



Cerebrovascular Manifestations of Pheochromocytoma and the Implications of a Missed Diagnosis

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Abstract

Background and Purpose Cerebrovascular complications are a rare manifestation of pheochromocytoma. We report a case of pheochromocytoma presenting initially with reversible posterior leukoencephalopathy and subsequently a cerebral infarction.

Summary of Case A patient with a prior history of episodic hypertension and reversible posterior leukoencephalopathy presented with headache, palpitations, and weakness of the right leg. A magnetic resonance angiogram revealed narrowing of the basilar and right middle cerebral artery. She was diagnosed as having presumed vasculitis and underwent a conventional cerebral angiogram during which she developed a hypertensive crisis and worsening neurological deficit. Further investigations revealed the presence of a pheochromocytoma, which was subsequently resected.

Conclusions It is important to be cognizant of the possibility of pheochromocytoma in patients presenting with hypertension and cerebrovascular manifestations, as commonly used investigations (e.g. catheter angiography) and treatment modalities (e.g. β -blockers to treat hypertension, corticosteroids to treat suspected vasculitis, etc.) can lead to life threatening complications.

Keywords Pheochromocytoma · Cerebral vasospasm · Hypertension · Stroke

Introduction

Pheochromocytomas are catecholamine producing neuroendocrine tumors that usually arise from the adrenal medulla. Patients often present with paroxysmal or sustained hypertension, headache, sweating, panic attacks, adrenal incidentalomas, or as part of familial diseases such as multiple endocrine neoplasia II and neuroectodermal syndromes. Symptoms usually arise from the pharmacologic effect of excess catecholamines in the circulation that can also cause vasospasm and end-organ ischemia resulting in myocardial infarction, claudication, or stroke.

We report a case of pheochromocytoma presenting initially as a posterior reversible leukoencephalopathy syndrome (PRES), and subsequently as a stroke due to suspected vasculitis, to illustrate the varied neurological manifestations and treatment challenges seen in this condition.

Case Report

A 43-year-old caucasian female with a history of Crohn's disease was admitted to a local hospital with complaints of right thigh numbness, headaches, and palpitations for a few days. Shortly after admission the patient developed complete paralysis of her right leg. A magnetic resonance imaging scan (MRI) of the brain was unremarkable. MRI of the thoracic and lumbar spine revealed "an incidental finding of a unilateral Rt. renal cyst or adrenal mass." A magnetic resonance angiogram (MRA) and a CT-angiogram of the brain

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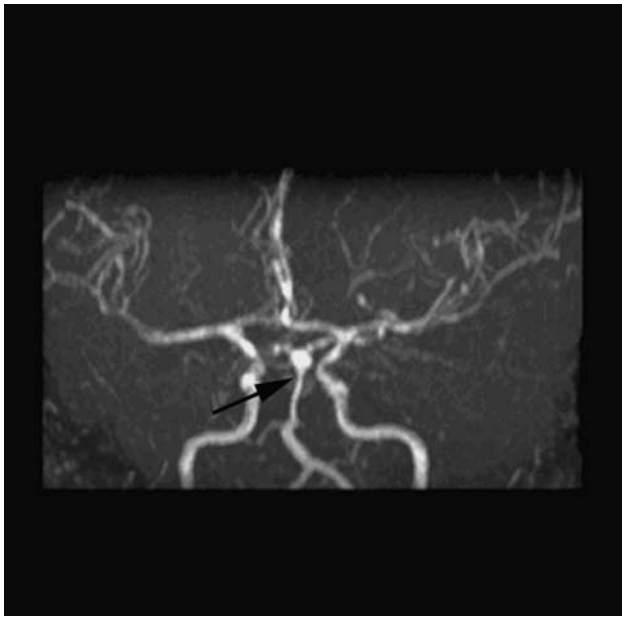


Fig. 1 Magnetic resonance angiogram illustrating vasoconstriction of the distal basilar artery

revealed multifocal diffuse narrowing of the right middle cerebral artery (MCA) and narrowing of the distal basilar artery consistent with vasculitis or vasospasm (Fig. 1). The patient was started on methylprednisolone for presumed vasculitis and transferred to our institution.

