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The experience of a referral center

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BACKGROUND: *Paragangliomas (PGL) are neuroendocrine tumors arising from neural crest-derived chromaffin cells in the parasympathetic ganglia or in sympathetic ganglia located in the adrenal glands (Pheochromocytoma, PHEO), or extra-adrenal location and around 30-40% of PGL can be hereditary (MEN2, Von Hippel Lindau syndrome, von Reklingausen syndrome and Pheochromocytoma-Paraganglioma syndrome).*
METHODS: *We retrospectively evaluate 127 patients with PHEO/PGL treated at our Institution from 1992 to 2018 and report our experience, focusing on different surgical treatment based on hereditary syndrome. Genetic analysis was performed in patients with features suspected for hereditary syndrome to search genetic mutations of RET, VHL, SDHD and SDHB.*
RESULTS: *Hereditary syndrome was diagnosed in 30 patients (7 patients affected by MEN2A, 6 VHL, 9 NF1, 2 PGL-1, and 6 PGL-4). 17 patients with monolateral PHEO underwent adrenalectomy (laparoscopic approach since 1998); 8 patients with bilateral adrenal lesions underwent bilateral adrenalectomy with cortical-sparing approach of almost one gland.*
CONCLUSIONS: *Syndromic PGLs are rare conditions; surgery is the treatment of choice. Adrenal PGL requires laparoscopic adrenalectomy with transperitoneal lateral approach as gold standard. For genetic syndrome such as MEN2 and VHL, laparoscopic cortical sparing adrenalectomy of at least one gland should be considered.*

KEY WORDS: Adrenalectomy, Endocrine Surgery, Hereditary Syndromes, Paraganglioma, Pheochromocytoma

Introduction

Paragangliomas (PGL) are neuroendocrine tumors arising from chromaffin cells present in the parasympathetic ganglia (head and neck paraganglioma HN-PGL) or in sympathetic ganglia located in the adrenal glands, or extra-adrenal location such as thorax, abdomen and pelvis [1,2].
Considering the similar origin of the adrenal medulla cells and sympathetic ganglia and their production of catecholamine and metabolites, Pheochromocytoma (PHEO) can be defined as a sympathetic-derived PGL arising from adrenal medulla; thus, they can be considered the same entity from a clinical, biochemical and histopathological point of view. PHEO have an incidence of 4-5% in patient with incidentaloma and may affect 0.1-2% of hypertensive patients [3-7]. Around 30-40% of PGL can be hereditary, associated with germline mutations and with other tumors (Syndromic PGL) [8]. Compared to sporadic variants, syndromic PGL often develop in young patients as bilateral tumors if PHEO, or with multiple location if PGL. Moreover, they present a high risk of recurrence and malignancy and may be associated with not secreting HN-PGL.
Syndromic PGL occur in Multiple Endocrine Neoplasia type 2 (MEN2), Von Hippel Lindau (VHL) syndrome,

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von Reklingausen syndrome (alternatively Neurofibromatosis type 1, NF1) and they are associated with the following gene mutations, respectively: RET, VHL and NF1. In addition, mutations of the subunit of SDH (SDH-B, SDH-C, SDH-D e SDH-AF2, grouped as SDHx) were recently associated with specific Pheochromocytoma-Paraganglioma syndromes (PGL syndromes). PGL-1 is the PGL syndrome associated to SDH-B mutation and PGL-4 derived from SDH-D mutation [9]. Surgery is the treatment of choice for syndromic PGL and required an accurate diagnosis and correct medical preparation (10-13). The aim of our study is to report a 26-years experience of a referral center for adrenal disease, focusing on different and specific surgical treatment and management of syndromic PGL based on different hereditary syndrome.

Material and Methods

From 1992 to 2018, 127 patients with PHEO/PGL were analyzed and treated at our Institution. Diagnosis was based on clinical suspect (classical or suspicious symptoms, severe hypertension or resistant to treatment) or based on imaging (CT/MRI) showing adrenal incidentaloma. Complete physical investigation such as blood pressure or heart rate measurements (clino- and orthostatic position) was acquired as well as familial history was investigated. In addition, all relevant exams for adrenal functional study were performed such as 24-hour urinary collection for the quantification of total urinary metanephrine and vanillil mandelic acid.

All patients underwent a total body CT and a dedicated MRI of the abdomen to correctly locate the lesions, likewise ^{123}I-metaiodobenzylguanidine (I-123-MIBG) scintigraphy was performed to confirm the effective uptake. Malignant PHEO/PGLs were defined according to the presence of distant metastases (liver, lung, bone).

