CASE REPORT

Pheochromocytoma: clinical review based on a rare case in adolescence

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SUMMARY

Pheochromocytomas are rare tumours originating in chromaffin cells, representing 0.1–1% of all secondary hypertension (HT) cases. The majority are benign and unilateral, characterised by the production of catecholamines and other neuropeptides. Mainly located in the adrenal gland, they are more frequent between the 3rd and 5th decades of life; however, 10–25% can be associated with genetic familial syndromes (multiple endocrine neoplasia type 2 (MEN 2), type 1 neurofibromatosis and Von-Hippel-Landau disease in younger ages). The authors present a rare case of secondary HT due to a pheochromocytoma in a 15-year-old patient, whose metanephrine assay confirmed the diagnosis, and abdominal ultrasound and CT localised the tumour in the adrenal gland. HT was controlled with α and β blockers, with posterior retroperitoneal laparoscopic surgical intervention and subsequent resolution of HT. Age and concomitant hyperparathyroidism compelled genetic testing for the exclusion of MEN 2, which was negative.

BACKGROUND

Arterial hypertension (AHT) is a common disease worldwide and 5–10% of cases have a potentially curable secondary cause.¹ This possibility should be excluded in cases of AHT presenting before the age of 20 years and after the age of 50 years, in refractory AHT with serious end-organ damage or in patients who present symptoms, signs or laboratorial findings suggestive or specific for a secondary cause.

Among the causes of secondary AHT are endocrine (primary hyperaldosteronism, pheochromocytoma, Cushing syndrome and hyperparathyroidism), renal (parenchymal and renovascular) or others such as obstructive sleep apnoea, aortic coarctation and intracranial tumours.²

Pheochromocytoma is a rare neuroendocrine tumour that produces catecholamines and other neuropeptides, originating in the adrenal gland medulla. The majority of cases are sporadic, but 10–25% can be associated with genetic syndromes such as Von Hippel-Landau (VHL) disease, type 1 neurofibromatosis (NF1) and multiple endocrine neoplasia type 2 (MEN 2), implying genetic testing in selected cases.³

Sustained or paroxysmal ATH is the most frequent sign, possibly associated with the classic triad: episodic headaches, sudoresis and tachycardia.⁴ Cardiovascular complications due to adrenergic stimulation can potentially be fatal, emphasising the importance of timely diagnosis and an effective therapeutic strategy.

CASE PRESENTATION

A 15-year-old gypsy girl student with a history of migraines diagnosed 2 years before the current clinical picture, began having symptoms of non-pulsatile frontal headaches 9 months before hospital admission, with worsening symptoms in the last 2 months associated with palpitations. She turned to the emergency room (ER) where she presented AHT (blood pressure (BP) 160/123 mm Hg) for which she was then treated, discharged and referred to her treating physician (without medication).

On 9 February 2012, she returned to the ER because of worsening headaches and new visual symptoms (blurred vision of the left eye). She was evaluated by ophthalmology, which observed the following changes in visual acuity: right eye 9/10 and left eye 4/10. Funduscopy and angiography revealed small venous occlusions with sparing of the macula. The patient was medicated (eye drops) and referred to ophthalmology, paediatrics and neurology consults, which she failed to attend.

On 10 February 2012, she turned to the ophthalmology ER because of worsening visual symptoms: bilateral ‘cloudy’ vision most pronounced in the left eye, presenting aggravated retinopathy with macular detachment and superficial peripapillary haemorrhages. She was referred to a consult and observed 6 days after with worsening visual acuity (right eye: 1/10, left eye with the capability of only counting fingers). Funduscopy with cotton wool spots, haemorrhages and macular oedema were most pronounced in the left eye, without oedema of the optic disc. The patient was transferred to the general ER of the Hospital São Francisco Xavier and referred to Internal Medicine with the diagnosis of hypertensive crisis.

The patient denied relevant pathological medical history including smoking, alcohol use or drug consumption, and had had no previous hospital admissions. She was on no regular medication, including oral contraceptives.

Regarding her family history, the patient’s mother was diagnosed with AHT at the age of 38 years and chronic kidney disease. No familial hereditary diseases were known.

Medical examination showed BMI of 17.5 kg/m² and no skin lesions. BP was 187/139 mm Hg—overlapping values in all four limbs with no asymmetric pulse. Heart rate was 130 bpm—rhythmic and without heart murmurs, abdomen without murmurs or palpable masses and without oedema. Funduscopy with grade II retinopathy, was without papillary oedema. The remaining neurological examination was normal.