Her past medical history was significant for an episode of intense occipital headache with hypertension, diaphoresis, and flushing after a CT-scan of the abdomen with iodinated contrast performed 8 months ago. Several hours after the study she had blurry vision, disorientation, and a brief generalized tonic-clonic seizure. She was admitted to a local hospital where a brain MRI revealed bilateral occipital hyperintensities on the T2-weighted fluid-attenuated inversion recovery (FLAIR) image (Fig. 2), which completely resolved on a subsequent MRI (not available for review). A diagnosis of either reversible leukoencephalopathy syndrome or stroke was entertained. Other studies revealed mildly elevated troponin and an ejection fraction of 25% on transthoracic echo. Cardiac catheterization revealed normal coronary arteries. In the hospital, the patient was also noted to have episodically elevated blood pressure and was prescribed ramipril and carvedilol. Following discharge, she experienced episodic headaches, flushing, palpitations, and bouts of hypertension, which were attributed to premenopausal symptoms or side effects of steroids used for Crohn's disease flare-ups. She was also started on sertraline for panic attacks.

On evaluation at our institution, she had a blood pressure of 209/84 mm Hg. Neurological examination revealed a flaccid hyperreflexic monoplegia of the right leg with a right upgoing toe. The ESR was elevated (78 mm/h). A cerebral angiogram after premedication with steroids and antihistaminics was

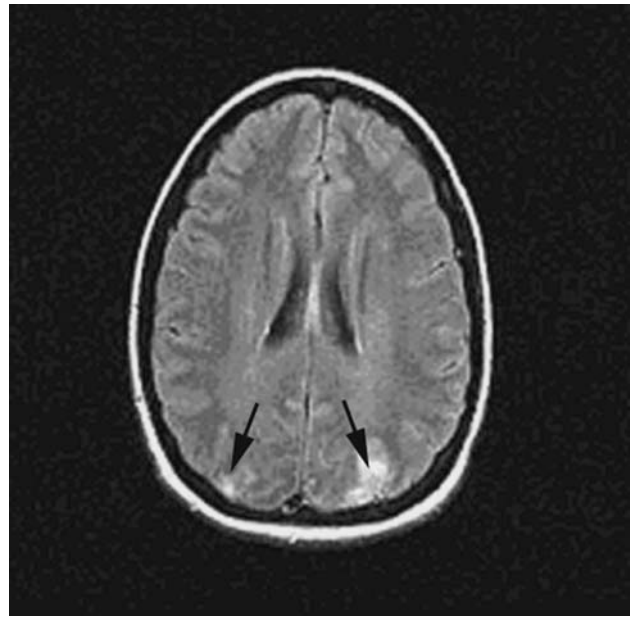


Fig. 2 T2-weighted fluid-attenuated inversion recovery (FLAIR) MR image showing posterior white matter hyperintensities

ordered for further evaluation of the changes seen on MRA. During the procedure, the patient had sudden severe hypertension, tachypnea, tachycardia, hypoxemia, and ST-segment depression in anterior chest leads on EKG. The angiogram was aborted prematurely but multifocal diffuse narrowing was noted in cervical vertebral arteries, and M-1 and M-2 segments of the right MCA (Fig. 3), and severe diffuse vasospasm was noted in the left iliofemoral vessels. The left carotid artery and the basilar artery could not be imaged. After the angiogram, she was noted to have developed proximal right arm weakness. Follow-up MRI revealed changes consistent with an acute left cortical frontal infarction (Fig. 4) as well as a right cortical parietal infarction (not shown).

In light of the incidental adrenal mass seen on the MRI spine and the autonomic instability, MRI of the kidney was

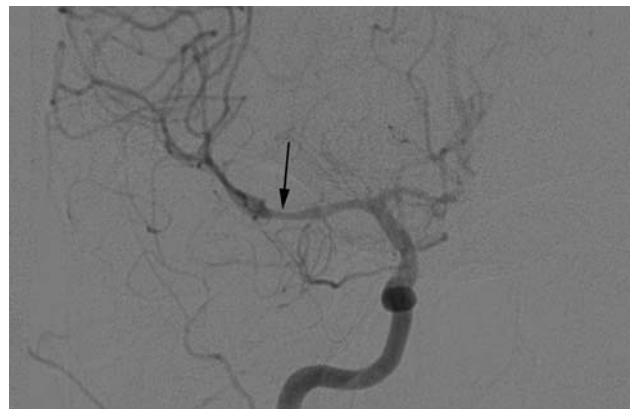


Fig. 3 Cerebral angiogram illustrating diffuse narrowing of the right middle cerebral artery trunk and branches

