UNIVERSITI TEKNOLOGI MARA

FAMILIAL PHEOCHROMOCYTOMA

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Introduction:

Here we presented a case of a young boy who presented with familial pheochromocytoma. Pheochromocytoma is a catecholamine-secreting tumor and is very rare. It is critical not to miss or delay the diagnosis as it is potentially life threatening from the complications of malignant hypertension and if treated is curable. A missed diagnosis as in this case had landed him with a hypertensive crisis which could have been avoided if it was diagnosed and investigated earlier. This could lead to fatal outcomes such as myocardial infarction, stroke, cardiac arrhythmia, renal failure and dissecting aneurysm.

Case presentation:

We report a case of a 17 years old gentleman who presented with episodic symptoms of palpitations, headache and sweating for a year since May 2016. He had multiple visits to his general practitioner but was treated symptomatically. He then developed severe headaches and presented to a private hospital with hypertensive crisis with a blood pressure of 205/139 mmHg and was subsequently investigated for secondary cause of hypertension. Apart from the severe headaches he had no blurring of vision, chest pains, nausea and vomiting, dyspnea nor focal neurological symptoms. There was no history of sudden weight gain, easy bruising or proximal muscle weakness. There is no neck swelling nor symptoms to suggest hypercalcemia. There was no cutaneous swellings or skin changes. He had no hearing loss. He is the youngest of 4 siblings and his eldest brother was diagnosed with pheochromocytoma at 4 years old and underwent right adrenalectomy followed by left adrenalectomy at 8 years old. No other family member has hypertension or any endocrinopathy on both maternal and paternal side.

On physical examination, he had no marfanoid appearance. There were no café au lait spots, freckling or neurofibromas and no goiter. Funduscopic examination did not show any retinal angiomas. His blood pressure was 166/98 mmHg and pulse rate was 80 beats per minute. There were no signs to suggest Cushing's, Cushing's syndrome or acromegaly. Cardiovascular and respiratory examination is unremarkable. There were no masses felt on abdominal examination and there was no focal neurological deficit.

Investigation revealed elevated 24 hours urine noradrenaline (norepinephrine) excretion 8865 nmol/24 hours (40-780), adrenaline (epinephrine) excretion: 55 nmol/ 24 hours (5-80) and dopamine excretion 2165 nmol/24 hour (200-3500) and creatinine excretion 8 mmol/ 24 hour (9.2-23.6). Normal potassium level of 4.3 mmol/L, suppressed overnight dexamethasone test 21nmol/L, normal aldosterone level 83 pmol/L and direct renin level 42 mU/L with low aldosterone to renin ratio 2. Moderate hypercalcemia, calcium level of 2.95 mmol/L, normal albumin 51 g/L, normal intact parathyroid hormone level of 2.3 pmol/L. Repeat calcium level was normal. Thyroid function was normal with free T4 12.6 pmol/L, free T3 5.45 pmol/L and Thyroid stimulating hormone 0.55 mIU/L.

Magnetic resonance imaging of abdomen showed bilateral adrenal masses, on the right side, the mass is at the suprarenal area while on the left side it is generally at the anterior aspect of left kidney (Figure 1 and 2). The mass is generally hypointense on T1WI and hyperintense in T2WI. The mass measures about 5.7 x 5.2 x 7.9 cm on the right and left

side 3.9 x 2.9 x 4.9 cm. There is distortion of the right kidney by the mass. The renal parenchyma shows homogenous signal intensity bilaterally, no associated hydronephrosis. No enlarged para-aortic lymph nodes. No ascites. Other organs are normal. Ultrasound of the neck showed both thyroid lobes were normal with no focal thyroid nodules and no parathyroid lesions.

