22). A recent study advocates that plasma free or urinary fractionated metanephrine levels are recommended as the first line test for diagnosis (23). Imaging technique depends on the modality of diagnosis (clinical, biochemical or imaging), if the tumor is functional, metastatic or multicentric (24). Recent studies suggest that NF1 patients had the most unstable intraoperative behaviour and severe postoperative complications (probably related to large tumors, increased catecholamine secretion and more often open resection) (22). Factors predicting malignancy are larger tumor size, elevated dopamine secretion, high chromogranin A level, SDHB mutation and extra-adrenal location (25) and when malignant PGLs have a more aggressive postoperative course than PCCs (26).

MATERIAL AND METHODS

The aim of our study was to analyze the spectrum of clinical appearance, pathology and treatment outcome of PCC/PGL's in recent years in Northern Ireland (NI). 86 PCC/PGL treated in a UK Teaching Hospital between January 2010-January 2019 were included in a retrospective study. Clinical

data was retrieved from patients' medical electronic records. Our department is a tertiary referral and sole centre for adrenalectomy in NI for approximately 3 decades. Demographics, symptoms, blood pressure, histology, preoperative catecholamines, imaging, days in hospital /HDU/ICU and postoperative complication were noted. For the first half of the study period for biochemical diagnosis we used urinary noradrenaline (50-60 nmol/24h), adrenaline (5-120 nmol/24h) and dopamine (300-3900 nmol/24h) and for the second period we switched to determine normetanephrines (440-2960 nmol/24h) and metanephrines (141-1289 nmol/24h). In order to compare the results, we calculated (for every patient) a ratio between the highest observed hormone level and the upper limit of normal range. All patients operated for PCC/PGL's were admitted overnight to HDU/ICU (high dependency/intensive care unit) after surgery and inotropes requirement was defined as follows (short dose – for 4-6 hours postoperatively, intermediate dose for 24 hours and prolonged dose >24 hours). Patients in our study were screened either before or after surgery for the following gene mutations: CDKN1B, EGLN1, EGLN2, KIF1B, MAX, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL. Patients were divided into three subgroups based on the modality of diagnosis: discovered incidentally during imaging performed for other reasons (incidentaloma group IG) during genetic testing for cases with positive family history (genetic group GG), symptomatic group (presenting with classic or paroxysmal symptoms SG). Classic triad symptoms included headaches, palpitations, and sweatings. Paroxysmal symptoms included hypertensive episodes, headache, chest pain, dizziness, nausea, palpitations, flushing, and diaphoresis not related to stress or emotional distress. We compared age, gender, different preoperative symptoms, preoperative blood pressure with levels of hormones, size of tumor, histology for the entire group and between the 3 subgroups.

Statistical analysis

Data were considered as nominal or quantitative variables. Nominal variables were characterized using frequencies. Quantitative variables were tested for normality of distribution using Kolmogorov-Smirnov test and were characterized by median and (minimum-maximum) or by mean and standard deviation (SD), when appropriate. A chi-square test was used in order to compare the frequencies of nominal variables. Quantitative variables were compared using t test,

Table 1. The distributions for the three subgroups during the study years

Year	Total	IG	GG	SG
2010	6	1	0	5
2011	8	5	0	3
2012	8	4	1	4
2013	7	7	0	0
2014	12	12	3	3
2015	14	14	4	2
2016	10	10	2	2
2017	9	9	0	3
2018	11	11	0	4

IG=incidentaloma group, GG= genetic group, SG= symptomatic group.

Mann-Whitney test, ANOVA test or Kruskal–Wallis test, when appropriate. The correlation between quantitative variables was assessed using Spearman's rho correlation, when appropriate. We used the Bonferroni and Dunns correction in order to account for multiple comparisons. The level of statistical significance was set at $p < 0.05$. For statistical calculations, Graph Pad 3.6 State Software, San Diego, California, USA, and Statistical Package for Social Sciences (SPSS, version 20, Chicago, IL, USA) was used.

RESULTS

Demographics

The current population of Northern Ireland is approximately 1.8 million people with an average PCC incidence of 5.30 cases/1 million population during our study period and a distribution per years as follows: 2010 - 3.33/million, 2011 - 4.5/million, 2012 - 4.5/ million, 2013 - 3.9/million, 2014 - 6.67/million, 2015 - 7.8/ million, 2016 - 5.6/ million, 2017 - 5/ million, 2018/2019 - 6.1/ million (Table 1).

