Neurogenic hypertension associated with an excessively high excretion rate of catecholamine metabolites

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SUMMARY A 60 year old hypertensive patient suffered several cerebral infarctions. A phaeochromocytoma was suspected because the excretion rates of vanillylmandelic acid and its methoxy derivatives were raised and the patient had hypertensive crises. No tumour was found, however, by ^{131}I -iodobenzylguanidine scintigraphy and computed tomography of the abdomen. Moreover, the enhanced orthostatic plasma catecholamine response suggested that the high excretion rates of catecholamine metabolites were more likely to be caused by the syndrome of raised catecholamines after cerebrovascular accidents than a phaeochromocytoma.

A phaeochromocytoma should not be diagnosed within several months of cerebral infarction without first excluding the possibility of a hyperadrenergic state induced by cerebral infarction.

Hypertension associated with increased excretion of catecholamines has been described in several conditions that simulate phaeochromocytoma.^{1,2} We describe a hypertensive patient who had several cerebral infarctions and excessively high excretion rates of catecholamine metabolites that persisted for several months. Phaeochromocytoma, whether adrenal or ectopic, was not demonstrated despite the use of specific and sensitive diagnostic techniques. An excessive increase in plasma catecholamine concentration in response to standing up suggested a non-tumoral pattern that was consistent with a neurogenic hyperadrenergic state.

Case report

A 60 year old man was referred to our hospital on 2 December 1984 with severe resistant hypertension and a high excretion rate of catecholamine metabolites. He had a two year history of asymptomatic untreated hypertension with no other relevant medical or surgical history. On 4 October 1984 right facial palsy with dysarthria developed suddenly and he was admitted to another hospital. Fluctuating

high blood pressure was found. Examination disclosed a mild right hemiparesia without sensory loss. Clinical examination was otherwise normal. Standard laboratory values were normal. An electrocardiogram disclosed typical signs of left ventricular hypertrophy and normal sinus rhythm. A chest radiograph showed mild cardiomegaly but no mediastinal tumour. Intravenous digitised cervical angiography showed major atherosclerotic lesions of both vertebral arteries without obstruction. The urinary excretion rate of catecholamine metabolites was measured 10 days after admission.³ It gave the following results: vanillylmandelic acid 6.21 mg (31.3 μmol)/24 h (normal < 8 mg (40.4 μmol)/24 h); metanephrine and normetanephrine 1407 μg (normal < 700 μg)/24 h; normetanephrine 972 μg (5.3 μmol)/24 h.

Blood pressure remained unstable despite the administration of several antihypertensive drugs (figure). Excretion rates of catecholamine metabolites remained raised and concentrations of normetanephrine predominated over those of metanephrine. The excretion rate of vanillylmandelic acid reached 11.8 mg/24 h (59.5 μmol /24 h) on 16 November 1984. On 28 November the patient had a left hemiparesis that spared his face.

At admission the patient was drowsy. Supine blood pressure was 214/108 mm Hg and the pulse

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Figure Clinical course of the patient. Broken lines represent the upper limit for normal values. The small arrow indicates the time the patient had his second cerebral infarction. The large arrow indicates the time of admission to our hospital. Daily dosage of antihypertensive drugs is indicated. MAP, mean arterial pressure. Values are the means of two or three daily supine blood pressure measurements; MN + NMN, metanephrine + normetanephrine. MN 1 μmol = 197.23 μg ; NMN 1 μmol = 183.20 μg .

rate was 66 beats/minute. He did not have a history of headache, excessive sweating, or palpitation. Neurological examination revealed a mild left sided pure motor deficit sparing the face, fluctuating consciousness, and frequent yawns. Clinical examination was otherwise normal. Lumbar puncture yielded a sample of normal cerebrospinal fluid. A cerebral computed tomogram revealed multiple areas of reduced density. The blood pressure continued to fluctuate, with supine systolic pressure ranging from 140 to 250 mmHg. Blood pressure peaks were not accompanied by headache, sweating, or tachycardia. Irrespective of the treatment the patient was taking, there was a mean drop of systolic and diastolic blood pressure of 25 and 10 mmHg respectively and a concomitant 30% average increase of heart rate when he stood up. Micturition did not induce headache, sweating, tachycardia, or variation in blood pressure. The results of intravenous pyelography were normal. A computed tomogram of the adrenal glands did not show a tumour. Whole body ^{131}I -iodobenzylguanidine scintigraphy, which included the head, did not show any abnormal uptake. Urinary bladder uptake revealed no important abnormality.