A blood sample was obtained for the extraction of DNA from peripheral blood leukocytes in patients with suspicious features of hereditary syndrome such as juvenile presentation, bilateral or extra-adrenal lesions, malignancy, familiarity for PGL or genetic syndrome, development of other tumors associated to genetic syndromes (medullary thyroid carcinoma for MEN2, clear cell renal carcinoma for VHL). Genetic analysis was performed seeking for RET mutations (exons 10,11,13,14,15,16) such as VHL, SDH-D and SDH-B mutations (all exons, respectively).

Hypertensive patients or patients with increased lab level of catecholamines underwent α-adrenoceptor antagonist (α-blocker) therapy, and, if arrythmias or tachycardia was present, β-adrenoceptor antagonist (β-blocker) were given to patients during 2-3 weeks before surgery, to stabilize blood pressure and heart rate.

After surgery, histological examination of the surgical specimen was performed by immunohistochemical staining for the neurospecific enolase, chromogranin A, synaptophysin and S-100 protein.

Results

Patient Population

From January 1992 to December 2018, a total of 127 patients (61 male and 66 female, mean age 47) affected by PGL had surgery at our Institution. One-hundred and six patients (83%) presented symptoms at the time of diagnosis, and the typical triad of palpitations, headache and diaphoresis was observed in 39 patients (30%) associated with paroxysmal hypertension and hypertension resistant to medication whereas 12 patients (10%) presented the typical triad of symptoms without hypertension. Twenty-six patients (20%) were already under antihypertensive medication, whereas 23 patients (18%) presented mild hypertension and paroxysmal attack. After surgery a follow-up was performed from 6 months to 15 years, and normotension status was restored in 45% of patients. Despite 35% of patients remained hypertensive with an overall good blood pressure control, no paroxysmal attacks were observed, and 20% of patients reduced antihypertensive medication indeed.

Clinical Point of View

Syndromic PGL was diagnosed in 30 of 127 patients (23.6%) divided as follows: 7 patients affected by MEN2A, 6 VHL, 9 NF1, 8 PGL-syndrome (2 PGL-1, and 6 PGL-4). Full results are listed in Table I .Seven patients affected by MEN2A presented unilateral adrenal lesions in 3 cases and bilateral lesions in 4 cases. Six patients affected by VHL syndrome presented unilateral PHEO in 3 cases and bilateral PHEOs in the other 3 cases. Nine patients with already clinical diagnosis of

Table I - *Hereditary Syndrome and Genetic Mutation.*

Syndrome	Genetic Mutation	N°patients	Percentage
MEN2	RET	7	23.3%
Von Hippel-Lindau	VHL	6	20.0%
Von Reklingausen	NF1	9	30.0%
PGL-1	SDHB	2	6.7%
PGL-4	SDHD	6	20.0%

Table II - *Characteristics of Patients with PHEOs.*

PHEO	Syndrome/N°patients		
Unilateral (17)	MEN2	3	
	VHL	3	
	NF1	9 (1 with rectal jejunal NFs)	
	PGL-1	1	
	PGL-4	1	
Bilateral (8)	MEN2	4	2 synchronous
			2 metachronous
	VHL	3	2 synchronous
			1 metachronous
	PGL-1	1 metachronous	

TABLE III - *Characteristics of 8 Patients affected by PGL-4 and PGL-1 syndrome.*

Case N°	Sex, age	Symptoms	Tumor localization	Genetics	Other tumors	Syndrome
1	F, 69	Dyspnoea, paroxysmal hypertension	Heart paraganglioma	SDHD ex 4 (444-445 ins ATCT)	Mediastinal and carotid paraganglioma	PGL1/ SDHD
2	F, 23	Paroxysmal hypertension, cerebral haemorrhage	Multiple abdominal paragangliomas	SDHD ex 4 (CAA>TAA, Gin>Stop)	Carotid paraganglioma	PGL1/ SDHD
3	F, 43	Paroxysmal hypertension, headache, sweating, palpitations	Bilateral Pheocromocytoma	SDHD ex 1 (GGT>AGT: Gly>Ser)	Bilateral breast carcinoma	PGL1/ SDHD
4	M, 63	Hypertension	Left adrenal Pheocromocytoma	SDHD ex 1 (GGT>AGT: Gly>Ser)	Prostate cancer	PGL1/ SDHD
5	F, 27	Paroxysmal hypertension, palpitations, headache, sweating	Left adrenal Pheocromocytoma	SDHB codon 139 (139 G>T)	Right left atrial shunt with bicuspid aorta	PGL4/ SDHB
6	F, 76	Paroxysmal hypertension	Pelvic paraganglioma	SDHD ex 4 (444-445 ins ATCT)	Carotid paraganglioma	PGL1/SDHD
7	F, 21	BP paroxysms during micturition,	headache, palpitations Pelvic paraganglioma (bladder)	SDHB codon 139 (139 G>T)	–	PGL4/SDHB
8	F, 30	Paroxysmal hypertension, palpitations, cerebral haemorrhage	Multiple abdominal paragangliomas	SDHD ex 4 (CAA>TAA, Gin>Stop)	–	PGL1/SDHD

