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A Case of Paediatric Hypertension

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The Patient

Presenting History

A 13 year old girl presented with an 18 month history of episodes of excessive sweating, facial flushing, occasional fainting attacks and episodes of frontal headache relieved by paracetamol. She had nine months previously presented to a GP with similar symptoms and at that time investigations were normal and reassurance was given. She had started menstruating at around the same time as these symptoms started. Periods were regular with some dysmenorrhoea. Just prior to most recent presentation she had had one episode of palpitation associated with sweating lasting for a few minutes.

Examination

On examination there were no unremarkable signs apart from a raised blood pressure of 142/92 initially and 145/84 after a five minute interval. Retinal examination, chest and abdominal examination in particular were normal.

Differential diagnosis

- Hypertension ?cause
- Anxiety
- Menstrual disorder
- Hyperthyroidism
- Pheochromocytoma
- Carcinoid syndrome

Investigations

- Urea, creatinine and electrolytes
- Liver and thyroid function tests
- Full blood count
- Bone profile
- Urinalysis
- Electrocardiogram
- 24 hour urinary collection for noradrenaline, normetadrenaline, adrenaline, dopamine and 5 hydroxyindole acetic acid (5HIAA)

Results

All blood tests and electrocardiogram were normal. Urinary 5HIAA was in normal range.

24 hour urinalysis showed high noradrenaline at 14596 nmol/24 hour (normal range 90–600), dopamine 6163 nmol/24 hour (range 480–3100), normetadrenaline 28.0 umol/24 hour (range 0.2–2.8) and normal adrenaline level at 71 nmol/24 hour (range 0–190).

Management plan

These results were phoned to the GP and an urgent paediatric review was arranged the next day. She was admitted from the clinic monitored as BP was found to be high at 170/100. Blood pressure rose as high as 180/105, at which stage pharmacological treatment was commenced. A diagnosis of presumed pheochromocytoma was made and CT scan showed a 5.5 x 3.8 cm tumour in the vicinity of the right renal artery.

Phenoxybenzamine 5mg three times a day was started and she was referred to a tertiary endocrine centre where she was seen by a paediatrician, endocrinologist, surgeon and anaesthetist.

The MIBG (^{131}I-metaiodobenzylguanidine) scan confirmed a unilateral right extra adrenal pheochromocytoma with no further lesions identified. Surgery was arranged once blood pressure was controlled with phenoxybenzamine 10mgs twice daily plus atenolol 25mgs and excision of an extra adrenal pheochromocytoma was carried out and confirmed histologically as benign.

Blood pressure returned to normal at 110/70 with the patient off all treatment and follow up was arranged in a year with 24 hour urinary collection screening then.

Epidemiology and Pathophysiology

The first case of an adrenal medullary tumour was described by Dr Felix Frankel in 1986 but it was not until 1912 that a pathologist, Dr Ludwig Pick coined the term 'phaechromocytoma'. Pheochromocytoma is a catecholamine-secreting tumour of chromaffin cells of which 90% are found in the adrenal medulla[1]. Extra adrenal sites include the sympathetic trunk (in which case the cervical site has the highest preponderance), paragangliomas within the abdomen and tumours in the bladder. Most tumours are benign, 10% are within a familial context, 10% are malignant and 10% are bilateral. The incidence of pheochromocytoma among patients with hypertension is 0.2%. Most cases are sporadic, but about 24-27% of apparently sporadic phaechromocytoma are associated with germ line mutations and these inherited forms often form part of a syndrome, such as multiple endocrine neoplasia (MEN), Von Hippel-Lindau syndrome, succinate dehydrogenase type B complex or neurofibromatosis[1].

Presentation

The diagnosis of pheochromocytoma should be suspected when the constellation of clinical symptoms is present to support the diagnosis[1,2]. It is a tumour that is frequently sought but rarely found. A family history of pheochromocytoma should also be ascertained as it is occasionally inherited as an autosomal dominant trait and may be part of a pluriglandular neoplastic syndrome. The most common symptoms are headache, sweating and palpitations but can include anxiety attacks, tremor, cold extremities with pallor, cardiac arrhythmias including atrial and ventricular fibrillation and rarely unexplained lactic acidosis.

Hypertension can be mild to severe, sustained or uncontrolled paroxysmal hypertensive episodes can develop. Hypertension is usually sustained and postural hypertension occurs in 70% of cases. Hypertensive crisis may be precipitated by beta-blockers, tricyclic antidepressants, metoclopramide and naloxone.

Investigation

The diagnosis requires both biochemical demonstration of inappropriately increased catecholamine production as well as anatomical localization of the tumour[3]. Investigation of a patient who might have pheochromocytoma includes measurement of urinary catecholamine metabolites including vanillyl mandelic acid (VMA), metanephrines and plasma catecholamines[4]. Multiple collections may be necessary to confirm the diagnosis. VMA levels (a catecholamine metabolite) are not specific since several dietary substances including vanilla essence can give a false positive test. 15% of patients with essential hypertension have a false positive VMA. Urinary catecholamines such as noradrenaline, dopamine and adrenaline are more specific. Urine collections must be completed before pentolinium or clonidine tests since withdrawal of these compounds can give a false positive result[4].

