HYPERTENSION DUE TO EXTRA-ADRENAL PHAEOCHROMOCYTOMA

6 YEAR FOLLOW-UP AFTER SURGICAL REMOVAL

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Arnott, in discussing the treatment of cardiac failure in a recent article[1] in the *British Medical Journal*, prefaces his comments with the following remarks: 'Treatment is in general only palliative, but the prospect of effecting any great improvement in a patient's condition or even curing him lies in the direction of identifying a removable cause'. This is possible in only a minority of cases, but should always be kept in mind.

The following case emphasizes the importance of diligently searching for remediable factors in patients with seeming essential hypertension and mild congestive cardiac failure.

A hypertensive patient whose phaeochromocytoma was diagnosed and successfully removed in 1960, has been followed-up for 6 years. She was presented to the College of General Practitioners at a weekend course at Somerset Hospital in 1965, and the full case history is recorded below. An unusual feature was the situation of the tumour, which pressed on the right renal artery, producing a non-functioning kidney on intravenous pyelography.

CASE REPORT

W.M., a 51-year-old Coloured female printer's assistant, consulted me on 17 May 1960 with a 3-month history of progressive exertional dyspnoea, paroxysmal attacks of palpitations associated with profuse sweating and ice-cold extremities, lassitude, anorexia, weakness, a loss of 27 lb. weight in 6 months, oedema of the feet for 2 weeks, orthopnoea and paroxysmal nocturnal dyspnoea for 1 month.

Examination showed pallor of the mucous membranes, raised jugular venous pressure, pulse rate 120 regular, hypertension 220/120 mm.Hg, cardiomegaly with a left ventricular lift, and a tender 1-finger hepatomegaly. Urinalysis; albuminuria ++, glycosuria ++.

She was referred to an outpatient department with a diagnosis of congestive cardiac failure on the basis of hypertension and the question of diabetes mellitus was raised. She was admitted to hospital where her cardiac failure was treated. She was digitalized and given diuretics.

Her stay at hospital was complicated by a severe menorrhagia in June. Her haemoglobin was 8·6 G/100 ml. Treatment was by dilatation and curettage; 20 minutes after commencement of the anaesthetic, there was a precipitous drop in the blood pressure. The curettings were histologically normal.

She was discharged on 25 July 1960 to be followed-up in the outpatient department, but she did not reattend. On 8 August 1960, I was again consulted with the following story: She had woken up with precordial pressure, palpitations, dyspnoea, and profuse sweating. Examination showed signs of cardiac failure, raised jugular venous pressure, slight oedema, 2-3-finger hepatomegaly, and crepitations at both lung bases, pulse rate 140/minute, cardiomegaly, blood pressure 190/120 mm.Hg. The history suggested ischaemic heart disease; however, an electrocardiograph at this stage did not confirm myocardial infarction.

During the next 3 months she began complaining of a recurring pattern of symptoms which increased in frequency. At first her hands would become clammy, she would experience a warm, choking feeling in the chest, ice-cold extremities with a pale white colour. Associated with these local symptoms, she would experience tachycardia and profuse sweating.

It then became abundantly clear that she was suffering from a condition precipitated by the periodic release into the body, of a chemical with local and systemic effects similar to adrenaline. She was once again referred to hospital with the firm clinical diagnosis of phaeochromocytoma. This time she was admitted to Barkly Ward, Somerset Hospital.

On admission she was in mild cardiac failure, with cardiomegaly, gallop rhythm, and a wide, fixed, splitting P2. Fundi showed grade 2 hypertensive retinopathy. Blood pressure (between attacks) 130/90; blood pressure (during attacks) up to 260/180; haemoglobin 13 G/100 ml.; PCV 39%. Urine showed a trace of protein intermittently, with slight intermittent glycosuria. Temperature chart (*b.d.*)—no pyrexia.

