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LEVODOPA-INDUCED PSEUDOPHEOCHROMOCYTOMA

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ABSTRACT

Pseudopheochromocytoma is a pathological condition presenting with paroxysmal hypertension with normal or moderate elevation in catecholamines and metanephrine levels, but no evidence of a tumoural cause. Imaging studies and I-123 metaiodobenzylguanidine scintigraphy are essential for exclusion of pheocromocytoma.

We describe a case of pseudopheochromocytoma related to levodopa in a patient with paroxysmal hypertension, headache, sweating, palpitations and increased plasmatic and urinary metanephrine levels, without adrenal or extra-adrenal tumour. The beginning of the patient´s clinical symptoms coincided with the initiation of the levodopa treatment and the complete resolution of the symptoms occurred after the discontinuation of levodopa.

KEYWORDS

Pseudopheochromocytoma, paroxysmal hypertension, levodopa, Parkinson's disease

LEARNING POINTS

- Pseudopheochromocytoma and pheochromocytoma may have the same clinical and laboratorial presentation but different aetiologies.
- The diagnosis of pseudopheochromocytoma is based on paroxysmal hypertension with normal or increased plasma and urine levels of catecholamines or metanephrines after exclusion of a tumoural process.
- The pseudopheochromocytoma may be associated with levodopa, alone or in combination with other drugs that are likely to interfere with dopamine or catecholamine metabolism.

CASE DESCRIPTION

A 79-year-old, Caucasian female was admitted to the hospital with hypertension paroxysmal attacks (230/110 mmHg), tachycardia (130 bpm), headache, sweating and palpitations, which started two years previously. She had a history of hypertension for 20 years, medicated with isosorbide dinitrate, paroxysmal atrial fibrillation for eight years, medicated with rivaroxaban, depression for five years medicated with paroxetine and alprazolam, also Parkinson's disease for two years medicated with levodopa-carbidopa (25/250 mg tid and 50/200 mg prolonged release od), ropirinole and rivastigmine. She denied any other relevant symptoms and physical examination was unremarkable.

The cell blood count, ESR, liver and kidney function tests, sodium, potassium, calcium, troponin, muscle enzymes, thyroid function tests and urinalysis were within normal limits. Chest X-ray and ECG were unremarkable. On the echocardiogram there was moderate left atrial dilatation

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with mild mitral valve insufficiency. On abdominal ultrasound and arterial doppler the kidneys had normal morphology, the adrenal glands were normal and there was no evidence of renovascular pathology. Brain and abdominal CT scan and abdominal MRI showed no abnormalities.

During hospitalisation, daily hypertensive paroxysms without a circadian pattern associated with headache, sweating and tachycardia were noticed.

Urinary measurements of cortisol and serum renin, aldosterone, parathyroid hormone and chromogranin A were normal. Plasma-free metanephrine was 547.7 pg/ml (normal <196) and 24-hour urine-free metanephrine was 1248.1 ug/24h (normal <527). I-123 metaiodobenzylguanidine (MIBG) scintigraphy excluded an extra-adrenal tumour.

Therapy with doxazosin was started; however, the patient maintained recurrent crises. The diagnosis of pseudopheochromocytoma related to levodopa-carbidopa was admitted; the drug was progressively discontinued, and no further episodes were observed.

After discharge, the patient remained normotensive with amlodipine treatment; asymptomatic and methanephrine levels moved to normal. Since there was no worsening of her neurological condition, the patient was sent to a neurologist for the diagnostic review.

DISCUSSION

Pheochromocytoma is a catecholamine-secreting tumour from the chromaffin adrenal cells or from extra-adrenal chromaffin tissue of the nervous system, also known as paraganglioma. Pseudopheochromocytoma is a pathological condition presenting with severe paroxysmal vasoconstriction with normal or mild-to-moderate elevation in catecholamines and metanephrine levels, but no evidence of a tumoural cause[1].

In both cases, after the adrenergic system activation the patients show severe paroxysmal hypertension associated with headache, palpitations, and diaphoresis[2]. In addition to atrial or ventricular fibrillation, cardiac complications such as myocarditis, cardiomyopathy, myocardial infarction, and pulmonary oedema have also been reported. Neurological complications include hypertensive encephalopathy, characterised by altered mental status, focal signs, or seizures, and ischaemic or haemorrhagic stroke[3]. Plasma or urinary metanephrines are usually the most sensitive tests for the diagnosis of these conditions. Some patients with pseudopheocromocytoma can have normal laboratory tests while others may have abnormal laboratory tests due to certain medications or clinical conditions, with no symptoms consistent with pheocromocytoma. The tumour can be detected by CT scan, MRI or I-123 MIBG scintigraphy if the MRI is inconclusive.

The pathogenesis of pseudopheocromocytoma is unclear. Patients with normal hormonal levels may present a imbalance of central autonomic centres. In these cases, elevated catecholamine and metanephrine levels may not always be detected, probably because of a highly transient crisis[1]. In patients with increased hormonal levels, an increased adrenal release of epinephrine and exaggerated cardiovascular responsiveness to catecholamines might contribute to the paroxysmal hypertension and the related symptoms. Moreover, it is possible that an altered function of the autonomic nervous system exists, or an abnormal disposition of catecholamines released from neurons within the brain[4].

Three underlying processes might also be considered in pseudopheocromocytoma: the increase in catecholamine precursor substrate, increased release or inhibition of catecholamine reuptake and the inhibition of their metabolism[5]. Levodopa is one such substrate. The drug, used in Parkinson's disease normally associated with carbidopa, is transformed into dopamine and afterwards into noradrenaline, adrenaline, and their metabolites. Dopamine can cause vasodilation by stimulating the D1 receptor, having as a secondary effect postural hypotension, but at high doses it can lead to an increase in noradrenaline levels, with activation of vascular alpha1 adrenergic receptors[6].

Some cases of hypertension have been reported in patients using levodopa, including severe paroxysmal crises when associated with selegiline, which is an inhibitor of noradrenaline degradation[7,8]. Ropirinole and rivastigmine do not seem to be associated with high blood pressure. Paroxetine is an antidepressant that inhibits serotonin reuptake and in high doses it is also a noradrenaline reuptake inhibitor. It has been linked to de novo hypertension or worsening of an already known hypertension in the context of serotonergic syndrome[9], but in this case the patient does not express the characteristic neuromuscular hyperactivity. There was clinical improvement without discontinuing paroxetine and the syndrome is not associated with increased metanephrine levels.

In our patient the Adverse Drug Reaction Probability (Naranjo) scale[10] scored 5, which indicates this is considered to be a probable adverse drug reaction and that levodopa was the main cause of the clinical findings. However, a possible synergistic effect of paroxetine and the consequence of the extreme anxiety during the paroxysms cannot be excluded. The diagnosis of drug-induced pseudopheochromocytoma was based on clinical findings, increased plasma and urinary metanephrine levels, absence of pheocromocytoma and exclusion of other pathological causes. In addition, the clinical symptoms at the beginning were related to the initiation of the levodopa treatment; complete symptoms resolution was observed after the levodopa discontinuation, with normal plasma and urinary tests.

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