Research Paper

Diagnosis and treatment of neuroendocrine tumors – A series of 13 clinical cases (2014–2017)

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A B S T R A C T

Paragangliomas and pheocromocytomas are rare neuroendocrine tumors with different clinical presentation, being responsible for secondary arterial hypertension with target-organ lesions. Surgery is a curative therapy in these tumors and demands a multidisciplinary approach.

These tumors are more frequent between the 4th and 5th decades of life and their clinical manifestations are related to catecholamines production: headache, palpitations, variable blood pressure.

This article presents 13 clinical cases of patients with neuroendocrine tumors, with an median-age of 56,7 years, submitted to surgery between 2014 and 2017. The diagnosis was made based on clinical suspicion, serum and urinary catecholamines and metanephrins, imagiologic evaluation with CT or abdominal and pelvic MRI and MIBG scintigraphy.

After surgery, the majority of patients remained with normal blood pressure, without anti-hypertensive therapy and follow-up was maintained in Outpatient Clinic, with periodic blood tests and imaging reevaluation.

1. Introduction

Paragangliomas and pheocromocytomas are rare neuroendocrine tumors, with variable clinical presentation and their diagnosis remains an important challenge [1]. Being responsible for secondary arterial hypertension with target-organ lesions they are an area of interest in clinical investigation, diagnosis and treatment. It implies a multidisciplinary approach, with clinical and laboratory evaluation by Internal Medicine and, after that, a surgical curative treatment. These tumors are more prevalent between the 4th and 5th decades, with equal incidence between men and women [2].

Neuroendocrine tumors originate in chromaffin cells [3,4] and secrete catecholamines (norepinephrin, epinephrin and dopamine). 20% of them are located outside adrenal medulla and, therefore, are classified as paragangliomas [1]. Their prevalence is about 0.1–0.6% and there are also sporadic and hereditary forms like neurofibromatosis, multiple endocrine neoplasia and von Hippel-Lindau syndrome [2]. 10% of

pheocromocytomas and 20% of paragangliomas are malignant, with local invasion or metastasis [2,4].

Classical symptoms are related with catecholamines overproduction and patients can have headache, palpitations, sweating and variable blood pressure [3], according to their age and type of tumor. There are even patients without hypertension [1,4]. Catecholamin profile can also be related with hypertension pattern: norephinefrin is responsible for sustained hypertension, epinephrine is related with paroxistic and orthostatic hypertension and, generally, patients with dopamine-producing tumors have no hypertension [3].

80–90% of patients with pheocromocytoma have hypertension, so they have target-organ lesions that occur mainly in brain (hypertensive encephalopathy, ischemia), heart and blood vessels (arterial stiffness, disrythmias, myocardial ischemia). Catecholamine cardiomyopathy may also occur, which is the result of arterial hypertension, myocardial hypoxia and myocarditis caused by catecholamines. This can be chronic or acute and, in the last case can result in ischemia or Takotsubo

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cardiomyopathy [3,5–7]. As a result, these patients have an increased cardiovascular risk compared to general population due to the toxic effect of catecholamines [5].

The diagnosis of these tumors is based on clinical presentation and endocrine blood and urinary tests, of which urinary metanephrines is the most sensible [8,9]. Abdominal CT-scan (with 88–100% sensibility) must be done in all patients and MRI in metastatic disease. MIBG scintigraphy is also of diagnostic value to exclude tumors outside adrenal glands [8] (see Fig. 1).

Genetic test is recommended to all patients with neuroendocrine tumors [8,10] because more than a third of these have a germline mutation which has implications in the diagnosis and treatment of family members. Besides, the risk of new cardiovascular events in genetically determined pheocromocytomas is twice relatively to the sporadic cases [10].