TABLE IV - *Surgical treatment of patients affected by syndromic PGLs*

N° of patients	Clinical manifestation	Surgical treatment
17	Unilateral PHEO	7 patients: open adrenalectomy (before 1998)9 patients: laparoscopic adrenalectomy by transperitoneal approach (after 1998)1 patient: laparotomic unilateral adrenalectomy plus abdominal neurofibromas resection
8	Bilateral PHEO	4 patients: laparoscopic adrenalectomy of the larger lesion and laparoscopic cortical sparing adrenalectomy of the smaller lesion3 patients: metachronous lesions. Unilateral laparoscopic adrenalectomy for the initial lesion, after f/u laparoscopic cortical sparing adrenalectomy was performed for the contralateral lesion1 patient: Unilateral laparoscopic adrenalectomy for the initial lesion, after f/u laparotomic adrenalectomy of the contralateral lesion.
2	multiple abdominal PGLs	laparotomic lesion removal
1	Cardiac PGL	cardiothoracic surgery
2	Pelvic PGL	laparotomic lesion removal

NF1 (cutaneous neurofibromas or Café-Au-Lait macules) presented PHEOs, one of them associated with abdominal lesions (pararectal and jejunal wall neurofibromas). Full characteristics of patients with PHEO are listed in Table II. Eight patients showed PGL-syndrome (Table III): unilateral PHEO was present in 2 patients and bilateral PHEOs in 1 case; moreover, cardiac PGL associated with carotid body was found in 1 patient whereas 2 patients presented multiple abdominal PGLs and 2 patients were affected by pelvic PGLs.

SURGICAL POINT OF VIEW

All 30 patients affected by Syndromic PGL underwent surgical treatment. Seventeen patients with unilateral PHEO underwent open adrenalectomy until 1998, while lately laparoscopic adrenalectomy by transperitoneal approach was performed. Eight patients presented bilateral adrenal lesions: laparoscopic adrenalectomy of the larger lesion and laparoscopic cortical sparing adrenalectomy of the smaller lesion was performed in 4 patients (2 MEN2A and 2 VHL) presenting synchronous lesions. Three patients (2 MEN2A and 1 VHL) with metachronous lesions underwent unilateral laparoscopic adrenalectomy for the initial lesion; during follow-up PHEO was found on the contralateral gland in a time span between 8 months and 2 years, and laparoscopic cortical sparing adrenalectomy was performed. In addition, another 1 patient with metachronous lesions underwent

TABLE V - *PGL's characteristics based on the syndrome*

	VHL	RET	NF1	SDHD	SDHB
Frequency in sporadic tumors	6-10%	1-5%	Unknown	2-8%	4-9%
Predisposition to malignancy	3%	<3%	11%	50%	50%
Adrenal disease	++	++	++	+	+
Extra-adrenal disease	+	-	+	++	++

bilateral adrenalectomy in two different steps: a right laparoscopic adrenalectomy was performed for initial PHEO removal; the histological examination resulted malignant pheochromocytoma and genetic analysis revealed SDHD mutation. Thus, 16 years after the first diagnosis patient showed a contralateral adrenal relapse and underwent laparotomic left adrenalectomy.
Two patients with multiple abdominal PGLs, previously correctly identified by imaging or nuclear examinations, underwent laparotomic lesions removal. One patient with cardiac PGL underwent cardiothoracic surgery. Two patients with pelvic PGLs underwent surgical treatment by laparotomy: one case was mesenterial localization of PGL whilst the other one was a bladder PGL which required bladder resection and left ureteral reimplantation. Complete results are listed in Table IV.

