BRIEF COMMUNICATION

Pheochromocytomas and Parangliomas: Experience of a Buenos Aires General Hospital

Feocromocitoma y paragangliomas; Experiencia de un hospital general de Buenos Aires

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ABSTRACT

We report phechromocytoma and paraganglioma case studies followed-up in the Hospital General de Agudos "José M. Ramos Mejía" Division of Endocrinology between 1994 and 2014. Twenty two patients were diagnosed and treated, 17 women and 5 men. Sixteen patients presented with typical signs and symptoms, 2 had associated ischemic limb necrosis, and 4 were normotensive (3 with incidentalomas and 1 with hyperglycemia and asthenia). Elevated urinary catecholamine and metanephrine levels were found in all patients. Twelve patients exhibited unilateral adrenal disease, (8 right and 4 left), 5 had bilateral disease and 5 extra-adrenal disease Ten patients had familial syndromes. Eleven patients underwent laparoscopic surgery and 11 required conversion to laparotomy due to tumor size or bleeding. During follow-up, biochemical recurrence was observed in four patients, two with local recurrence, one with metastasis, and one with untraceable tumor). This report of our institutional experience emphasizes the importance of a multidisciplinary approach to treat this disease.

Key words: Pheochromocytoma – Paraganglioma – Surgery – Hypertension – Catecholamines - Incidentaloma

RESUMEN

Se presenta la casuística de feocromocitomas y paragangliomas seguidos en la División Endocrinología del Hospital General de Agudos "José M. Ramos Mejía" entre 1994 y 2014. Fueron diagnosticados y tratados 22 pacientes, 17 mujeres y 5 varones. Dieciséis presentaron signosintomatología habitual, 2 necrosis isquémicas de miembros asociadas y 4 se hallaban normotensos (3 incidentalomas y uno con hiperglucemia y astenia). En todos los pacientes los niveles de catecolaminas o metanefrinas urinarias se encontraban elevados. Doce pacientes exhibieron localización adrenal única (8 derechas y 4 izquierdas), 5 fueron bilaterales y 5 extraadrenales. Diez pacientes eran portadores de síndromes familiares. Once pacientes fueron operados por vía laparoscópica y 11 convertidos al procedimiento convencional, por tamaño o sangrado. En el seguimiento ulterior, cuatro pacientes tuvieron recurrencia bioquímica, dos con recidiva local, uno metastásica y otro sin localización. En esta comunicación de nuestra experiencia institucional se enfatiza en la importancia del abordaje multidisciplinario en el tratamiento de esta patología.

Palabras clave: Feocromocitoma - Paraganglioma - Cirugía - Hipertensión - Catecolaminas – Incidentaloma

Abbreviations

A	Adrenaline	**HTN**	Hypertension
VMA	Vanillylmandelic acid	**NA**	Noradrenaline
PHEO	Pheochromocytoma	**PGL**	Paraganglioma

INTRODUCTION

Pheochromocytomas (PHEO) and paragangliomas (PGL) are catecholamine-secreting tumors that arise from chromaffin cells of the adrenal glands or the ganglia of the sympathetic or parasympathetic nervous system, respectively. (1, 2)

They are one of the known causes of endocrine hypertension, with mean prevalence of 0.5%, high morbidity and mortality and protean clinical manifestations.

The present study reports the 20-year experience in the diagnosis, treatment and outcome of PHEO

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and PGL patients in the Division of Endocrinology at Hospital General de Agudos "José M. Ramos Mejía", focusing in the forms of presentation and primary complications of the disease and its therapy.

METHODS

A retrospective analysis was performed of the clinical records of patients referred to the Division of Endocrinology at Hospital General de Agudos "José M. Ramos Mejía" with presumed and later confirmed diagnosis of PHEO or PGL between 1994 and 2014.

Urinary adrenaline and noradrenaline were assessed by fluorometric tests, with normal values of 0-8.5 μg/day and 18-100 μg/day, respectively. Vanillylmandelic acid (VMA) was evaluated by spectrophotometry, with normal values of 1.8 to 8.5 mg/day, and HPLC was used to measure metanephrine levels (normal values 39 to 606 μg/day).

A patient was considered to be free from disease when catecholamine levels were in the normal range 15 days after surgical treatment and they remained normal at the 6-month control. A patient was considered to have persistent disease when excess catecholamine levels did not decrease after the initial treatment, and recurrent disease when after a negative period catecholamine levels increased again.

In the presence of overt persistence and/or biochemical recurrence, disease localization was routinely performed. The disease was defined as recurrent when it was localized in areas of chromaffin tissue (ganglia of the sympathetic nervous system and adrenal glands) and as metastasis when it was situated in organs where normally there is no chromaffin tissue.

Microsoft Excel for Windows 8 software and Primer 2000 were used for data analysis.

RESULTS

Among the 22 diagnosed and treated patients, 17 were women and 5 men, with median age of 37 years at the time of diagnosis (17-69 years).