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Table 1 Laboratory tests

		Ref.
Fasting glucose (mg/dL)	97	74–106
PTHi (pg/mL)	111.5	7.8–53.8
Renin (pg/dL)	16.7	1.1–16.5
Aldosterone (ng/dL)	11.8	5–14.5
Cortisol (µg/dL)	11.8	8.7–25
ACTH (pg/mL)	22.8	<46
Calcitonin (pg/mL)	<2	<5
Phosphorus (mg/dL)	5.5	2.8–4.8
Calcium corrig (mg/dL)	9.8	8.4–10.3
Chromogranin A (nmol/L)	47.7	<6
Serum catecholamines (ng/L)		
Total	22 326	<598
Norepinephrine	20 591	<420
Epinephrine	1318	<84
Urinary metanephrines (µg/24 h)		
Metanephrines	2570	<90
Normetanephrines	>4800	<180

Values in bold - values that differ from reference.

ACTH, adrenocorticotrophic hormone; PTHi, intraoperative intact parathyroid hormone.

Blood work with complete blood count, renal function and hepatic enzymes, was normal. Urine was without proteinuria. ECG showed sinus tachycardia, HR of 126 bpm and signs of left ventricular hypertrophy. Chest radiograph and cerebral CT were normal.

The patient was admitted with the diagnosis of severe AHT and retinopathy. She began perfusion of labetalol until BP control was achieved, with progressive clinical improvement, and regression of headaches and visual symptoms.

The clinical picture of recurrent AHT in a young patient made us suspect underlying secondary hypertension.

The recurrent episodes of severe AHT with end-organ damage, tachycardia and sweating, prioritised the possibility of pheochromocytoma. Medical examination without any anomaly of arterial pulses and normal renal function relegated to the background the possibility of aortic coarctation and renal artery disease.

INVESTIGATIONS

To prove our diagnostic hypothesis of secondary hypertension in a young non-obese patient, without previous cardiac disease, hormonal assays were ordered, which revealed elevated serum,

urinary catecholamines and metanephrines, chromogranin A and parathyroid hormone (PTHi; [table 1](#)).

To exclude other less probable diagnoses, a transthoracic echocardiogram was carried out, which revealed normal cardiac chambers and normal ejection fraction (70%).

Renal Doppler ultrasound revealed a solid nodule in left adrenal gland and normal permeability of the renal arteries.

Abdominal CT scan confirmed the presence of a heterogeneous nodular 6.5×5.3×6.0 cm mass in the left adrenal gland, compatible with a pheochromocytoma ([figure 1](#)).

Metaiodobenzylguanidine (MIBG) scintigraphy only identified hyperfixation in the left adrenal gland ([figure 2](#)).

Thyroid and parathyroid ultrasound revealed a small nodular 6×9×4 mm formation posteroinferior to the left lobe, suggestive of a probable parathyroid.

With the diagnoses of pheochromocytoma and associated hyperparathyroidism in a young patient, although no lesions suggestive of thyroid carcinoma existed, possible MEN was admitted, so genetic testing was performed, which revealed a negative RET gene.

TREATMENT

Therapy with α and posteriorly β -adrenergic blockers was started (intradermal phenoxybenzamine 10 mg and propranolol 20 mg) with adequate BP control.

The patient was submitted to laparoscopic left adrenalectomy from a retroperitoneal approach on 28 March 2012.

A 6 cm tumour was removed and the pathological examination confirmed the diagnosis of pheochromocytoma ([figure 3](#)).

After surgery, there was normalisation of the BP profile and catecholamine, metanephrine and chromogranin A assays, without need for maintenance of antihypertensive medication. PTHi remained increased.

Because of the presence of hyperparathyroidism, vitamin D assay was requested: 54 nmol/L (normal value 75–250 nmol/L), and parathyroid scintigraphy was normal. A probable hyperparathyroidism secondary to vitamin D deficit, frequent in this population, was admitted, and vitamin D deficiency correction was started.

OUTCOME AND FOLLOW-UP

At the first year follow-up, the patient remained asymptomatic and without headaches or visual problems; she was normotensive, with normal serum metanephrine assays. Funduscopy revealed no alterations.

Figure 1 Abdominal tomography with a left adrenal gland nodule over 6 cm.

Figure 2 Focal hyperfixation in the left adrenal gland (compatible with pheochromocytoma), without other abnormal images.

DISCUSSION

The described clinical case presents a 15-year-old girl with AHT, secondary to a pheochromocytoma, with severe hypertensive retinopathy. The young age, the severity of the clinical picture and the associations of disease required a complex differential diagnosis.

