

## Case Report

# Multiple aetiologies of secondary hypertension in one patient

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### Abstract

Apart from seeking target organ damage, the investigation of hypertension is primarily aimed at finding a treatable cause of the hypertension. The finding of one such cause is usually construed as being the sole culprit responsible for the patient's elevated blood pressure. The existence of multiple aetiologies of secondary hypertension in one patient is infrequent. In this report, we describe such a patient in whom secondary hypertension due to Cushing's disease, renovascular and finally baroreflex failure was successively documented.

**Keywords:** baroreflex failure; Cushing's disease; renovascular hypertension; secondary hypertension

### Introduction

Secondary hypertension accounts for ~5–10% of all cases of hypertension. Although this reported prevalence is true in referral centres, it is probably much lower in the primary care outpatient setting. The importance of secondary hypertension lies in the fact that the hypertension may be remediable on treatment of the underlying cause. There are many conditions that can result in an elevation of blood pressure commonest among them being renal parenchymal disease, renovascular disease, primary hyperaldosteronism, endocrine hypertension, obstructive sleep apnea, pheochromocytoma and various drugs, notably NSAID and cocaine. Investigation for secondary hypertension follows an algorithm ultimately aimed at defining one specific cause of the hypertension. It is unusual to find three different successive causes of secondary hypertension in the same patient.

We hereby present a woman who was initially diagnosed as secondary hypertension due to Cushing's disease.

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After undergoing a trans-sphenoidal resection of an ACTH secreting pituitary adenoma, she was then found to have a right renal artery stenosis for which successful percutaneous angioplasty (PTRA) was performed. Her blood pressure, however, remained extremely labile, and she was finally diagnosed with baroreflex failure.

### Case report

A 56-year-old Caucasian woman, a past heavy smoker (40 pack years), was first evaluated in 2001 for resistant hypertension of 5-year duration. A year before, duplex sonography of the carotid arteries, performed because of visual disturbances, had demonstrated critical stenosis of the left internal carotid artery and she successfully underwent endarterectomy. During the previous years, the patient had gained 10 kg weight and had noticed the appearance of facial hirsutism and wide purple striae on her lower abdomen. Her blood pressure was 180/100 mmHg, and she was moonfaced with a buffalo hump, abdominal obesity and relative wasting of limb musculature. Fundoscopy showed grade II hypertensive retinopathy, and echocardiography revealed mild left ventricular hypertrophy. Relevant laboratory data are shown in Table 1. The patient's clinical picture and biochemical profile were consistent with a diagnosis of Cushing's syndrome either of pituitary origin or an ectopic, indolent source. On magnetic resonance imaging (MRI) of the sella turcica, the existence of a 6–7 mm pituitary microadenoma was suspected. Inferior petrosal sinus sampling clearly showed excessive pituitary ACTH excretion. In October 2002, a 1 cm ACTH staining adenoma adherent to the cavernous sinus was surgically removed. A day following the surgery, serum cortisol was undetectable necessitating maintenance prednisone treatment. Over the next 2 years, there was a gradual but complete regression of the patient's cushingoid habitus. However, her blood pressure remained elevated and fluctuated between extremes of high to low (Table 2).

Twenty-four-hour urinary excretion of catecholamines as well as plasma metanephrines was all within normal

**Table 1.** Endocrinological workup for suspected Cushing's disease

Test	Cortisol (mcg/dl)	ACTH (pg/ml)	Interpretation
Basal serum	54.5 <sup>a</sup>	35 <sup>b</sup>	Serum cortisol markedly increased Serum ACTH—usually normal in pituitary Cushing
1 mg ODST	22.7		Expected (<5 mcg/dl)
8 mg ODST	3.3		Absence of suppression Expected (<5 mcg/dl)
24-h UFC	350.2 mcg <sup>c</sup>		Normal suppression Markedly increased (×4 normal)

ODST = oral dexamethasone suppression test; UFC = urinary free cortisol.

<sup>a</sup>Normal, 7–25 mcg/dl; <sup>b</sup>normal, 9–52 pg/ml; <sup>c</sup>normal, 20–90 mg.

**Table 2.** Blood pressure values during the patient's course

	At presentation	After resection of Pituitary microadenoma	After PTR A	After the diagnosis of baroreflex failure
SBP	210–160	240–76	210–120	168–96
DBP	110–90	130–40	114–74	100–48

PTRA = percutaneous angioplasty.

limits. An MIBG scan showed no abnormal findings. In January 2003, renal ultrasound revealed the left kidney to be 11.2 cm in length (longitudinal axis) versus 9.5 cm of the right kidney. Duplex sonography of the renal arteries demonstrated a systolic peak (500 cm/s) at the origin of the right renal artery with a parvus tardus pattern over the right intrarenal arteries. Magnetic resonance angiography confirmed the presence of a significant 7 mm stenosis of the right main renal artery beginning 0.5 cm from its origin. In February 2003, PTR A with stent insertion was successfully performed.