Sixteen patients (73%) presented with usual signs and symptoms: sustained or paroxysmal hypertension (HTN), palpitations, sweating and flushing. In these patients, blood pressure ranged from 140/90 to 200/100 mmHg, and they were mainly treated with calcium blockers (18/22 patients). Four patients received concomitant treatment with alpha plus beta blockers and one with thiazide diuretics.

In addition to HTN, two patients (9%) presented with ischemic limb necrosis; one with partial necrosis of both feet (which reversed after surgery) and another with supracondylar amputation of the right lower limb prior to left adrenal PHEO diagnosis, in the context of a paroxysmal hypertensive crisis, associated to cephalea and flushing.

A patient presented with HTN associated to renal agenesis ipsilateral to PHEO.

Four patients (18%) were normotensive, one presenting only hyperglycemia and asthenia. The other three (14%) were diagnosed in the context of an adrenal incidentaloma.

Laparoscopic surgery has been performed in our hospital since 1994 to treat this disease. In 11 of the study patients, conversion to laparotomy was necessary due to tumor size or serious bleeding. Most patients had intraoperative HTN due to tumor manipulation (13/20 patients, 59%), and 19 patients (86%) evolved with hypotension in the immediate postoperative period. Mean hospital stay was 6 to 10 days in the case of laparoscopic surgery and 4 to 5 days for laparotomies.

All patients, except one, had elevated urinary noradrenaline (NA), adrenaline (A) or VMA. Five patients (23%) presented with normal NA, another 23% normal A, and three patients (12.5%) normal VMA. Preoperative urinary NA range was 19 to 2,678 pg/day, with a mean value of 738 pg/day, the range of A was 0 to 986 pg/day, with a mean value of 223 pg/day, and finally, the range of VMA was 0 to 60.4 mg/day, with a mean value of 20 mg/day. The female patient presenting normal urinary catecholamines was diagnosed by elevated urinary and serum metanephrine levels.

Tumor size varied between 23 and 91 mm, with predominance of tumors over 39 mm.

Regarding prevalence of sporadic or hereditary PHEO or PGL, 12 patients presented with sporadic tumors (55%) and 10 hereditary forms (45%), four of which were MEN 2 A, 2 VHL, and 4 PGL due to SHDB mutation.

Two patients (9%) had malignant tumors, one simultaneously with bone metastasis and the other with liver metastasis 15 years after initial surgery. The localization of metastases was defined by nuclear magnetic resonance.

Fourteen patients continue under surveillance (range 10 months-20 years, median 11 years). In the immediate postoperative period, 14 patients normalized their blood pressure, 3 continued being hypertensive with values below preoperative ones, and one female patient, with persistent disease for bone metastasis at the time of diagnosis, worsened her hypertension.

In the long-term follow-up, four patients (18%) presented biochemical recurrence of the disease. Two of them required a second surgery to complete the initial intervention. An ipsilateral nephrectomy was performed in one of the patients to remove the adrenal tumor. The third female patient presented with local-persistent PHEO and liver and retroperitoneal metastases, 15 years after the initial diagnosis. The fourth female patient presented with biochemical NA recurrence, with marginal increase at 5 years of initial treatment, but without confirmed localization to the present date. This patient is under triple antihypertensive therapy with amlodipine, losartan and doxazocin with adequate response. The two already mentioned patients with metastases died: the patient with metastases synchronous to the first surgery died close to diagnosis and initial treatment, and the other 15 years after diagnosis and treatment initiation.

Figure 1 shows long-term outcome.

The remaining patients are free from disease, and

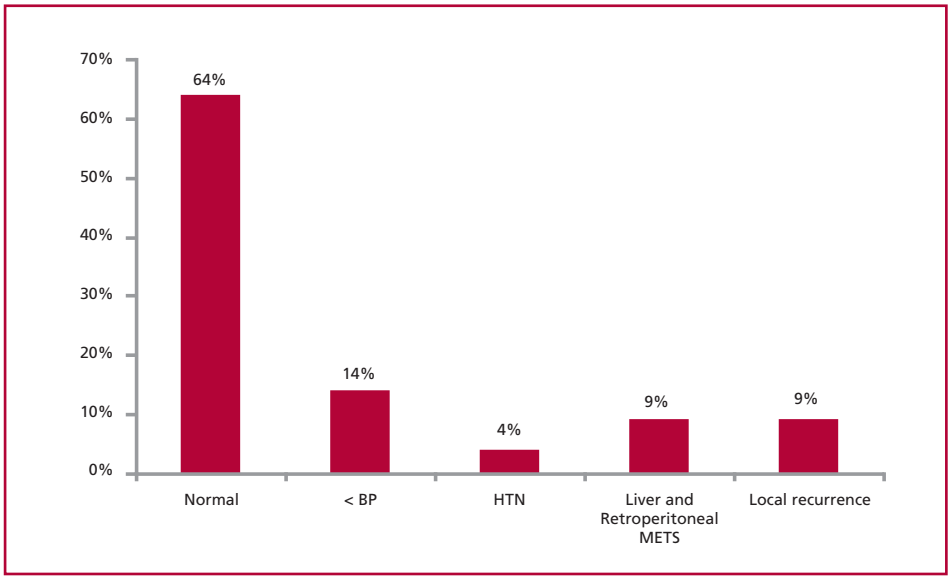

Fig. 1. Disease progression and rate of recurrence. The patient with persistent hypertension was due to metastases synchronous to diagnosis and initial surgery. Both patients with metastases died. Normal: Normotensive. < BP: Blood pressure lower than in the preoperative period. HTN: Hypertension: METS: Metastasis.

they are all normotensive, except for three that have mild essential HTN, controlled with one drug. Four patients abandoned control surveillance and four died: one due to thyroid medullary carcinoma complications, two because of progression of their metastatic disease (one with concomitant persistent PHEO diagnosis and another 15 years after initial therapy) and one for unknown cause.