Surgery is the recommended treatment with complete excision of the tumor or adrenalectomy. To avoid surgery complications, like tachyarrhythmias, pre-surgery treatment with alpha and beta-blocker is recommended. Alpha-blocker must be started 7–14 days before surgery (eg: fenoxibenzamine) and, after that, a beta-blocker is initiated (eg: propranolol), to reduce blood pressure and heart rate, respectively. Labetalol could be an alternative to propranolol, although more difficult to use because it needs invasive blood pressure monitoring and has more risk of hypotension and bradycardia. When patients are intolerant to all these, a calcium-channel blocker can be used with no different outcomes [11].If hypotension is feared after surgery, volume expansion with fluids must be done [8]. It is also important to note that some medication (eg: metoclopramide) can unmask hypertensive crises and this is the reason why the clinical interview and the complete medical history are crucial.

Follow-up with annual urinary or serum metanephrine dosing is recommended during at least 10 years after surgery [8,10]. Imaging reevaluation is also recommended every two years in metabolically inactive disease [10].

2. Material and methods

In this article, we present 13 clinical cases of neuroendocrine tumors submitted to surgery, diagnosed between 2014 and 2017.

During this period, we evaluated 4 men and 9 women with a median-age of 56.7 years. Clinical presentation was variable, with palpitations (23%), sweating (15.4%), blood pressure variability (15.4%), blurred vision (15.4%) and headache (15.4%). One patient presented lower left abdominal pain (7,7%), three of them (23,1%) had no complaints and one had a previous diagnosis of von Hippel-Lindau syndrome (7,7%).

Patient evaluation included catecholamines, metanephrines, vanilmandelic acid, abdominal and pelvic CT and MRI and MIBG scintighraphy (Table 1) (see Fig. 2).

We used fenoxibenzamine in a maximal dose of 10 mg three times a day to obtain systolic blood pressure lower than 100 mmHg. Only one patient was previously treated and maintained on doxasozin. After that, we initiated propranolol, a beta-blocker with short half-life and easy to adjust (maximal dose of 20 mg three times a day). Only one patient was intolerant and, in this case, we used a calcium-channel blocker instead.

3. Results

To avoid intra-operatory complications, all patients were admitted at Surgery Ward 9.4 days (in average) before surgery to initiate therapy with alpha and beta-blocker. Every patient was submitted to surgery with systolic blood pressure inferior to 120 mmHg and heart rate inferior to 80 ppm, with no complaints.

13 adrenalectomies were performed, 7 on the right and 6 on the left side. The preferred access route was laparoscopic (11 patients), and the open route (right subcostal) was used in 2 cases. The mean surgical time was 73.7 min, ranging from 40 to 102 min for the laparoscopic approach. In the 2 cases of laparotomic access, the mean surgical time was 123.5 min, ranging from 97 to 150 min. In patient nº.6, a 6,5 cm tumor was diagnosed in the right adrenal gland, suspected of malignancy, with peri-pancreatic adenopathy, and symptomatic cholelithiasis was also reported. This patient underwent adrenalectomy, cholecystectomy and biopsy of adenopathy at the same operative time. The pathological study revealed a pheochromocytoma of uncertain behaviour, and no neoplastic lesions were identified in the lymph nodes biopsies. In the case of patient nº.10, a pheochromocytoma of 7 cm was diagnosed, with no cleavage plane with the left psoas muscle and homolateral kidney. During surgery, blood pressure lability was observed with a maximum systolic pressure of 220 mmHg and the need for administration of sodium nitroprusside and esmolol. Except for the latter case, an excellent response to the pre-operative blood pressure control measures was observed in all patients.

All patients underwent prophylactic antibiotic therapy with cefazolin. In the intraoperative period there was a case of difficult-to-control hypertension. Patients remained hospitalized after the surgical procedure for an average for 4,6 days, ranging from 2 to 9 days. There were two cases of morbidity recorded, one following an infectious complication (patient nº.10) and one due to hemodynamic instability (patient nº.12). No cases of mortality to be reported (Table 2).