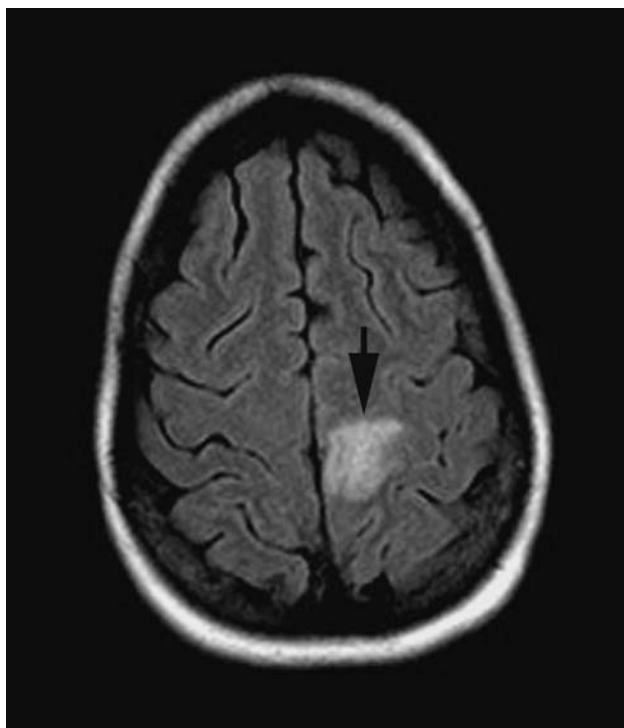


Fig. 4 T2-weighted fluid-attenuated inversion recovery (FLAIR) MR image showing changes consistent with a left cortical frontal infarction

obtained which confirmed the presence of a 4 cm right adrenal mass whose contrast pattern was suggestive of pheochromocytoma. Urine metanephrines and normetanephrines were 5,119 mcg/day (Normal: 30–350 mcg/day) and 15,543 mcg/day (Normal: 50–650 mcg/day), respectively. Plasma normetanephrines and metanephrines were 25.9 nmol/l (Normal: 0.00–0.89 nmol/l) and 7.44 nmol/l (Normal: 0.00–0.49 nmol/l), respectively, highly suggestive of a pheochromocytoma. The patient was started on phenoxybenzamine and subsequently propranolol. She underwent laparoscopic adrenalectomy, and histopathological examination confirmed the diagnosis of pheochromocytoma. She became normotensive after surgery and was discharged home.

Discussion

Pheochromocytoma is often suspected in young patients presenting with sustained or paroxysmal hypertension, especially if they have other autonomic symptoms such as diaphoresis, flushing, or palpitations. However, this condition is often not considered in patients presenting with hypertension and focal neurological deficits. We present this case to (a) illustrate the cerebrovascular complications of pheochromocytoma: a rare manifestation of a rare disease,

and (b) to heighten awareness of the potential dangers of a missed diagnosis of pheochromocytoma.

Cerebrovascular manifestations of pheochromocytoma can occur due to one of two mechanisms. Extreme elevation of blood pressure can lead to hypertensive encephalopathy or the syndrome recognized as PRES, characterized by reversible white matter hyperintensities in the parieto-occipital lobes seen on magnetic resonance imaging [1]. In addition, these patients can also develop catecholamine-mediated arterial vasospasm leading to cerebral ischemia. The vasospasm mimics vasculitis on an angiogram, but due to the reversible nature of the vasculopathy with treatment of the underlying condition and the normal histology of blood vessels on biopsy, the term “reversible cerebral vasoconstriction” is perhaps more appropriate, though the term “pseudovasculitis” has also been used to describe this phenomenon [2]. Our patient had both of these phenomena (PRES and vasospasm) occurring at different periods during the course of her illness. This case also illustrates the overlap between several syndromes that is being increasingly appreciated in recent times. These syndromes include (a) Hypertensive encephalopathy, manifesting as extreme elevation of blood pressure, alteration of sensorium, and multifocal cerebral vasoconstriction; (b) Peripartum angiopathy, manifesting as cerebral infarction or focal subarachnoid hemorrhage in the peripartum state with multifocal intracranial arterial narrowing on the cerebral angiogram; (c) Reversible cerebral vasoconstriction syndrome, reported in patients presenting with sudden severe headache and angiographic abnormalities with or without focal neurological signs and symptoms; (d) Thunderclap headache, in patients presenting with sudden severe headache that often mimics headache due to an aneurysmal subarachnoid hemorrhage, but without signs of focal neurological dysfunction or angiographic abnormalities; and (e) Posterior reversible leukoencephalopathy, characterized by parieto-occipital hyperintensities seen on MR imaging, and often associated with the use of chemotherapeutic agents. Although on initial review, these syndromes appear quite distinct, the symptoms, signs, and the neuroradiological abnormalities often overlap and the diagnosis given to an individual patient may reflect the most prominent imaging abnormality and/or the clinical scenario in which the syndrome manifests (Fig. 5). A very important clue supporting this hypothesis has become apparent with the recent discovery of the role of soluble vascular endothelial growth factor receptor 1 (sVEGFR1) (also known as soluble fms-like tyrosine kinase 1 [sFlt 1]) in these conditions. High circulating levels of sFlt 1 are seen in patients with pre-eclampsia and eclampsia where hypertension and posterior white matter abnormalities are often seen [3]. Furthermore, patients with cancer treated with anti-VEGF therapy can also develop a syndrome characterized by hypertension and