Although essential AHT in the child/adolescent is the most frequent, in this case, the presence of severe AHT with end-organ damage (retinopathy) without obesity in a young age required investigation of a secondary cause.

Because of the age group, the most probable aetiologies would be renal/renovascular, endocrine diseases or aortic coarctation.

Renal/renovascular aetiologies are the most frequent in infancy.⁵ However, the absence of abdominal murmurs, normal renal function and Doppler ultrasound of the renal arteries without areas of stenosis excluded this diagnosis.

Recurrent episodes of AHT, headaches and palpitations led to the suspicion of pheochromocytoma, although rare in this age group.

AHT, intermittent or sustained, is the main manifestation of the disease and may be accompanied by a great variety of clinical signs and symptoms.^{2 6 7}

Increased levels of serum catecholamines (especially norepinephrine), urinary metanephrines, chromogranin A and an adrenal gland mass confirmed the diagnosis. Urinary and serum

Figure 3 Left laparoscopic adrenalectomy (A), macroscopic examination, 6 cm tumour (B). Microscopic examination: neoplasm of the adrenal medulla with eosinophilic cytoplasm of large cells with positive fine granular chromogranin A (C), round and oval nucleus and sustentacular cells S100+ (D)—pheochromocytoma.

assays of metanephrines are the most sensitive and reliable tests for the diagnosis.^{7 8}

After clinical and laboratorial suspicion of a pheochromocytoma, tumour localisation is essential with imaging tests such as abdominal CT or MRI and I123-MIBG or I131-MIBG scintigraphy.

In the present case, the abdominal CT and scintigraphy confirmed the diagnosis of pheochromocytoma with a single lesion of the right adrenal gland, even though in this age group there is usually extra-adrenal or multifocal origin in association with genetic syndromes (10–20%) such as VHL, type 1 neurofibromatosis syndrome (NF1) and MEN 2. It could be the first sign of potentially fatal tumours such as medullary thyroid carcinoma (MTC) in MEN 2 syndrome, cerebral tumours and renal tumours in the VHL syndrome.⁹

Because of concomitant hyperparathyroidism in this patient, although in the absence of findings suggestive of MTC, genetic testing was performed. The absence of the RET gene mutation ruled out an underlying MEN 2. The MEN 2 (MTC, pheochromocytoma and primary hyperparathyroidism) associated with the RET gene mutation can be associated with pheochromocytoma in 10–30% of cases, complicating the patient's prognosis.⁹

Pheochromocytoma normally appears after the diagnosis of MTC or simultaneously, but in 13–27% of cases, it is reported as a first manifestation.¹⁰

With the diagnosis of pheochromocytoma, the treatment of our patient was surgical (laparoscopic via retroperitoneal access) after BP control with α and β adrenergics, as stipulated in the literature.^{11 12}

Laparoscopic surgery is the preferred surgical approach, with low mortality and morbidity, after which 75% of patients become normotensive. Abdominal and retroperitoneal laparoscopic approaches have both successfully been used, although evidence exists that the retroperitoneal approach is preferred, especially when it comes to surgical time, blood loss, hospital stay duration and complication rates.¹³

Learning points

- Five to 10% of patient had a secondary cause for hypertension. This possibility should be excluded in cases of hypertension presenting before the age of 20 years and after the age of 50 years, in refractory hypertension with serious end-organ damage.
- Pheochromocytomas are rare tumours originating in chromaffin cells and representing 0.1–1.0% of all secondary hypertension cases.
- They present varied symptoms, but in presence of hypertension with a triad of headaches, tachycardia and sweating, we have to suspect pheochromocytoma.
- It is rare in young age and in this case it is important to exclude genetic syndrome.
- After confirmation of diagnosis, the treatment is surgical after blood pressure control with α and β adrenergics.
- The possibility of relapses of the tumour makes lifelong follow-up obligatory.

After surgery, the patient evolved with controlled BP without need for antihypertensive medication, with posterior normalisation of serum metanephrines. At 1-year follow-up, she remained asymptomatic and with normal serum metanephrine values.

This situation is usually associated with a good prognosis (except in patients with metastases) and low recurrence rate (<10%), although recurrence is greater in children, namely in familial syndromes.¹⁴

All patients should undergo catecholamine measurements approximately 1 week post-operation to confirm a cure. Long-term follow-up is required for all patients because of the possibility of recurrence. Levels of catecholamines should be measured yearly until the likelihood of recurrence is very low (>5 years). Patients with germ line mutation and no evidence of active illness should undergo continued follow-up for pheochromocytoma.¹⁵

The present case has apparently had a favourable prognosis, however, the possibility of tumour relapse requires long-term patient follow-up.

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