Pathological diagnoses were: 6 benign pheochromocytomas, 2 pheochromocytomas of uncertain behaviour (classified according to the Weiss scale), 1 adrenal adenoma, 1 histological examination compatible
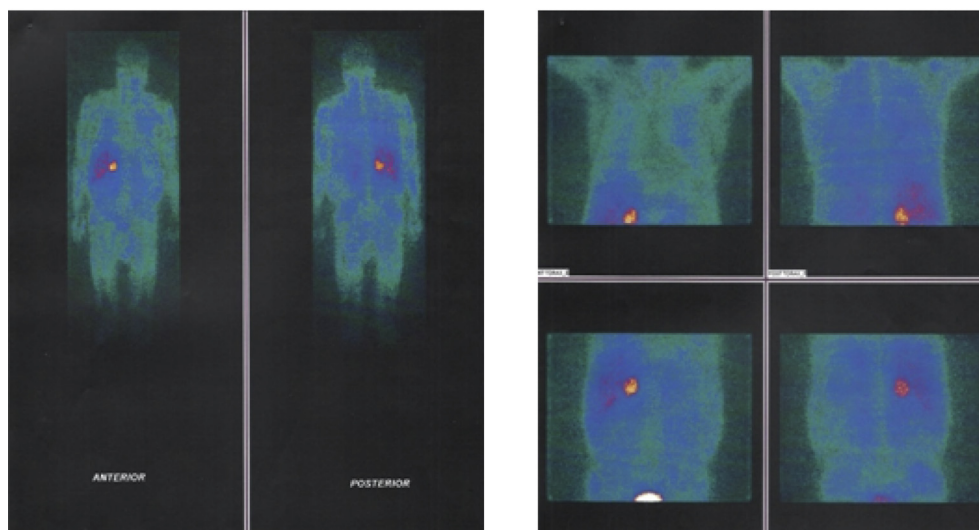

Fig. 1. Example of MIBG scintigraphy in patient with right adrenal Pheocromocytoma.

Table 1
Patient demographic data, laboratory tests and other exams.

Pat.	Gen.	Age	Clinical complaints	Laboratory evaluation													MIBG
				PAdr. (<100 pg/mL)	PNorad. (<600 pg/mL)	PDop. (<100 pg/mL)	PCat. (<800 pg/mL)	PMet. (<90 pg/mL)	PNormet. (<180 pg/mL)	VMA (1,8-6,7 mg)	UAdr. (0,6-19,9 mcg)	UNorad. (15-80 mcg)	UDop. (64,8-399 mcg)	UMet. (74-297 mcg)	UNormet. (105-354 mcg)	UCat. (<110 mcg)	
1	M	70	Dizziness, sweating, blurred vision, headache	1157,3	1186,5	55,7	2399,5			17,6	253,5	357,2	5758,4	5077,2	2692,6	417	+
2	F	79	Blood pressure variability														+
3	F	48	None (von-Hippel-Lindau syndrome)								25,1	145	1060,3	401	417,7		+
4	F	50	Palpitations	718,5	632,8	49,7	1401			19,9	221,1	94,7	532,2	247,2	13826		+
5	F	46	Tachycardia, alopecia, sweating								65,8	81,9	380,8		563,9		+
6	F	30	Dizziness, headache	144,5	896,6	65,6	1106,7			15,8	7,3	318,2	295,1	249,3	8249,3		N/R
7	F	55	Palpitations, dizziness, blurred vision							17,4	239,6	468,1	854,2				N/R
8	M	72	None	53,1	864,9	95,7	1013,6		238,9	12,1	4,6	63,8	349,2	636	1778,4		N/R
9	F	59	Hypertension							4,8	43	117	310,3	215,8			+
10	F	79	Dizziness, palpitations, left lower abdominal pain							8,8	65	284,3	315,6	39000			+
11	M	61	Hypertension	98,6	475,8	26,2	600,6			5,8	17,8	21,6	108,8	139,8	174,2		−
12	M	52	Blood pressure variability					69,7	1066,2								+
13	M	36	None						367,7	8,2	34,7	235,4	450,1	400,9	2457		−