Investigations. Blood urea 16 mg./100 ml., serum electrolytes normal, serum proteins normal. Fasting blood sugar 110 mg./100 ml., ECG examination showed left bundle-branch block and X-ray of the chest showed cardiomegaly.

Progress and management. Three special tests strongly supported the clinical diagnosis of phaeochromocytoma, namely:

(*i*) Intravenous histamine test (between attacks)—positive pressor response.

(*ii*) Intravenous phentolamine (Regitine) test (during attacks)—positive depressor response, and
(*iii*) Cat test on urine—pressor activity marked on 9 December 1960.

Intravenous pyelogram demonstrated a non-functioning right kidney. Ureteric catheterization showed complete lack of urine flow on the right side. The retrograde pyelogram was normal.

Operation, 13 December 1960. Transabdominal operation was performed on 13 December 1960 by Drs. L. Chanock, S. Scher and L. Sarembok. A tumour measuring 3 cm. by 5 cm. was removed. It was situated above the right kidney and arose from the right side of the coeliac ganglion. The right renal artery was stretched across the tumour and the right kidney was also removed. During the operation, blood pressure rose to 170/135 mm.Hg, and she was given intravenous Regitine until the tumour was removed. The blood pressure fell at once and could not be recorded. She required intravenous noradrenaline for 30 hours and thereafter remained normotensive. (During this period, she sustained a noradrenaline 'burn' on the leg.)

Histologically the tumour was a phaeochromocytoma. The capsule contained well-formed nerve bundles and autonomic ganglia. Prof. N. Sapeika reported that the tumour showed extreme pressor activity on biological testing.

The main right renal artery did not show any evidence of tumour infiltration. However, the lumen of the vessel was reduced to a mere slit as a result of concentric intimal proliferation and must have seriously impaired the blood flow to the kidney. The most striking feature in the kidney sections was tubular atrophy and dilatation affecting the distal convoluted tubules of the cortex. Some of the vessels of the kidney and even of the ureter had thickened and had hypertrophied walls.

Follow-up, 1960 - 1966. The disabling attacks ceased, she has felt perfectly well and has resumed work. Her weight has risen from 106 lb. at the time of her discharge from hospital to 149 lb. Blood pressure has varied between 140/80 and 150/90 mm.Hg. Electrocardiograph still shows left bundle-branch block. On chest X-ray there is still some cardiomegaly. The urine is free of sugar and albumin.

DISCUSSION

The patient with a phaeochromocytoma is suffering from a potentially fatal illness and its diagnosis is of vital importance, as the patient harbours a tumour with grave risks to life and health.

Kirkendall *et al.*[2] reported the death of 2 patients after apparent hypertensive crises precipitated by a simple movement such as a sudden change of position. One stooped over to pick up an object off the floor and died from a cerebral haemorrhage. Furthermore, in his series, 7 cases were undiagnosed before death, 3 dying while undergoing incidental surgery.[2] This patient had a perturbing fall in blood pressure during a minor operation. She might easily have succumbed. This is a reminder that the cause of collapse during operation on a hypertensive could be due to an undetected phaeochromocytoma.

The diagnosis in this case was relatively easy because of the presence of the classical clinical features.

In the Mayo Clinic series of 76 cases,[3] the following symptoms are listed:

(*i*) Abrupt onset of headache, severe and of short duration.
(*ii*) Excessive perspiration.
(*iii*) Palpitations.

All but one of the patients with paroxysmal hypertension and all but 2 of the patients with persistent functioning tumours had at least 1 of the 3 symptoms.

Thirty-one of the 37 patients with paroxysmal hypertension and 24 of the 39 with persistent functioning tumours had 2 of the symptoms. Our patient complained of excessive perspiration and palpitation associated with her paroxysmal hypertension. Headache was not a prominent symptom. The paroxysms occur spontaneously, but can be precipitated by movement of the body. Her attacks also occurred spontaneously.