Forty-five female and 41 male patients were included in our study. Female patients were more prevalent within the SG when compared to the other groups but the male and female patients were equally distributed within the total study group.

The average age of presentation in our study group was 54.5 (28-83 years). Patients with a genetic background were younger [mean age 40.92 (15-51)] while patients from IG and SG had similar mean age of onset when compared to the entire study group (Table 2).

Forty-six patients had genetic testing, 22 were negative and 24 patients were linked to one of the following genetic mutations (SDHD 4, SDHB 7, VHL 5, NF1 6, MEN2A 2).

Table 2. Age within the groups

Groups	Mean age (years)	Std. Deviation	N
Genetic	40.92	11.30	12
Incidentaloma	59.84	11.95	51
Symptomatic	49.74	15.62	23
Total	54.50	14.59	86

Clinical

IG included 51 patients (59.3%), GG 10 patients (11.62%) and SG 25 patients (29.06%). 57/86 (66.3%) had abnormal high blood pressure before surgery (normal blood pressure $< 140/90$ mmHg). Paroxysmal ($p = 0.0087$) and classic triad symptoms ($p = 0.0004$) were pinpointed in younger patients. Females are presenting more frequently with paroxysmal symptoms than men ($p = 0.011$) and have the same incidence of classic triad symptoms ($p = 0.052$). Females and males have the same median value of preoperative blood pressure levels (systolic $p = 0.931$, diastolic $p = 0.951$).

Biochemical

Patients with paroxysmal symptoms had higher levels of preoperative hormones ($p = 0.0048$, median value 7.09 vs. 3.16 for yes vs. no) and separately those presenting with headaches and sweating presented higher levels of preoperative catecholamines ($p = 0.00479$, and $p = 0.0025$). Levels of preoperative catecholamines did not influence the classic symptoms, palpitations and preoperative systolic/diastolic BP ($p > 0.05$ in all three categories).

Diagnosis

Seventeen out of the 51 incidentaloma group patients (33.34%) were delayed more than 6 weeks (usual time scale to investigate a newly discovered incidentaloma). For the 17 cases the mean delayed interval was 22.95 months (4-120 months).

Pathology

Seventy-three PCC's (84.9%) (44 left sided and 29 right sided) and 13 PGL's (15.12%) were diagnosed. PASS score was reported for 63/86 patients (73.3%). A score more than 4 was considered as potential aggressive behaviour and risk for metastasis. For the rest of 23 cases, Ki67 index was found in the pathology report. Tumor size is similar for women and men ($p = 0.454$). No connection was found between the size of tumor and presence of classic triad symptoms ($p = 0.15$) or BP levels (systolic and diastolic) ($p > 0.005$).

Postoperative Course

The necessity of postoperative inotropes,

Table 3. Distribution of symptoms

Symptoms	Number/total number	Symptoms	Number/total number
Classic Triad	27/86 (31.34%)	Shortness of breath	2/86 (2.32%)
PCC	22/73 (30.13%)	Collapse	2/86 (2.32%)
PGL	5/13 (38.46%)	Tachycardia	1/86 (1.2%)
Headache	38/86 (44.2%)	Feeling cold	1/86 (1.2%)
Palpitations	40/86 (46.5%)	Pulmonary oedema	1/86 (1.2%)
Sweating	38/86 (44.2%)	Stroke	1/86 (1.2%)
None of Classic symptoms	34/86 (39.5%)	Sensation of dread	1/86 (1.2%)
Anxiety	10/86 (11.6%)	Pallor	1/86 (1.2%)
Flushing	9/86 (10.5%)	Nervousness	1/86 (1.2%)
Fatigue	9/86 (10.5%)	Visual disturbance	1/86 (1.2%)
Dizziness	7/86 (8.13%)	Loss of weight	1/86 (1.2%)
Nausea	5/86 (5.8%)	Diabetic Ketoacidosis	1/86 (1.2%)
Vomiting	3/86 (3.5%)	Diarrhoea	3/86 (3.5%)

the value of systolic and diastolic BP and rate of postoperative complications were not influenced by the tumor size (Table 4). Preoperative systolic and diastolic BP levels were similar regarding the requirement of postoperative inotropes ($p=0.12$ and $p=0.3347$) while patients presenting with preoperative paroxysmal symptoms required more inotropes postoperatively ($p=0.014$).