Gen.: gender; MIBG: metaiodobenzylguanidine scintigraphy; (+): positive for pheocromocytoma; (−): negative for pheocromocytoma; N/R: not realized; PAdr.: plasma adrenaline; PNorad.: plasma norepineohrine; PDop.: plasma dopamine; PCatecol.: plasma catecholamines; PMet.: plasma metanephrines; PNormet.: plasmanormetanephrine; UAdr.: urinary adrenalin; UNorad.: urinary norepinephrine; UDop.: urinary dopamine; UMet.: urinary metanephrine; UNormet.: urinary normetaneophrine; UCat.: urinary catecholamines; AVM: vanilmandelic acid.
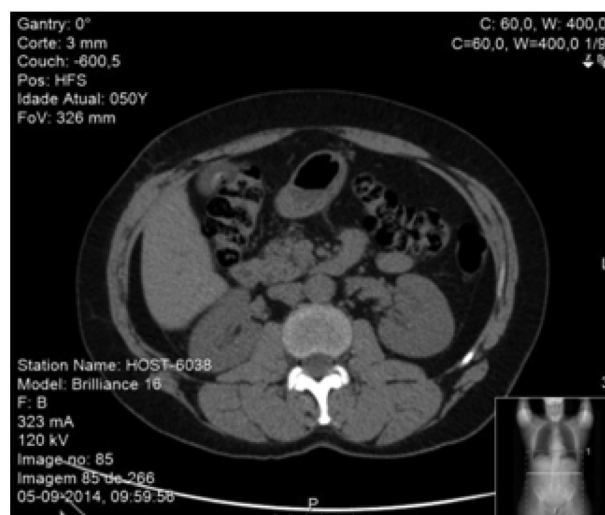

Fig. 2. CT-scan with nodular lesion in right adrenal gland.

with adrenal hyperplasia, 1 adrenal cortex neoplasia and 1 adrenal cortex paraganglioma.

After surgery, alpha-blocker therapy was discontinued in all cases propranolol therapy, gradually diminished until suspension, avoiding the rebound effect of this drug.

4. Discussion

The surgical removal of the adrenal gland should be considered mandatory in cases of hyperfunctioning adrenal masses, in the presence of suspect radiological evidence, in cases of discordant CT and scintigraphy findings and when the maximum diameter is 4 cm or more [12]. It can be performed either by open or laparoscopic approach, and since it was described by Gagner et al., in 1992, the last one quickly became the procedure of choice [13]. The advantages that come from laparocopic adrenalectomy for the patient and the surgeon are recognized, being proven its feasibility, safety and efficiency and comparable oncological outcomes compared with open adrenalectomy [14]. Besides, it is associated with lower morbidity, shorter hospital length of stay, and less pain following these procedures [15].

To this end, the existence of properly established protocols, the logistic capacity of the institution and the experience of the surgical and anaesthetic teams, assume its relevance. It is important to note that since the introduction of the laparoscopic adrenal surgery program in 1994 at Centro Hospitalar de Lisboa Norte, the Endocrine Surgery Unit performed an average of 15 of these procedures per year. The contraindications for the laparoscopic approach may be absolute or relative, according to the team's experience, the patient's biological conditions and the type of injury [16].

The preferred option of our team is a laparoscopic transperitoneal approach in lateral decubitus, with 3 ports on the left and 4 ports on the right side.

The main purpose of antibiotic prophylaxis in surgery is the reduction of the risk of the surgical site infection that occurs during the procedure. In all surgeries, a 1st generation cephalosporin (cefazolin) was used. There were no infections of the surgical site. In the postoperative period, only one pneumonia (case nº.10) and one episode of hypotension and bradycardia (patient nº.12) were recorded, with resolution after adjustment of propranolol therapy. According to Bai et al. independent risk factors for cardiovascular morbidity are low body mass index, large radiographic tumor size, coronary heart disease, no preoperative crystal/colloid administration, and intraoperative hemodynamic instability [17]. On the other hand, Bittner and colleagues assume that preoperative the risk factors that may influence patient outcomes include tumor size,

Table 2

–Surgical data.

