Ischaemic stroke as the initial presentation of a pheochromocytoma associated with neurofibromatosis type 1

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Abstract

Pheochromocytoma is a rare but well-recognised manifestation of neurofibromatosis type 1 (NF1). Ischaemic stroke has been rarely reported in patients with pheochromocytoma. It can be due to either hypertension or vasospasm. A 33-year-old woman presented with ischaemic stroke and was evaluated for young stroke. Examination revealed clinical diagnosis of NF 1. She had persistent regular tachycardia and mild hypertension. But she denied features suggestive of pheochromocytoma spells. 24-hour urinary metanephrine level was elevated and there was large left adrenal mass lesion. She underwent left sided adrenalectomy. Histology further confirmed the diagnosis of pheochromocytoma. There should be a lower threshold to suspect pheochromocytoma in patients with NF 1.

Keywords: pheochromocytoma, neurofibromatosis type 1, Ischaemic stroke

Introduction

Pheochromocytomas are rare neuroendocrine tumours arising from the adrenal medulla. It is considered as “the great masquerader” because these tumours secrete catecholamines and patients present with a wide spectrum of symptoms. Pheochromocytomas have the highest heritability among all the tumours. The well-known genetic syndromes associated with pheochromocytomas are multiple endocrine neoplasia syndrome 2 (MEN 2), Von Hippel Lindau syndrome (VHL) and neurofibromatosis type 1 (NF 1).

Around 3% of patients with NF 1 develop pheochromocytomas.(1) Ischaemic stroke has been rarely reported with pheochromocytoma.(2) It can be hypertension mediated, due to catecholamine induced vasospasm or due to dilated cardiomyopathy leading to thrombus formation and embolic stroke.(2) Few cases of catecholamine induced vasospasm leading to multifocal infarcts have been reported.(3) Here we discuss a patient presenting with ischaemic stroke as the initial presentation of underlying pheochromocytoma in the background of NF 1.

Case presentation

A 33-year-old woman presented with a sudden onset of headache, dizziness, vomiting and difficulty in swallowing. Examination revealed left sided facial and palatal weakness. Other components of neurological examination were normal. Clinical diagnosis of posterior circulation pathology was made. MRI brain confirmed the diagnosis of posterior circulation ischaemic stroke. Further examination showed persistent regular tachycardia (110-130 beats per minute) with mild hypertension. Abdominal examination identified a palpable left hypochondrial mass. She had cutaneous manifestations such as multiple café au lait spots, neurofibromas and axillary nodules.

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and inguinal freckling suggestive of NF 1 which was later confirmed (figure 1). Bilateral lisch nodules were identified during the ophthalmological assessment. She denied family history of similar cutaneous manifestations, young onset hypertension or stroke or any abdominal surgeries. Considering the features of tachycardia and hypertension in the background of NF 1, possibility of pheochromocytoma was considered. But she denied having palpitations, sweating, headache or features suggestive of pheochromocytoma spells.

Initial basic investigations were normal. ECG revealed sinus tachycardia without evidence of atrial fibrillation or left ventricular hypertrophy. 2D Echocardiogram was normal. There was a large para-aortic mass detected on the ultrasound scan abdomen. CECT abdomen was done to further characterise the lesion. It showed an intensely enhancing well defined adrenal tumour with non-enhancing cystic areas measuring 9 cm (AP)×9 cm (T)×13 cm (C) in size with few calcifications (figure 1). Non contrast radio density was 48HU. There was compression in the lower pole of the left kidney but there was no hydronephrosis or hydroureter. Further biochemical investigations were done to assess the secretory nature of the tumour. 24-hour urinary metanephrines were elevated to 6.39 mg/24 hours (Normal <1 mg/24 h). Other adrenal hormone profile including overnight dexamethasone suppression test, testosterone and DHEAS level were normal. The diagnosis of pheochromocytoma was made.

The diagnosis of pheochromocytoma was made approximately six weeks after the presentation with ischaemic stroke. During this period blood pressure values fluctuated between 100/70 mmHg to 150/90 mmHg. A left open adrenalectomy was planned. Prazosin was initiated 2 weeks prior to the surgery for the alpha blockade and the dose was titrated to maintain blood pressure < 130/80 mmHg with upright systolic blood pressure more than 90 mmHg. After adequate alpha blockade, oral propranolol was started to control tachycardia and to keep the heart rate 60-70 bpm in seated position and 70-80 bpm on standing. Both the BP and heart rate targets were achieved.