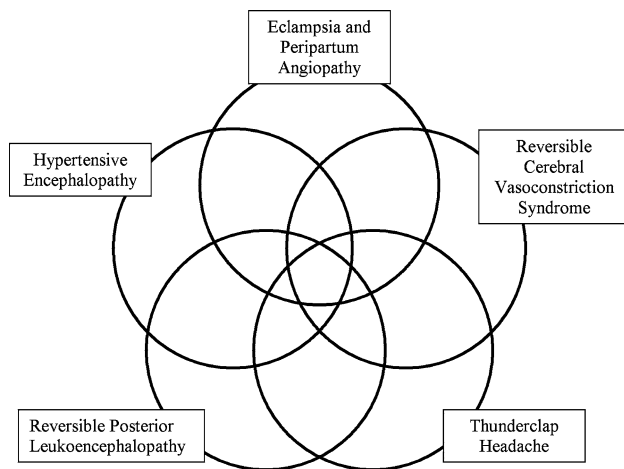


Fig. 5 Overlap between “cerebral vasoconstriction syndromes”

similar posterior white matter abnormalities on MR imaging [4]. These findings raise the possibility that the underlying pathophysiology of all these syndromes is a dysfunction of the endothelium due an imbalance of circulating angiogenic factors that ultimately leads to impaired cerebrovascular autoregulation.

As illustrated in this case, failure to consider a diagnosis of pheochromocytoma in a patient presenting with cerebrovascular manifestations can lead to a cascade of potentially life threatening iatrogenic complications. Patients presenting with hypertensive encephalopathy or elevated blood pressure in the setting of acute stroke symptoms are likely to be treated with intravenous labetalol or other beta-adrenergic receptor blockers. Inhibition of β_2 -adrenoceptor-mediated vasodilation leaves α -adrenoceptor-mediated vasoconstriction unopposed and can lead to severe adverse reactions such as hypertensive crises, pulmonary edema, and shock. Although labetalol is a dual α - and β -adrenoceptor blocker, when used without prior α -blockade, it can also precipitate crises in patients with pheochromocytoma due to the predominance of its β -adrenoceptor blocking action [5]. Sertraline, used to treat so-called panic attacks in our patient, can also lead to adverse reactions by inhibiting the reuptake of noradrenaline. Our patient subsequently presented with stroke symptoms and the vascular narrowing seen on MR angiography (in retrospect, most likely due to catecholamine-induced vasospasm) prompted a cerebral angiogram to further evaluate presumed vasculitis. Our patient twice developed symptoms of a hypertensive crisis and cerebral ischemia after receiving parenteral iodinated contrast. Peripheral injection of iodinated contrast has been associated with the release of catecholamines from pheochromocytoma

resulting in end-organ ischemia. It is not clear if the contrast induces a release of catecholamine directly or if the stress of the procedure itself is the culprit [6]. Finally, our patient was treated with steroids for presumed vasculitis. Several case reports have also noted precipitation of severe hypertensive crisis by the use of steroids in patients with pheochromocytoma [5].

Conclusion

Pheochromocytoma has been called “the great mimic” and this case illustrates the need to consider this diagnosis in patients presenting with hypertension and stroke symptoms. Specifically, cerebral vasospasm caused by a catecholamine-secreting tumor should be considered in the differential diagnosis of hypertensive encephalopathy, cerebral vasoconstriction syndrome, and cerebral vasculitis. Awareness of this condition and institution of α - and subsequently β -adrenoceptor blockade can help avoid potentially life-threatening complications caused by injection of contrast media or the use of steroids, β -adrenoceptor blockers and various other drugs.

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