Patient	Gender	Age	Preoperative hospitalization days	Procedure	Access way	Side	Surgery time (minutes)	Antibiotic prophylaxis	Intraoperative complications	Post-operative complications	Post-operative hospitalization days
1	M	70	22	Adrenalectomy	Laparoscopy	Right	80	Cefazolin	No	No	3
2	F	79	7	Adrenalectomy	Laparoscopy	Right	40	Cefazolin	No	No	3
3	F	48	8	Adrenalectomy	Laparoscopy	Right	77	Cefazolin	No	No	2
4	F	50	6	Adrenalectomy	Laparoscopy	Right	72	Cefazolin	No	No	3
5	F	46	8	Adrenalectomy	Laparoscopy	Left	102	Cefazolin	No	No	3
6	F	30	8	Adrenalectomy + cholecystectomy	Open	Right	150	Cefazolin	No	No	8
7	F	55	21	Adrenalectomy	Laparoscopy	Right	100	Cefazolin	No	No	4
8	M	72	7	Adrenalectomy	Laparoscopy	Left	82	Cefazolin	No	No	4
9	F	59	7	Adrenalectomy	Laparoscopy	Left	59	Cefazolin	No	No	4
10	F	79	7	Adrenalectomy	Open	Left	97	Cefazolin	Yes	Yes	9
11	M	61	7	Adrenalectomy	Laparoscopy	Right	62	Cefazolin	No	No	3
12	M	52	7	Adrenalectomy	Laparoscopy	Left	77	Cefazolin	No	Yes	3
13	F	36	7	Adrenalectomy	Laparoscopy	Left	60	Cefazolin	No	No	3

tumor histology and functionality, the need for concomitant procedures, and surgeon experience [15].

On average, the patients remained hospitalized for 4,6 days, being discharged to the outpatient clinic with normal blood pressure levels, referred for Hypertension and Endocrine Surgery consultations.

The follow-up of these patients has been without hemodynamic or other complications, with the exception of 2 situations: 1 case of benign pheochromocytoma, in which there was persistence of frequent supra-ventricular extrasystoles, associated with palpitations, requiring maintenance of calcium channel blocker and another case of neoplasia of the adrenal cortex, which manifested with secondary adrenal insufficiency.

To date, only two genetic tests have been performed: one negative and the other confirming von Hippel-Lindau syndrome. Even the strong genetic background of these tumors are established, none of the patients submitted to surgery had family members affected besides the one with von-Hippel-Lindau syndrome. However, it is still important to exclude germline mutations in all these patients. According to this, we perspective to do the genetic test to all them in the near future, considering also its importance when determining the surgical approach and extent of adrenalectomy [18].

Regarding maintenance therapy, patients exposed for a longer time to catecholamine toxicity (i.e. later diagnosed) may need to maintain antihypertensive therapy after surgery, probably because of irreversible vascular lesions caused by excessive catecholamine release. However, in most cases complete discontinuation of antihypertensive therapy was possible.

The follow-up of these patients was performed in the outpatient setting and the first evaluation occurred about 2 weeks after surgery, followed by a biannual control with endocrinological laboratory evaluation and imaging re-evaluation in cases of malignant histology, uncertain behaviour or if clinically justifiable.

5. Conclusion

To conclude, this paper intends to underline the importance of the diagnosis of these type of tumors, mainly because of their potential effects on blood pressure and, consequently, on target-organs. Additionally, it stresses the need to extend the genetic tests to all these patients and, eventually, to their family members.

Conflict of interest

Authors declare no conflicts of interest.

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