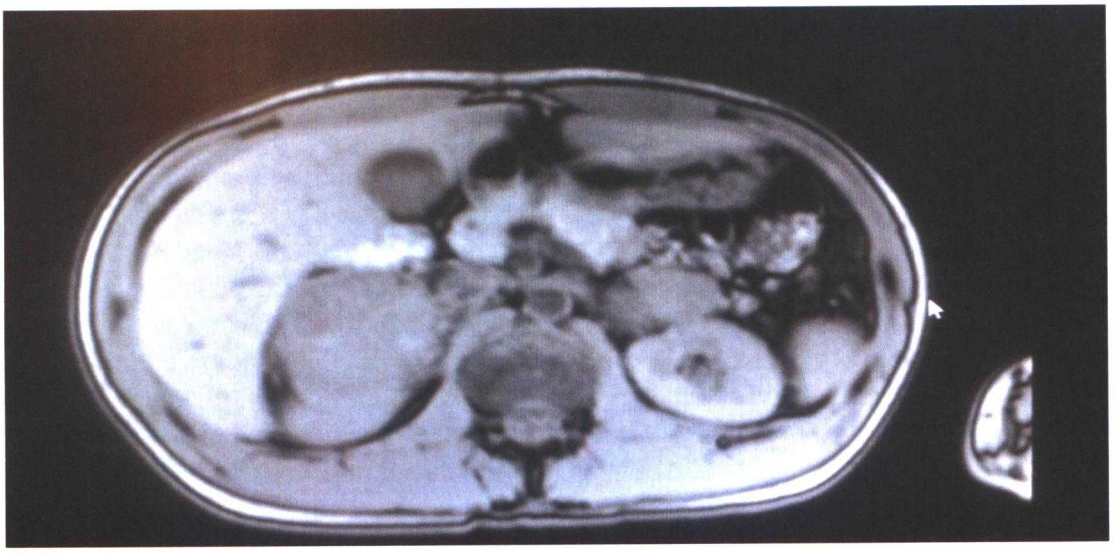

Figure 1

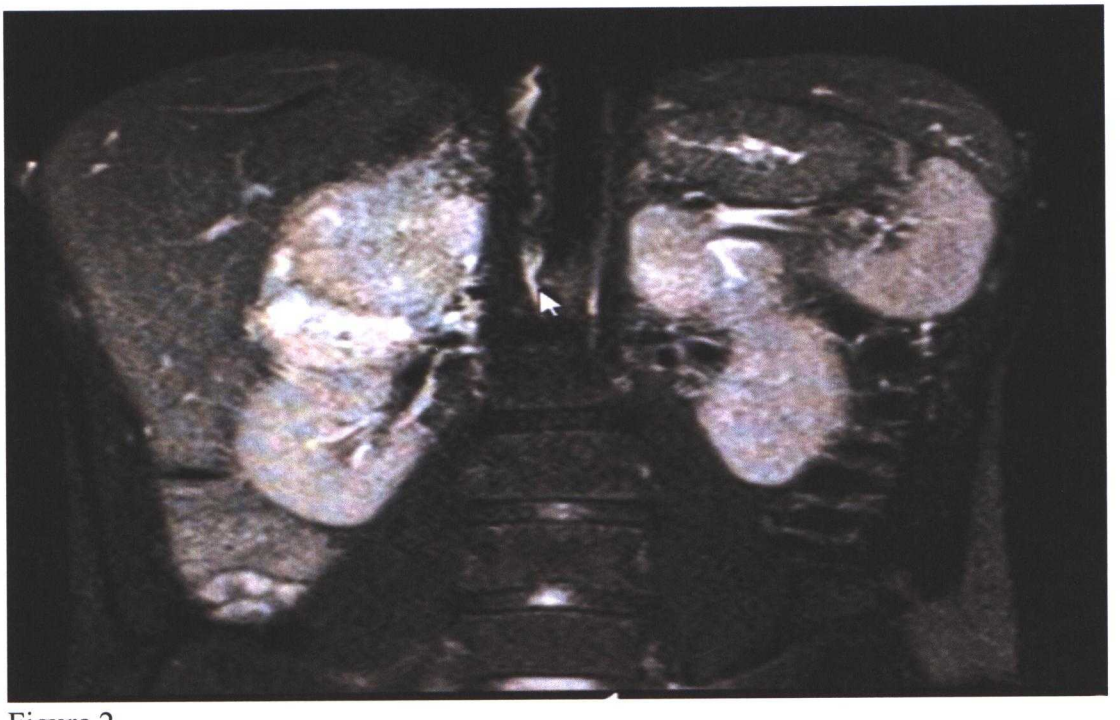

Figure 2

He was diagnosed to have familial bilateral adrenal pheochromocytoma and was commenced on tablet phenoxybenzamine 20mg on morning and 10mg in the evening and tablet propranolol 40mg twice a day along with high sodium and water intake with regular home blood pressure monitoring to target blood pressure less than 130/80 mmHg and heart rate of 60-70 beats per minute. He underwent a bilateral open conventional adrenalectomy with partial adrenalectomy. Intraoperative findings were bilateral adrenal tumor with right adrenal 7 x 5 cm (146g) and left 5 x 5 cm (60g) and

histopathological examination confirms bilateral pheochromocytoma with Ki 67 of 1-3% and clear surgical margin. There were no complications intraoperatively. Post operatively he recovered well and was with tablet hydrocortisone 10mg bd. A post-operative synacthen test 2 months later indicate inadequate response and he was maintained on hydrocortisone replacement. An MIBG scan postoperatively showed no scan evidence of MIBG avid disease. A repeat 24-hour urinary metanephrines postoperatively was normal indicating disease remission.

Discussion:

Pheochromocytoma is found in 0.1 percent of hypertensive patients (1). The annual incidence of pheochromocytoma is approximately 0.8 per 100,000 person years and most of the cases were diagnosed at autopsy (2). It can occur in both pediatric and adult group. In pediatric group the median age is between 12 and 14 years old with average age of 13 years old and in adult the average age is 47 years old (3,4). Sporadic pheochromocytoma typically occurs in older age while patient with genetic predisposition are often younger. Classically, patients with pheochromocytoma will present with triad of episodic headache, sweating and tachycardia due to episodic release of catecholamine into the circulation. Hypertension is due to activation of alpha-adrenergic receptors in the vascular smooth muscle, which lead to vasoconstriction and increase peripheral vascular resistance. It also activates beta-adrenergic receptor in the heart leading to increase in cardiac output and increase in renin secretion in the kidney and worsens systemic hypertension.