It is important to ensure that the patient is not on any medications that may interfere with biochemical testing as a number of drugs

can give a false positive result as can various physical stresses (see Table 1)[3].

Table 1. *Causes of false positive biochemical tests (adapted from Goh and Subramaniam[3])*

Drugs	Stresses
Nicotine replacement therapy	Acute withdrawal of illicit drugs/ethanol
Tricyclic anti-depressants	Heart Failure (NYHA 3 or 4)
Benzodiazepines	Obstructive sleep apnoea
Buspirone	Advanced renal failure
Haloperidol	Surgery
Levodopa	Acute hypoglycaemia
Bromocriptine	
Acetaminophen	
Phentolamine	

Hypertensive patients with raised serum glucose and reduced potassium may have a pheochromocytoma but these are both common features for treated hypertension (e.g. thiazide diuretics), or may indicate other endocrinopathies (e.g. Cushing's syndrome, Conn's syndrome, secretory adrenal carcinoma)[5].

Pentolinium suppression test needs two baseline samples before intravenous pentolinium 2.5mgs, and then blood is taken again at 10 and 30 minute intervals. Plasma catecholamines decrease in normal subjects following ganglion blockage with pentolinium. If the response is borderline and no hypotension occurs, then repeat with 5mg pentolinium[5].

An alternative to the pentolinium suppression test employs clonidine. Following two baseline samples, 0.3mg of clonidine is given orally and blood taken hourly for three hours. Again if raised catecholamines are due to anxiety they will suppress into the normal range with clonidine. Raised catecholamines fro pheochromocytoma will not be affected by clonidine[5].

Provocative tests like glucagons stimulation test and clonidine suppression tests are seldom used nowadays as they run the risk of severe hypertension and hypotension respectively[3].

More recently plasma free metanephrine has been suggested to be a good tool because of its excellent sensitivity of 99%. Serum chromogranin A levels correlate with tumour size and is increased in 80% of patients. It has a sensitivity and specificity of 98% and 97% respectively when combined with an increased plasma metanephrine, but by itself it has a poor specificity of 50%[6]

CT and MRI scans are the most valuable image techniques for anatomical localization of the tumour and sometimes a MIBG scan (^{131}or^{123} I-metaiodobenzylguanidine) is useful for localization of sites of active sympathetic tissue1[3,4,5]. Regional venous sampling may also be needed for localization of small tumours outside the usual adrenal sites (paragangliomas).

Left ventricular hypertrophy may develop. Left ventricular hypertrophy on electrocardiography is diagnosed when the sum of the R wave in V5 or V6 and the S wave in V1 exceeds 35mm (Sokolow criteria)[7]. ST segment depression and T wave inversion in the leads facing the left ventricle are occasionally present[5]. Echocardiography is superior to electrocardiography in the diagnosis of left ventricular hypertrophy[7]. This girl had a normal ECG even though she probably had hypertensive episodes for around 18months.

Treatment

Patients are sometimes volume depleted at presentation and should be rehydrated prior to initiation of alpha blockade otherwise severe hypertension may occur. Beta-blockade alone may precipitate a hypertensive crisis and must never be given prior to adequate alpha blockade. Labetalol is predominantly

a beta-blocker and should not be used alone[8]. Long acting alpha blockers prevent escape episodes. Initial alpha blockade is usually with phenoxybenzamine 10mg daily increasing gradually up to 40mg three times a day with close BP monitoring. When the blood pressure is controlled with phenoxybenzamine add a beta blocker (propranolol, labetalol, or in this case atenolol)

Surgical excision is the treatment of choice and is usually curative[1]. The patient undergoing operative excision of a pheochromocytoma must be well prepared pre-operatively with separate alpha- (phenoxybenzamine or phentolamine) followed by beta-blocking agents (propranolol, atenolol or labetalol). During surgery, intra-arterial pressure monitoring is mandatory, to register rapidly the wide swings of blood pressure which can occur. The anaesthetic trolley should include intravenous labetalol, phentolamine, or nitroprusside (in case of marked hypertension), as well as fluids and noradrenaline in case of severe falls in blood pressure.

Prognosis

In non-malignant pheochromocytoma, as in this case, the 5 year survival is higher than 95% (less than 50% in malignant pheochromocytoma), and the recurrence rate after surgery is less than 10%[1] In experienced hands surgical mortality is usually less than 2-3%[1] This girl was operated on in a tertiary unit by experienced surgeons and anaesthetists. Complete resection cures the hypertension in approximately 75% of patients with pheochromocytoma: in the remaining 25%, hypertension recurs but is usually well controlled with a standard antihypertensive regimen[1].

Reflection

It is important always to take seriously symptoms that are out of the ordinary in children, teenagers or young adults and examine and investigate appropriately. It is also important to remember that secondary causes of hypertension are more common in younger people presenting with hypertension, and all clinicians should remain vigilant to the various causes. These include pheochromocytoma, coarctation of the aorta and Conn's syndrome. For that reason recent British Hypertension Society guidelines suggest all patients under 20 years of age and those needing treatment under 30 years of age be referred for specialist opinion[9].

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