In addition she complained of weakness, lassitude, dyspnoea, warmth or flushing, which are all features mentioned in the Mayo Clinic series. Owing to the multiplicity of symptoms, the condition can be confused with many clinical entities, e.g. hyperthyroidism or anxiety states. This case may have been confused with the menopausal syndrome—she complained of listlessness, lassitude, hot flushes and had menorrhagia.

Clinical Signs

These patients are characteristically thin. Two-thirds of the Mayo Clinic series had hyperglycaemia and three-quarters had hypermetabolism. This patient had a weight loss of 27 lb. in 6 months and had intermittent glycosuria.

In the paroxysmally functioning tumour, the blood pressure was characteristically labile. Severe hypertensive retinopathy grades 3 and 4 and albuminuria, as would be anticipated, were found in the persistent functioning tumours. This patient's blood pressure varied between 130/90 and 260/180 mm.Hg; the fundi showed grade 2 hypertensive retinopathy and she had albuminuria.

Diagnostic Tests

Hypertension is a very common finding in practice. However, the complete screening of all hypertensives for phaeochromocytoma would not be a feasible proposition. Graham[4] found an incidence of 1:200 of all hypertensives selected for sympathectomy. General practitioners, who see most cases of hypertension, should be aware of this clinical entity. The following clinical patterns should 'ring a bell' and the presence of a phaeochromocytoma should be suspected: (*i*) Symptoms occurring in paroxysms, (*ii*) the thin hypertensive with glycosuria, and (*iii*) collapse during anaesthesia.

This case manifested all these clinical features. Having made the clinical diagnosis of phaeochromocytoma, the diagnostic tests recommended are:

A. Pharmacological Tests

(*i*) Provocative histamine test: intravenous injection of histamine stimulates the secretion of catecholamines which results in a pressor response if a tumour is present. Performed when blood pressure is less than 170/100 mm.Hg.
(*ii*) Suppressive phentolamine (Regitine) test. Regitine neutralizes the vasopressor effect of circulating catecholamines. Performed when blood pressure is greater than 170/110 mm.Hg.

B. Chemical Tests

(*i*) Estimation of urinary catecholamines and
(*ii*) VMA test—measuring catecholamine metabolites.

In this case, the histamine pressor test, the Regitine depressor test and the cat test were all positive. No chemical test for VMA was available at the time of admission in 1960.

A very unusual finding was the intravenous pyelogram which showed non-functioning of the right kidney. This could have made one erroneously diagnose unilateral reno-vascular hypertension and have led one to undertake nephrectomy alone, but fortunately the clinical data and special tests were overwhelmingly helpful in the diagnosis of phaeochromocytoma. From descriptions by both surgeon and pathologist, it appears that the right renal artery was stretched over the tumour, so probably the intimal proliferation was due to this chronic trauma. The Mayo Clinic refers to data of the effects of trauma of the intima.[5] Some of the abnormal kidney histology might have been due to this lesion of the main renal artery. Perhaps other changes were the result of the hypertension due to the phaeochromocytoma. The abnormal intravenous pyelogram did of course help to localize the lesion, and indicated on which side the surgeon would find the lesion.

SUMMARY

A 51-year-old female presented in 1960 with paroxysmal symptoms of palpitations, sweating, and coldness of the extremities, accompanied by tachycardia and intermittent hypertension. Loss of weight was a prominent feature. The suspected clinical diagnosis was supported by the cat test on the urine and by intravenous phentolamine and histamine tests.

A right extra-adrenal phaeochromocytoma was successfully removed from the side of the coeliac ganglion. An unusual feature was the presence of a non-functioning right kidney owing to the mechanical effect of the tumour on the main right renal artery. The kidney was also removed. During 6 years follow-up she has remained well, symptom-free, in excellent general health, and normotensive.

Before she was diagnosed and treated, she underwent general anaesthesia for a minor gynaecological procedure and had an alarming temporary collapse. There are records of similar and even fatal incidents in other cases of unsuspected phaeochromocytoma. Attention is drawn to ways in which cases of phaeochromocytoma could be suspected by general practitioners.

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