Discussion

PHEOs and PGLs are chromaffin cells tumors arising from adrenal medulla or sympathetic ganglia located in thorax abdomen and pelvis, able to produce catecholamine and their metabolites, thus they can be considered the same entity clinically, biochemically and histopathologically. They can occur in either sporadic or syndromic forms due to specific genetic mutations and their incidence is around 30-40% [1,8]. MEN2, VHL syndrome, NF1 and PGL syndromes may present PHEOs and PGLs, and they are associated with mutation of RET, VHL, NF1 and SDH-x (SDH-B, SDH-C, SDH-D, SDH-AF2, the latest germline mutations identified in succinate dehydrogenase subunits), respectively [14].
Syndromic PGLs are diagnosed based on one or more suspicious symptoms such as juvenile presentation, adrenal bilateral lesions, multiple localization for thoracic or abdominal PGLs, association with other tumor such as medullary thyroid carcinoma, clear cell renal carcinoma or HN-PGL. Nevertheless, the diagnostic certainty is based on genetic analysis. PGLs are more evident in syndromic forms compared to sporadic variants and have different characteristics based on the syndrome (Table V) [15]. Adrenal localization, often bilateral, is more prevalent in MEN2, VHL and NF1 syndrome while an extra-adrenal localization, often multiple, is observable in PGL-syndromes. Moreover, in syndromes PGL-1 and PGL-4, due to SDH-B and SDH-D gene mutation, respectively, a greater predisposition to malignancy is evident reaching almost 50%. Understanding the relationship between PGLs and different syndromes and its influence on the surgical management is essential. The genetic analysis can be useful before surgery.
In our clinical records, 13 patients were affected by MEN2 and VHL syndromes (n7 and n6 respectively), seven of them presenting bilateral adrenal lesions. In four cases (2 MEN2A and 2 VHL) synchronous lesions were presented: patient underwent laparoscopic adrenalectomy of the larger lesion and laparoscopic cortical sparing adrenalectomy of the smaller lesion [16]. Three patients with metachronous lesions underwent unilateral laparoscopic adrenalectomy for the initial lesion; during follow-up PHEO was found on the contralateral gland in a time span between 8 months and 2 years, and laparoscopic cortical sparing adrenalectomy was performed. Recently, Castinetti et al recommended to consider laparoscopic cortical sparing adrenalectomy in patients affected by MEN2 because of the high percentage of bilateral disease (61%) and low malignancy rate (0.5%); in patients with previous unilateral adrenalectomy or need to undergo surgery for bilateral PHEO, the preservation of almost one third of the gland is recommended, to avoid Addison's disease [17]. In addition, no significant difference was reported between total and cortical-sparing adrenalectomy regarding intraoperative complications in experienced centers [17]. Cortical-sparing adrenalectomy is also recommended in VHL due to the low risk of PHEO recurrence and all the benefits derived from a reduced need of lifelong steroid replacement therapy [18].
The majority of our population was composed by patients affected by Von Reklingausen syndrome (9 patients, 30%) with adrenal unilateral PGLs; in one patient unilateral PHEO was associated to visceral pararectal and jejunal wall neurofibromas. In NF1 population the risk of PHEO development is reported to be around 30%[19]. In our Institution, the treatment of choice in these patients was laparoscopic adrenalectomy. The only patient presented PHEO associated to abdominal neurofibromas underwent laparotomic adrenalectomy with simultaneous abdominal lesions excision [20].
Laparoscopic adrenalectomy is considered the treatment of choice in patients affected by NF1; it is recommended transperitoneal approach with the possibility of abdominal cavity exploration and potential localization of other lesion not correctly identified at imaging [21-24].
Surgical management of patients with SDHx mutation should consider the possibility of multiple location of

PGLs in thorax, abdomen and pelvis, often associated with HN-PGL. In addition, malignancy rate is even higher compared to sporadic forms (till 50% for SDH-B and SDH-D mutations) [25]. In our clinical records, one patient presented metachronous bilateral adrenal localization and SDH-D mutation: first clinical manifestation was right PHEO, thus laparoscopic adrenalectomy of the right gland was performed. Histological examination reported malignant PHEO and genetic analysis demonstrated SDH-D exone 1 point mutation. 16 years later, the patient presented contralateral recurrence of PHEO and consequently underwent left adrenalectomy by laparotomic approach because of history of malignant disease.

For HN-PGL, indication for surgical treatment depended of symptoms of compression [26].

