Pheochromocytoma
and Secondary Hypertension

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Pheochromocytoma, a rare cause of secondary hypertension, is often considered when hypertensive patients present with symptoms, paroxysmal hypertension or resistant hypertension. We present a case in which none of these were present, yet pheochromocytoma was a consideration.

A pheochromocytoma is a catecholamine-secreting tumour of neural crest cell origin. Traditionally taught as the "10% disease," we know that 90% originate in the adrenal medulla; 10% are bilateral and 10% are malignant.[1] Another traditional adage was that 10% of pheochromocytomas were inherited and 90% sporadic. Recently however, almost one quarter of patients with pheochromocytoma have been found to carry one of a handful of germline mutations.[2] One such mutation is von Hippel-Lindau disease (VHL).

VHL is an autosomal dominant inherited disorder characterized by benign or malignant tumours, typically: renal cell carcinoma, cerebellar and spinal hemangioblastomas, retinoblastomas and pheochromocytomas.[3] Most patients are diagnosed in their third or fourth decade. The estimated worldwide prevalence is two to three per 100,000 persons. The VHL gene, located on chromosome 3p26-25, functions as a tumour suppressor so that mutations in VHL gene lead to a variety of tumours.

Meet Sandra

Sandra, 31, was referred with a request to "please rule out pheochromocytoma." She had been diagnosed with von Hippel-Lindau type 2 disease at age 15, and had had multiple surgeries for cerebellar, cerebral and renal tumours. Recently, a 24 hour urine total metanephrines was reported as 7.62 mol (reference range 0.64-4.90).

She denied episodic symptoms or history of high blood pressure readings. Her medications included amitriptyline 100 mg h.s., a multiple vitamin tablet, and naproxen 250 mg *ad lib*.

On examination, she looked well. Her supine heart rate was 80, the blood pressure 114/72. With standing, her heart rate was 84 and the blood pressure 110/68 at 1 minute and 110/70 at 3 minutes. The remainder of the physical examination, including a neurologic exam, was normal.

A common abnormal genotype is 505 T C and 686 T C, so-called type 2 VHL disease, which has been linked to pheochromocytoma. Indeed, 10 to 20% of patients with VHL type 2 harbour a pheochromocytoma. Interestingly, pheochromocytomas in VHL differ from sporadic tumours in that they tend to occur at an earlier age, are more often bilateral and are less likely to be malignant, or extra-adrenal. They almost always exclusively excrete norepinephrine.

More on Sandra's case

We asked Sandra to stop amitriptyline and repeat the 24 hour urine collection three weeks later. The results:

Volume:	3200 ml
Creatinine:	11.5 mmol/day (0.15 mmol/Kg)
Total metanephrines:	3.92 mmol/day

We assured her that she did not have a pheochromocytoma at present, but, because of her genetic abnormality, she should have blood pressure checks at least yearly. Should she develop hypertension or symptoms compatible with pheochromocytoma, the 24 hour urine collection should be repeated.

Table 1
Falsely elevated 24 hour metanephrines

Drugs	Foods
tricyclic antidepressants	pineapple
levodopa	bananas
pseudephedrine	walnuts
buspirone	tomatoes
monoamine oxidase inhibitors	fava beans
beta-adrenergic antagonists	cheese
reserpine	fermented (pickled) food
ethanol	
acetaminophen	

In diagnosing pheochromocytoma, we rely on history, physical examination and the laboratory. About 90% of patients with pheochromocytoma have episodic symptoms: classically the triad of headache, sweating and palpitations occurring during, or after exercise in about 50% of patients. Other fairly common symptoms include orthostatic lightheadedness, tremor, weight loss and anxiety. Therefore, in sporadic cases, in which the prevalence of pheochromocytoma is less than 1%, the absence of symptoms rules it out beyond a reasonable doubt. Physical signs, other than hypertension in most, include pallor and orthostatic hypotension.

In patients diagnosed with VHL, the prevalence of pheochromocytoma is much greater. To "rule out" the disease with some confidence, we need to use the laboratory. By far the most common laboratory procedure is 24 hour total metanephrines. Done properly, this test provides 97% sensitivity and 82% specificity.[1] Common errors include an under, or overcomplete collection and interference by drugs or other substances. Some culprits include tricyclic antidepressants and serotonin/norepinephrine uptake inhibitors ("SNRIs").[4] Interestingly certain foods can contain catecholamines and produce falsely elevated metanephrines (see Table 1).[5] To our knowledge, no drugs or foods have been reported to cause falsely low total metanephrines, but catechol-o-methyl transferase inhibitors (etacapone, tolcapone) are theoretical possibilities.

To assess the completeness of collection, we measure the 24 hour creatinine excretion: it should be between 0.1 and 0.2 mmol per kilogram of body weight. If the 24 hour urine total metanephrines are "positive," repeat the collection adding catecholamines, and vanillylmandelic acid. While these are less sensitive, they do add specificity. When the diagnosis is established, the tumour, or tumours can be localized. Many experts order a metaiodobenzylguanidine (MIBG) scan first, especially when extradrenal tumours are suspected. This radioactive iodinated compound is taken up by sympathetic nervous system tissue, including pheochromocytoma. In large tumours outside the bladder wall, the test is about 80% sensitive, but almost 100% specific.[6] Labetolol a beta blocker with alpha receptor antagonism, prevents the uptake of

MIBG by the tumour, so this drug should be stopped prior to the scan.[7] If the scan is "positive," computed tomography can then be planned to delineate the anatomy.

Individuals with previously identified genetic syndromes (VHLD) which predispose them to pheochromocytomas, require adequate monitoring of blood pressure, adequate utilization of laboratory testing, and properly recording the patient's history to assess common and classic associated signs and symptoms.

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