Results for each and between subgroups

We were looking at each subgroup individually and compared the results between each subgroup, analyzing gender distribution, age of patients, clinical manifestations, biochemistry, genetics and postoperative course.

Gender distribution

There was no correlation related to gender regarding preoperative value of systolic and diastolic BP and size of tumor within the subgroups. Paroxysmal and classic triad symptoms showed the same distribution related to gender within the GG ($p>0.05$) IG ($p>0.05$) and SG ($p>0.05$). In regard to relation between gender and the preoperative levels of hormones, we did not find any correlation within the incidentaloma ($p=0.199$), symptomatic ($p=0.232$) and genetic groups ($p=0.87$).

Age

Patients from the GG are younger than those from the IG ($p=0.0001$) or SG ($p=0.178$).

Clinical manifestations

Within the GG, the systolic BP was higher than the SG ($p=0.036$) while the systolic BP was higher in the SG compared to the IG ($p=0.002$). Diastolic BP was significantly higher in SG when compared to the IG ($p=0.001$).

Biochemistry

Within the IG and GG, the preoperative hormone level ratio did not correlate with the existence of classic triad symptoms or headaches, palpitations and sweating separately (Table 4). The preoperative hormone levels were higher in patients from the SG associated with the classic triad and separately when only palpitations are present ($p=0.0086$, $p=0.0336$).

No correlation was identified between the preoperative hormone levels and the preoperative systolic and diastolic BP. SG patients have higher levels of preoperative hormone levels ($p=0.0191$) than IG and no difference was noted between the GG and IG and GG and SG. (Kruskal-Wallis test and Chi-square test).

Genetics

Patients with genetic background with higher systolic and diastolic BP needed postoperative inotropes more frequently when compared to IG and SG.

Postoperative course

Postoperative complications rate was not related to tumor size within the subgroups (IG $p=0.688$, SG $p=0.192$, GG $p=0.108$). Similarly, the need for postoperative inotropes between the subgroups was not linked to the dimension of the tumor. No association was identified between the diameter of tumor and presence of classic triad symptoms (incidentaloma vs. genetic vs. symptomatic group; $p=0.42$ vs. 0.95 vs. 0.32). GG and IG patients with paroxysmal symptoms needed more postoperative inotropes when compared to the symptomatic group ($p=0.02$, $p=0.049$ vs. $p=0.41$).

Other parameters found to have no correlation within the subgroups are mentioned in Table 4.