Left open adrenalectomy was performed. There was an abrupt rise in blood pressure during the surgery, to 240/130 mmHg. It was controlled with intravenous magnesium sulphate and glyceryl trinitrate (GTN). She was discharged on 10th postoperative day when blood pressure and heart rate were normal. Repeat biochemical assessment with urinary metanephrines revealed cure. Histology further confirmed the diagnosis of pheochromocytoma (figure 2). Further follow up with annual metanephrine assessment and imaging was planned if metanephrines are elevated.

Discussion

The symptoms of pheochromocytomas and paragangliomas (PPGLs) are well known to be non-specific and mimic many other clinical conditions leading to an exhausting evaluation process before the diagnosis is made. The typical presentation is with episodic headache, sweating and palpitations due to abrupt excessive release of catecholamines. These are the more frequent symptoms and hypertension is present in 80% of patients. Less commonly reported symptoms are fatigue, nausea, weight loss, constipation, flushing, anxiety, chest

Figure 1 - Café au lait patches and neurofibroma on the back of the chest A. CT abdomen showing large left adrenal tumour with cystic areas and causing compression of the lower pole of left kidney B
pain, pallor, tremulousness and abdominal pain. Ischaemic stroke has been rarely reported with pheochromocytoma.

NF 1 is an autosomal dominant disease. The prevalence of PHEO/PGL in patients with NF 1 is 2.9%. (1) Patients with NF 1 develop pheochromocytoma usually in the fourth or fifth decade after some typical cutaneous manifestations of NF 1 have become evident. Therefore, the diagnosis of NF 1 can be made clinically without the need for genetic testing. Most pheochromocytomas in NF1 are benign and unilateral. Though the metastatic risk in NF 1 associated pheochromocytomas are very low, recent guidelines for screening of patients with high risk for endocrine cancers recommend initiation of biochemical screening of asymptomatic NF 1 mutation carriers every 3 years from the age of 10-14 years.(4) Imaging is recommended only if biochemical screening is positive. Emerging literature also suggests screening in people with NF 1 undergoing surgical procedures, pregnancy and delivery since these procedures can trigger cardiovascular crises.(5)

Diagnosis of Pheochromocytoma is made biochemically with elevated plasma or 24-hour urinary metanephrines. Once the biochemical diagnosis is made, imaging should be done to localise the lesion. The first line imaging modality used to investigate and localise the tumours is computed tomography.

Laparoscopic adrenalectomy is the procedure of choice for solitary, intra-abdominal pheochromocytomas. But in large tumours more than 6-8 cm, open adrenalectomy is needed. Adequate preoperative preparation is deemed necessary to avoid paroxysmal crisis pre or intraoperatively and to reduce intraoperative haemodynamic instability. Cardiac risk assessment, blood pressure and heart rate control and hypovolaemia correction are the essential components of pre-operative preparation. Hypertensive crisis during the surgery, quickly after induction of anaesthesia or with the handling of tumour needs to be treated with prompt initiation of the first-line parenteral vasodilators such as sodium nitroprusside (SPN), phentolamine, or magnesium sulphate. Intravenous glyceryl trinitrate (GTN) can be used when the first-line options are not available or as an add-on medication if blood pressure is not adequately controlled. GTN is less potent than SPN in blood pressure reduction as it is a venodilator in comparison to SPN which predominantly causes arteriolar dilatation.(6)

Post surgical surveillance is an essential part of the management of pheochromocytomas due to the risk of recurrent, multifocal, or metastatic disease. Biochemical assessment should be done 2-6 weeks after surgery to confirm biochemical remission. How long these patients need to be followed up with biochemistry and imaging is questionable but lifelong monitoring is preferred because the metastasis has been reported even after 50 years of initial diagnosis. (7) Patients with syndromic disease with pheochromocytomas require an individualised

Figure 2 - Excised large adrenal tumour A; Tumour cells with large prominent vesicular nuclei arranged in a prominent cell-nesting pattern called zellballen, characteristic of pheochromocytomas and paragangliomas (PPGLs) B
approach according to affected genes and other associated tumours or comorbidities. Genetic counselling is also an important aspect to be considered.

Conclusion

The possibility of pheochromocytoma should be considered in patients with ischaemic stroke associated with hypertension when there are clinical features of pheochromocytoma or the features suggestive of genetic syndromes known to cause pheochromocytoma. Though regular screening for pheochromocytoma in all patients with NF 1 is not cost-effective, there should be a lower threshold to screen them. It is advised to exclude pheochromocytoma in NF 1 patients who are about to undergo major surgeries.

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest to be addressed regarding this case report.

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