The correct imaging strategy (CT/MRI associated with I-123-MIBG scintigraphy) with the identification of lesions is mandatory for secreting PGLs. In our cases, patients affected by PGL-1/4 syndromes with multiple extra-adrenal localization underwent surgical treatment by laparotomic approach due to the great variability of localizations, higher incidence of multiple and bilateral lesions, malignancy rate, and great vessels relationship [27]. In 2 cases of pelvic localization of PGL, laparotomic approach was performed: one patient had mesenterial localization of PGL and the other one was affected by bladder PGL and required bladder resection and left ureteral reimplantation. Recently, mininvasive excision of PGLs via transperitoneal [28] or retroperitoneal [29] was described while Jawad et al reported their experience of laparoscopic excision of giant retroperitoneal PGL despite the size of the mass [30], but no one of these studies reported genetic analysis. Pre-operative genetic analysis can be very efficient and can influence the surgical management and strategy of PHEO and PGLs [14,31], due to the presence of mutations, like SDH-B and SDH-D, with an elevated malignancy rate: patients are accountable for laparotomic approach [32]. Surgeon and the equipe's experience are relevant factors: send patients to referral centers is becoming mandatory for the correct management of such a rare disease and to guarantee the best peri-operative management. This study should be evaluated considering some limitations. Our population comprised a small number of cases due to the extremely low prevalence of the disease and the small percentage of PGLs with genetic component; thus, a high number of records remain very complicated to obtain. Moreover, our monocentric study was performed in a retrospective way; therefore, prospective multicentric studies should useful to group a greater number of data coming from several referral centers for further development. In conclusion, syndromic PHEO and PGL are rare conditions suspected in young patient with bilateral or extra-adrenal lesions, malignancy, familiarity for PHEO or for genetic syndrome, development of other tumors associated to genetic syndromes. Diagnostic process in referral centers requires complete clinical, genetic and instrumental analysis of pathology and opportune medication before surgery, which remains the only curative treatment. For adrenal PGL, laparoscopic adrenalectomy with transperitoneal lateral approach is considered the gold standard. Nevertheless, for genetic syndrome such as MEN2 and VHL, which have a high percentage of bilateral PHEO and low risk of malignancy, laparoscopic cortical sparing adrenalectomy of at least one gland should be taken into account considering the actual trend to avoid bilateral adrenalectomy. Laparotomic approach need to be still considered when extra-adrenal PGLs are evident also connected to germline mutation of SDHx, due to often multiple localization of lesions and the elevate malignancy rate.

Riassunto

I paragangliomi sono tumori originanti da cellule cromaffini di derivazione dalla cresta neurale che si localizzano nei gangli simpatici (sede toracica, addominale, pelvica) e parasimpatici (testa e collo, *head and neck paraganglioma*, HN-PGL). Quando il paraganglioma origina dalle cellule cromaffini della midollare del surrene assume il nome di feocromocitoma. Le forme ereditarie di Paraganglioma raggiungono una percentuale del 30-40%. Le sindromi familiari in cui ritroviamo il paraganglioma sono la MEN2, VonHippel-Lindau (VHL), von Reklingausen (NF1) e sindromi PGL. Ognuna di esse ha localizzazione caratteristica dei paragangliomi (surrenalica o extra-surrenalica, singola o multipla) e diversa predisposizione alla malignità. Per tale motivo la sindrome genetica può influenzare una diversa gestione dal punto di vista chirurgico. Abbiamo studiato retrospettivamente 127 pazienti con feocromocitoma e/o paraganglioma trattati presso il Centro di riferimento per le patologie surrenaliche del Policlinico Umberto I dal 1992 al 2018. Tutti i pazienti erano stati sottoposti a studio completo della funzionalità surrenalica, TC o RM dell'addome per corretta localizzazione della lesione e scintigrafia con ^{123}I-metaiodiobenzilguanidina (I-123-MIBG) per confermarne l'effettiva ipercaptazione. Nei pazienti con caratteristiche sospette per sindrome genetica non ancora nota è stato effettuato esame genetico per mutazioni della linea germinale dei geni RET, VHL, SDHD e SDHB. Tutti i pazienti sono stati trattati chirurgicamente e abbiamo posto particolare attenzione al tipo di trattamento chirurgico effettuato in base alla sindrome genetica da cui il paziente è risultato essere affetto. I pazienti con feocromocitoma surrenalico singolo sono stati sottoposti a surrenectomia laparoscopica; i pazienti con feocromocitoma surrenalico bilaterale sono stati trattati, dal 2000 in poi, con surrenectomia laparoscopica monolaterale della lesione di dimensioni maggiori o ipercaptante alla scintigrafia, follow-up della lesione controlaterale minore e successivo trattamento chirurgico (laddove possibile surrenectomia parziale cortical-sparing laparoscopica) del surrene residuo. I pazienti con paragangliomi addominali multipli sono stati sottoposti a

laparotomia e asportazione delle lesioni localizzate tramite accurato studio radiologico e nucleare. La gestione chirurgica dei pazienti affetti da paraganglioma sindromico deve tener conto delle caratteristiche di manifestazione e della predisposizione alla malignità di ciascuna delle sindromi genetiche sottostanti.

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