Table 4. Characteristics of PCC/PGL patients

Characteristics	Total Group	Incidentaloma Group	Symptomatic Group	Genetic Group	Other
Age	54.5 (28-83) y	59.84 ($\pm$ 11.9) y	49.74 ($\pm$ xx 15.6) y	40.92 (15-51) y	
Number of patients	86	51 (59.3%)	25 (29.06%)	10 (11.6%)	
F/M	45/41	22/29	15/8	7/5	
Symptoms					
Headaches			23/23 100%	2/12 16.67%	SG>IG>GG
Palpitations	38/86 44.2%	12/51 23.5%	20/23 86.9%	6/12 50%	SG>GG>IG0.0001
Sweating	40/86 46.5%	14/51 27.5%	22/23 95.6%	5/12 41.67%	SG>GG>IG0.0001
Paroxysmal Symp	38/86 44.2%	12/51 23.5%	18/23 78.3%	3/12 25%	SG>GG>IG0.0001
Classic triad	21/86 24.4%	2/51 3.92%	19/23 82.6%	2/12 16.67%	SG>GG>IG0.0001
BP systolic	27/86 31.34%	6/51 11.8%	SG>IG p-0.002	GG>SG	
BP diastolic			SG>IG p- 0.001	p-0.0036	
Tumour size		IG=GG	SG>IG p-0.0169	GG=SG	Kruskal-Wallis test
Hormone level ratio		IG=GG	SG>IG p-0.0019	GG=SG	Kruskal-Wallis test
Inotropes		IG=SG=GG p-0.29			Chi-square test
Postop complications		IG=SG=GG			Crosstab
Days in HDU/ICU		IG=SG=GG p-0.10			Kruskal-Wallis test
Length of hospital stay		IG=SG=GG p0.27			Kruskal-Wallis test
Paroxysmal symptoms vs. age	Younger if with symp p-0.0087	No p-0.52	No p-0.6	No p-0.89	Student test
Classic triad vs. age	Younger if with symp p-0.0004	Yes, younger if with symp p-0.038	No p-0.11	No p-0.49	Student test
Gender vs. paroxysmal symptoms	F>M p-0.011	No p>0.05	No p>0.05	No p>0.05	Crosstab
Gender vs. classic triad	F>M p-0.052	No p>0.05	No p>0.05	No p>0.05	chi-square test
Paroxysmal symptoms vs. preop hormone ratio	Yes with p-0.0048	No no p possible	No p-0.779	No p-0.0074	Man Whitney test
Headaches vs. preop hormone ratio	Yes with p-0.00479	No p-0.24	No p value possible	No p-0.68	Man Whitney test
Sweating vs. preop hormone ratio	Yes with p-0.0025	No p-0.36	No p-0.21	No p-0.25	Man Whitney test
Palpitations vs. preop hormone ratio	No p-0.27	No p-0.61	Yes p-0.033	No p-0.67	Man Whitney test
Gender vs. BP(sys/dias)	No p-0.93	No p-0.19	No p-0.67	No p-0.078	Student test
Gender vs. tumour size	No p-0.45				Man Whitney test
Classic triad vs. tumour size	No p-0.15	No p-0.42	No p-0.32	No p-0.95	Man Whitney test
Tumour size vs. BP	No p>0.005				Spearman test
Gender vs. preop hormone ratio		No p-0.19	No p-0.23	No p-0.87	
Classic triad vs. preop hormone ratio	No p-0.635	No p-0.62	Yes with p-0.0086	No p-0.95	Man Whitney test
Tumour size vs. inotropes	No p-0.82	No	No	No	Kruskal Wallis and Dunns test
BP vs. inotropes					
Sys	No p-0.12	No	No	Yes higher	Kruskal Wallis and Dunns test
Dias	No p-0.33			Yes higher	
Paroxysmal symp vs. inotropes	Yes more ino with p-0.014	Yes more ino with p-0.049	No p-0.41	Yes more ino with p-0.02	chi square test
Tumour size vs. postop complications	No p-0.64	No p-0.688	No p-0.192	No p-0.108	Mann Whitney test

DISCUSSION

Similar to other published data (almost half of PCC's/PGL's in a study from 2004 were discovered by imaging), the majority of our patients were diagnosed as incidentalomas (51/86) highlighting the importance of investigating and taking a proper history from patients discovered to have an incidental adrenal tumor (27). Guerrero *et al.* (2009) published an incidence of incidentaloma discovered PCC/PGLs of 30% with a 53% prevalence of symptomatic patients (19). Our data showed that increasing numbers of CT/MRI from the last decades revealed much more cases of silent PCCs. In a nationwide study and systematic review by Berends *et al.* incidence of PCC/PGLs increased significantly over the past two decades, most likely due to changes in clinical practice and increasing use of imaging studies and biochemical tests for detecting these tumors (1).

Our centre performs all adrenalectomies in Northern Ireland (in a stable population) with an overall incidence over the last 9 years of 5.30 cases/1 million population. There was an increasing incidence of diagnosis (3.33/million in 2010 to 6.1/ million in 2018) probably due to increasing numbers of CT/MRI or PET scans (Table 2) similar to data noticed in recent literature (1-8 per/million) (2, 3).

Gender distribution was equal between females and males in opposition with the US study from 2009 where PCC/PGLs were more frequent in women (19).

Palpitations, headaches and sweating are the most frequent symptoms and only 27/86 (31.4%) patients had all three classic symptoms (with equal distribution between PCCs and PGLs) which is similar to data by Baguet *et al.* (24%) (27). In our study 44.5% of patients are truly asymptomatic which is higher percentage than in a study by Oczko-Wojciechowska *et al.* (one third were truly asymptomatic) (28). Majority of patients in our study group were diagnosed as incidentalomas and only about one in four presented with typical symptoms. These represented 59.3% of patients, number similar in a study from Sweden (64%) (29). Older data published by Plouin *et al.* showed different outcomes with incidentally discovered lesions accounting for only 25% of all PCC/PGLs (9). As expected, majority of patients from the SG presented with paroxysmal and classic triad symptoms. Surprisingly, about a quarter of patients from the IG reported headaches, palpitations or sweatings but only 11.8% had all the classic triad symptoms. Patients with a genetic background had one in four paroxysmal symptoms and about 17% claimed all classic symptoms.