Diagnosis of pheochromocytoma is made by measuring 24 hour urine fractionated metanephrines and catecholamines collection according to 2014 Endocrine Society clinical practice guideline (5). Perry et al showed that measurements of urine fractionated metanephrines by mass spectrometry provide excellent sensitivity (97%) and specificity (91%) (6). A positive test includes one or more of the following findings are normetanephrine >900 mcg/24 hours or metanephrine > 400 mcg/ 24 hours, norepinephrine > 170 mcg/ 24 hours (> 29 nmol/24 hours), epinephrine > 35 mcg/ 24 hours (> 5.9 nmol/24 hours) and/ or dopamine > 700 mcg/ 24 hours (>107 nmol/24 hours).

Once confirmed biochemically, radiological evaluation is needed to locate the tumor. More than 90 percent of cases are adrenal in origin and the rest mostly localized in the abdomen (7). Computed tomography (CT) or magnetic resonance imaging (MRI) of abdomen of abdomen and pelvis is often the first test. In our case MRI is chosen in order to reduce radiation exposure. It is often described as a mass with low signal intensity at T1-weighted imaging and with high signal intensity at T2-weighted imaging on MRI. Other common imaging is Metaiodobenzylguanidine (MIBG) scintigraphy. It is useful to exclude metastases, confirm pheochromocytoma in multiple tumors when CT or MRI is positive or in clinically suspected pheochromocytoma that cannot be localized by CT or MRI. Malignancy is less likely in our patient because the adrenal mass is less than 10 cm and no metastases seen on MRI abdomen or MIBG scan. Large tumor (> 10 cm) or paragangliomas increase risk of malignancy (9).

Pheochromocytoma is most often unilateral, right side, sporadic and benign. However, 20 percent of cases were found to be bilateral (10). Bilateral adrenal pheochromocytoma is more likely to be a part of familial disorders and found in

younger age group. 50 percent are seen in Multiple Endocrine Neoplasia 2 (MEN2) associated with mutations in the RET proto-oncogene, followed by 10 to 20 percent in Von Hippel-Lindau (VHL) syndrome associated with mutations in the VHL tumor suppressor gene and 0.1 to 5.7 percent in Neurofibromatosis 1 associated with mutations in the NF1 gene. A third of all patients with pheochromocytoma and paraganglioma (PPGL) have disease- causing germline mutations. A mutation of SDHB may lead to metastases in 40 percent of affected patients (5).

The Endocrine society guidelines on pheochromocytoma and paraganglioma recommends a clinical feature-driven diagnostic algorithm to prioritize specific genetic testing in PPGL patients with suspected germline mutations (5). In our case, it is priority to detect familial germline mutations in view of positive family history of bilateral pheochromocytoma in line with the recommendations. If there were history and clinical features of a syndromic presentation along with the diagnosis of PPGL, a specific targeted genetic testing is employed. If there isn't as in this case, the genetic testing is then based on clinical features of metastases, site of PPGL involvement and biochemical activity of these tumors. Following the algorithm, this patient has no typical syndromic presentation, has no metastases on latest MIBG scan and has bilateral adrenal pheochromocytoma predominantly noradrenergic activity which could indicate a screening for Von Hippel Lindau and followed by SDHD, SDHB, SDHC and MAX genetic mutations. Genetic testing is crucial in this case to detect germline mutations in the family that can aid early diagnosis and management of affected family members.

Furthermore, based on endocrine society guidelines, surgery is the treatment of choice following appropriate medical preparation. Medical therapy is aimed to control hypertension and tachycardia and volume expansion. Combinations of alpha-adrenergic blockade (e.g., phenoxybenzamine) and beta- adrenergic blockade (e.g., propranolol) are commonly used. On the second or third day of alpha-adrenergic blockade patient is advice to take high sodium diet due to effect of orthostasis and catecholamine-induced volume contraction from the effect of drug. For large tumor (> 6 cm) and bilateral disease similar to our patient, open resection with cortical- sparing bilateral adrenalectomy is better to ensure complete tumor resection, prevent tumor rupture and avoid local recurrence. Cortical sparing is done to prevent permanent glucocorticoid deficiency. In this case patient was given steroid replacement on discharge and cortisol level will be assess later.

Conclusion:

In conclusion, early detection is crucial in preventing morbidity and mortality of pheochromocytoma. Although it is a rare neuroendocrine tumor, it should be considered in-patient with malignant hypertension. Basic vital signs such as blood pressure and pulse rate should be done for each patient to prevent missed or delayed diagnosis at presentation. Genetic testing is recommended in young patient with positive family history and with bilateral disease. Once diagnosis is confirmed and tumor located, stabilization of blood pressure and volume expansion required prior to surgery. For best outcome and minimal complication, surgery should be done in a center with expertise.

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