Despite the success of the PTR A, the patient's blood pressure continued to fluctuate widely while being treated with maximal doses of five anti-hypertensive drugs and a pharmacological replacement dose of prednisone (15 mg/day) (Table 2). In view of her carotid surgery and the nature of her blood pressure profile, baroreflex failure was suspected. Noninvasive measurements of beat-to-beat blood pressure and heart rate were done by using a finger pulse photoplethysmographic device (Portapres, TNO Institute of Applied Physics Biomedical Instrumentation). The patient performed a Valsalva manoeuvre, maintaining an airway pressure of 30 mmHg for 12 s. During the manoeuvre, blood pressure decreased during phase 2 with an overshoot during phase 4. Baroreflex-cardiovagal gain was estimated from the relationship between interbeat interval and systolic blood pressure during phase 2 of the Valsalva manoeuvre, beginning with the peak pressure and ending with the nadir blood pressure. A scatterplot was constructed relating the interbeat intervals to the systolic pressures with a 1-beat delay from the previous heartbeat. The baroreflex-cardiovagal gain (as defined by the slope of the regression line of best fit) was 0.07 ms/mmHg. Supine and upright blood pressure and heart rate were 145/78 mmHg; 71 bpm and 142/77 mmHg; 79 bpm, respectively. Norepinephrine levels were high normal at baseline, 487 pg/ml,

and markedly increased to 927 pg/ml after 5 min of standing up. These results are indeed compatible with the diagnosis of baroreflex failure.

## Discussion

The coexistence of three different causes of secondary hypertension in one patient is unusual. It is noteworthy that even though our patient presented with 'textbook' features of Cushing's syndrome, she was treated for resistant hypertension for 5 years before the diagnosis was established. Trans-sphenoidal resection of an ACTH secreting pituitary adenoma was successful in achieving complete regression of the patient's cushingoid state. Suppression of the hypothalamic-pituitary-adrenal axis, as evidenced in our patient, is an expected sequela of the operation. Blood pressure, however, remained refractory to treatment. Whereas previously it was persistently elevated, it was now characterized by being extremely labile swinging from excessive highs to symptomatic episodes of hypotension. This rightly prompted continued search for an additional cause of secondary hypertension. As the clinical picture was highly compatible with pheochromocytoma, investigation was focused towards this end. It proved to be negative but significant right renal artery stenosis was found. Although renovascular hypertension is usually typified as being persistently elevated, the patient underwent PTR A with stent insertion. Duplex sonography a month after the procedure and computerized angiography 4 years later on showed the stent to be patent with good blood flow through the previously stenosed artery. There was, however, no demonstrable effect on blood pressure.

At this stage due to the variability of the patient's blood pressure, baroreflex failure was suspected. The baroreflex-cardiovagal gain during phase 2 of the Valsalva manoeuvre was virtually zero, consistent with an inability of the heart rate to respond to a reduction in blood pressure. This constitutes a major feature of baroreflex failure confirming the diagnosis in our patient [1]. The blood pressure pattern during Valsalva and the high plasma norepinephrine and marked increase with orthostasis rule out autonomic failure.

The baroreflex mechanism is a central part of the regulation of the cardiovascular system. It serves to buffer abrupt transients of blood pressure and prevents pressure from rising or falling excessively. Baroreflex failure is a rare, quite possibly underdiagnosed cause of secondary hypertension [2]. As exemplified in our case, it is characterized by drastic changes in blood pressure due to denervation of the baroreflex. It may occur idiopathically but has mostly been reported following carotid artery endarterectomy [3], carotid body tumour resection [4] and postirradiation for cervical cancer [5]. As nearly complete loss of afferent baroreflex function is needed for baroreflex failure, it is puzzling why the condition develops following unilateral carotid endarterectomy [3] or the unilateral resection of a chemodectoma [6]. A plausible explanation is the existence of undetected baroreflex impairment on the contralateral side. Such pre-existing damage could be due to various causes, for example, trauma or atherosclerosis. Our patient certainly had evidence of diffuse atheroma. Thus, although she underwent unilateral carotid surgery, it is highly likely

that the procedure contributed to her baroreflex failure. Treatment of this condition is difficult. Although clonidine was added to our patient's anti-hypertensive medications, the response has been far from optimal.

In summary, we have presented the unique circumstance in which three different causes of secondary hypertension were found in one patient. Evolving from this is the understanding that the presence of one cause of secondary hypertension does not necessarily rule out the existence of other causes. Additionally, it should be borne in mind that apart from the usually considered pheochromocytoma, the extreme variability of blood pressure should raise suspicion of baroreflex failure. This latter condition is often both a diagnostic challenge and a therapeutic nightmare.

*Conflict of interest statement.* None declared.

## References

1. Robertson D, Hollister AS, Biaggioni I *et al.* The diagnosis and treatment of baroreflex failure. *N Engl J Med* 1993; 329: 1449–1455
2. Timmers HJ, Wieling W, Karemaker JM *et al.* Baroreflex failure: a neglected type of secondary hypertension. *Neth J Med* 2004; 62: 151–155
3. Timmers HJ, Buskens FG, Wieling W *et al.* Long term effects of unilateral carotid endarterectomy on arterial baroreflex function. *Clin Auton Res* 2004; 14: 72–79
4. Timmers HJ, Karemaker JM, Wieling W *et al.* Baroreflex control of muscle sympathetic nerve activity after carotid body tumor resection. *Hypertension* 2003; 42: 143–149
5. Sharabi Y, Dendi R, Holmes C *et al.* Baroreflex failure as a late sequela of neck irradiation. *Hypertension* 2003; 42: 110–116
6. Gomez Esteban JC, Boyero S, Fernandez C *et al.* Baroreflex failure after chemodectoma resection. *Neurologia* 2004; 19: 452–455

*Received for publication:* 20.2.08

*Accepted in revised form:* 3.11.08