In our group patients with paroxysmal and classic triad symptoms were younger than those without which is similar to previous data (29,18). Females are presenting more frequently with paroxysmal symptoms than men (but have the same incidence of classic triad symptoms) which is in opposition with data from a Swedish study (males were more likely to present with severe symptoms) (29), while data published by Guerrero *et al.* showed that females are more prone to be symptomatic than men (19). We noticed in our study that female and male patients have similar preoperative hormone levels, systolic and diastolic blood pressure values and tumor size.

Patients with preoperative paroxysmal symptoms more frequently required post-operative vasopressors and at higher doses than asymptomatic patients.

Interestingly, this held true in the GG and IG where patients with paroxysmal symptoms also had an increased postoperative inotropes requirement when compared to the asymptomatic group.

BP (systolic and diastolic) was the highest in the symptomatic group with equal mean values within the GG and IG and 56/86 (65%) presented with elevated BP. These results are similar to data by Baguet *et al.* (59% =24/41) of patients suffered from hypertension (27).

Majority of patients had a tumor on the left side and over 15% were diagnosed with extra-adrenal PGL which is in contrast to data from another study [1210 patients with PCC (1114 (92%) had a unilateral localization originating in the right (53%) or left (47%) adrenal gland] (1).

The necessity and amount of postoperative inotropes, the value of systolic and diastolic blood pressure and the incidence of postoperative complications are not affected by the size of the tumor.

In a large study retrieving data from a Dutch pathology registry to identify all histopathologically confirmed cases of PCC/PGLs diagnosed between 1995 and 2015, the majority of the described tumors were PCC (80–100%) (28). Berendsa *et al.* showed that PGL were intra-abdominal/retroperitoneal (40–64%), intra-thoracic (3.5–60%) and in the urinary bladder (3.5%) and 17–42% of cases remained undetected until autopsy (3). In our study group the median diameter of the tumor was 4.24 (1.2–13.5) cm similar to data by Berendsa *et al.* [4.0 (2.5–6.50 cm)] (1) and Guerrero *et al.* (4.9 cm) (28). We are currently using the PASS score (developed in 2002 by Thompson *et al.*) (31) even if there are no clear diagnostic criteria of malignancy for PHEO and PGL (21). This score may serve as a means

to identify which patients require closer follow-up (26). The diagnosis was delayed for some of IG patients with a mean delayed interval of 23 months in our study. This highlights the importance that all patients with incidentalomas should have functional testing within a certain period of time even if not symptomatic. Higher levels of preoperative catecholamines and metanephrines were identified in patients presenting with paroxysmal symptoms, headaches and sweating which is similar to a large study from US (19). Deutschbein *et al.* showed that increasing age, male sex, and body mass index greater than 30 was associated with higher baseline levels of catecholamine metabolites (30). SG patients had larger tumors and higher levels of preoperative catecholamines/metanephrines compared with IG. Guererro *et al.* showed larger tumors produced the highest hormone ratios (19).

The GG needed the most inotropes (58.33%), 48% of SG needed vasopressors while those from the incidentaloma group needed the least (27.4%). Only 4 patients needed high amounts of inotropes, with no one from the GG. All patients stayed one day in HDU as part of our local protocol but within the GG there were significantly more patients staying for 2 days or more. By analyzing the subgroups we noticed that postoperative complications are more frequent within the GG (50%) and SG (43.5%) (the proportion of each group having complications). There was no difference in hospital stay within the three subgroups.

Our study has several limitations. First: it is a retrospective, single institution study; second: preoperative imaging data have been interpreted by different radiologists and the regular case discussion at a regional multidisciplinary meeting happened over the last part of the study; third: there were no standard laboratory examinations over the study period but by calculating the hormone ratio we tried to correct the difference.

In conclusion, the majority of patients with PCC/PGLs were diagnosed incidentally by the radiology department with an increased overall incidence over the last decade. If patients experience classic or paroxysmal symptoms, they were more likely to be females, younger, to have larger tumors and a higher preoperative hormone ratio. Symptomatic patients and those with genetic background will probably need postoperative inotropes and present a higher incidence of complications with closer observation. Medical teams should be aware that not a large proportion of patients are presenting with typical symptoms and prompt investigations should be offered to all patients with adrenal incidentalomas.

Conflict of interest

The authors declare that they have no conflict of interest.

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