Table 1 shows the correlation between preoperative catecholamine levels with disease associated to genetic disorders, bilateral disease, recurrence and metastasis rates.

DISCUSSION

We have reported our local 20-year experience in PHEO and PGL management in the Division of Endocrinology at Hospital General de Agudos "José M. Ramos Mejía" In our population, different from the literature, the prevalence of PHEO as part of genetic syndromes was 45%, compared to reported rates below 30%. (1, 4)

Nonetheless, our study has several similarities with published data. Firstly, there was greater prevalence of adrenal tumors, predominantly affecting the right adrenal gland. (1) The rate of patients presented as incidentalomas was 13% vs. 10% in the literature. (5) Moreover, similar to reported cases, 18% of patients were normotensive (1). The general clinical condition, average tumor size and postoperative outcome were comparable to the literature. (6-11) However, a high rate of conversion to laparotomy and intraoperative HTN was observed, possibly due to the lower experience in disease management during the first years of this study. (11)

Another remarkable occurrence was the presentation of two patients with ischemic limb necrosis associated to PHEO. Only 12 cases of ischemic necrosis have been reported (cardiac, intestinal and limb necrosis, from fingers to the four limbs), with great variation in the outcome, from massive amputation followed by death to complete restitution. (12) Sustained vasoconstriction is the postulated mechanism during prolonged adrenergic crises due to NA release. (13) Its potential sequels are important but reversible with alpha blockade, and the possibility of PHEO should be considered in a patient with limb ischemia and HTN. Also, the importance of alpha blockade is emphasized in patients with PHEO until surgical resolution of the pathology.

There are limitations in this study. Due to its retrospective nature, the population was heterogeneous as revealed by diagnostic biochemical and imaging testing, in addition to a referral bias that might explain the greater prevalence of genetic disease.

It is essential to emphasize that the diagnosis, treatment and follow-up of a patient with PHEO or PGL, carried out by a multidisciplinary endocrinology, cardiology, biochemistry, surgery and molecular biology team, allows optimizing patient management, reducing the elevated morbidity and mortality of this disease. Furthermore, considering the growing prevalence of familial forms of PHEO and PGL, it is important to mention that a comprehensive approach might also produce an adequate genetic advice and better management in the offspring of affected subjects

Conflicts of interest

(See author´s conflicts of interest forms in the web / Supplementary Material)

Patient Nº	Preoperative catecholamines			Genetic syndromes	Bilateral disease	Recurrence	METS
	A	NA	VMA				
nº 1	986	1,126	5.5	Sporadic	No	No	No
nº 2	696	245	50	Sporadic	No	No	No
nº 3	1.9	400	23	Sporadic	No	No	No
nº 4	411	330	9.8	Sporadic	No	No	No
nº 5	3.3	390	18.3	Sporadic	No	No	No
nº 6	124	190	6.9	Sporadic	No	No	No
nº 7	114	47	17	MEN 2 A	No	No	No
nº 8	42	62	8.5	MEN 2 A	No	No	No
nº 9	61	63	5.8	MEN 2 A	No	No	No
nº 10	498	200	19.4	MEN 2 A	No	No	No
nº 11	3,2	230	23.4	VHL	No	No	No
nº 12	0	1,130	16	VHL	No	No	No
nº 13	485	8,700	60.4	SHDB	No	No	No
nº 14	10	2,234	40	SHDB–	No	No	No
nº 15	6.6	287	5.5	SHDB	No	No	No
nº 16	8.5	2,110	10.6	Sporadic	No	No	No
nº 17	0	235	7.5	Sporadic	Yes	Yes	Yes
nº 18	128	10	10.1	Sporadic	No	No	No
nº 19	242	1,793	47	SHDB	No	No	No
nº 20	210	19.3	7.1	Sporadic	No	No	No
nº 21	78	195	5.8	Sporadic	No	No	No
nº 22	4.1	21.1	7.2	Sporadic	No	No	No

A: 24-hour urinary adrenaline (normal value: 0-8.5 µg/day). NA: 24-hour urinary noradrenaline (normal value: 18-100 µg/day). VMA: vanillylmandelic acid (normal value: 1.8-8.5 mg/day). METS: Metastasis

Table 1. Correlation between preoperative catecholamine levels and genetic syndromes, bilateral disease, recurrence and metastasis

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