The excretion rate of catecholamine metabolites (metanephrine, normetanephrine, vanillylmandelic acid) reached a peak three days after the occurrence of the left hemiparesis and remained raised during the next three months. Then a second rise occurred (figure). The specificity of the urinary determinations was borne out by the results of high performance liquid chromatography. An oral dose of 1 mg of prazosin produced a maximum drop of 4% in arterial blood pressure during a seven hour follow up.

Four and a half months after admission, 10 days after the withdrawal of guanfacine and while the patient was taking prazosin, nifedipine, and spironolactone, we measured plasma catecholamine concentrations while he was supine and after standing up.⁴ The following results were obtained: noradrenaline 5661 pg/ml (33.5 pmol/ml) supine and 11796 pg/ml (69.7 pmol/ml) after standing for five minutes (normal supine < 355 pg/ml (2.1 pmol/ml)); adrenaline 162 pg/ml (0.88 pmol/ml) supine and 287 pg/ml (1.57 pmol/ml) after standing for five minutes (normal supine < 85 pg/ml (0.46 pmol/ml)). Neurological examination was consistent with a so-called pseudobulbar palsy.

Discussion

This case emphasises the difficulty in distinguishing between phaeochromocytoma and cerebrovascular accidents causing raised concentrations of catecholamines. In hypertensive patients with raised excretion rates of catecholamine metabolites, the diagnosis of true (tumoral) phaeochromocytoma is suggested by several features. These are the triad of headache, sweating attacks, and palpitation. When this triad is absent, the probability of phaeochromocytoma is <1 in 1000.⁵ A prolonged (75 h) fall in blood pressure after the administration of prazosin is also suggestive of phaeochromocytoma.⁶ Crises precipitated by micturition have been described in patients with bladder phaeochromocytoma.⁷

Computed tomography can detect small tumours and is particularly useful for the diagnosis of ectopic tumours when these are indicated by scintigraphy or venous concentrations of catecholamines. The diagnosis and localisation of adrenal and extra-adrenal phaeochromocytomas has been improved by the use of ¹³¹I-iodobenzylguanidine scintigraphy, which has a sensitivity of 89% and a specificity of 95% for the diagnosis of true phaeochromocytomas.⁸

Plasma and urine catecholamine concentrations also help to distinguish between true phaeochromocytomas and the syndrome of raised catecholamines. Raised urinary concentrations of adrenaline usually indicate an intra-adrenal tumour; however, there are reports of false negative results.⁸ It has been suggested that a plasma adrenaline concentration of <200 pg/ml (1.1 nmol/l) associated with a noradrenaline plasma concentration less than twice the upper limit of normal indicates a non-tumoral cause for the hyperadrenergic state.⁹ The most important features in patients with phaeochromocytoma are the lack of an increase in plasma catecholamines in response to standing¹⁰ and the lack of a decrease in plasma catecholamine concentrations after pentolinium⁹ or clonidine.¹¹ When ¹³¹I-iodobenzylguanidine scintigraphy is negative but plasma catecholamine concentrations indicate the presence of a phaeochromocytoma, selective venous sampling of catecholamines is invaluable in determining the sources of the excess catecholamines.¹² This technique requires considerable radiological skill and expert assay facilities, however.

Cerebral infarction can increase total catecholamine concentrations in the peripheral venous plasma of hypertensive patients,¹³ and catecholamine urinary excretion rates.¹⁴ Stoica *et al* found that urinary noradrenaline excretion increased in the first week after cerebral infarction in 46 patients, whereas it was normal thereafter. The excretion rate of vanillylmandelic acid was normal during the first month.¹⁴ We believe that the clinical,

biological, and radiological picture in our patient rules out the presence of a phaeochromocytoma and suggests a hyperadrenergic state induced by cerebral infarction.

In hypertensive patients with high catecholamine excretion rates after cerebral infarction, ¹³¹I-iodobenzylguanidine scintigraphy and plasma catecholamine response to standing or suppression tests are most useful in distinguishing between a true phaeochromocytoma and the syndrome of raised catecholamines. Because blood pressure control was only achieved in our patient after administration of guanfacine and prazosin we suggest that hypertensive patients with high excretion rates of catecholamines after cerebral infarction should be treated with peripheral α_1 blocking agents and/or centrally acting α_2 agonists.

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