Cardiac Complications of Phæochromocytoma

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The following case histories are thought worthy of record, because the patients concerned developed several severe cardiac complications. It is believed that two of these, ventricular fibrillation and paroxysmal supraventricular tachycardia accompanied by hypotension, have not been described before in a case of phæochromocytoma.

CASE REPORTS

Case 1. A woman, aged 53, was admitted to Farnborough Hospital in March 1963 for a Manchester repair of uterine prolapse. She was a known hypertensive receiving treatment with rauwolfia. Her blood pressure on admission was 150/90 mm. Hg. During the operation, 3 days later, she developed a tachycardia of about 230 a minute. An electrocardiogram taken a few hours after the operation showed severe widespread myocardial ischaemia (Fig. 1A). Following the cardiogram she was given digoxin 0.5 mg. immediately, and 0.25 mg. thrice daily thereafter. A further tracing 4 days after operation showed extensive myocardial damage in addition to ischaemia (Fig. 1B). Serum glutamic transaminases were grossly raised, the oxaloacetic being 2300 Karmen units per ml. and the pyruvic 2800 Karmen units. Three days later the patient was observed during a hypertensive attack, in which her blood pressure rose to 200/130 mm. Hg, with a pulse rate of 110–130 a minute. She had severe peripheral cyanosis, with cold extremities and profuse sweating. She appeared very anxious and complained of palpitations. A provisional diagnosis of phæochromocytoma was made. 10 mg. phentolamine was given by slow intravenous injection and her systolic blood pressure fell to 85 mm. Hg. Estimation of urinary catecholamine excretion provided further confirmation of the diagnosis, the screening test being strongly positive and the level of 3-methoxy 4-hydroxymandelic acid being raised to 18.4 mg./24 hours.

The next day the patient was transferred to Guy's

Hospital for further investigation and treatment. On admission she gave a ten-year history of severe headaches, often lasting 8–24 hours. Sometimes, these seemed to be precipitated by eating food. They were associated with nausea and with profuse sweating. At 11 p.m. on the evening of admission she was seen during a further typical hypertensive attack, blood pressure 180/140 mm. Hg. Phentolamine was not given on this occasion and after about 10 minutes her blood pressure started to fall again spontaneously. Suddenly, the patient became very cyanosed and had a generalized epileptic convulsion. Her radial pulse was impalpable, and no heart sounds could be heard over the præcordium. External cardiac massage and intermittent positive pressure respiration were started immediately. An electrocardiogram (Fig. 1C) showed ventricular fibrillation which was successfully reversed with an external A.C. defibrillator. It was decided that, though surgical treatment was now a matter of urgency, an attempt should first be made to localize the site of the tumour. An intravenous pyelogram was inconclusive. Aortography was therefore arranged for the next day to be followed immediately by laparotomy under the same anaesthetic, and the patient was accordingly transferred to the surgical wards for this. Unfortunately, during the night before operation she developed a state of shock, with a pulse rate rising to 190 a minute and a blood pressure of 90/70 mm. Hg. This was accompanied by progressive displacement of the apex beat laterally, suggesting that cardiac failure was the cause of hypotension. An electrocardiogram showed paroxysmal nodal tachycardia (Fig. 1D). Her condition appeared so serious that it was considered that intravenous digitalization was justified despite the increased risk of ventricular fibrillation (she had received no digitalis for the previous 36 hours). Digoxin, 1 mg., was given intravenously and this was followed by a dramatic improvement in the clinical picture. The blood pressure rose to 180/100 mm. Hg and the pulse rate fell to 120 per minute. Twenty minutes later, however, ventricular fibrillation again developed. Subsequent attempts at resuscitation were unsuccessful.

Findings at Necropsy. The right adrenal gland was attached to a spherical soft pink tumour about 5 mm. in diameter, weighing 49 g. Histological examination

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FIG. 1.—Case 1.

- (A) Severe widespread myocardial ischaemia.
 (B) Four days later extensive myocardial damage in addition to ischaemia.
 (C) Four days after (B) ventricular fibrillation.
 (D) Two days later paroxysmal nodal tachycardia, rate 190 a minute.

of this tumour showed typical appearances of a pheochromocytoma. Examination of the tumour for catecholamine content gave values of 610 μ g. noradrenaline and 280 μ g. adrenaline/g. tumour tissue. Macroscopic examination of the heart showed minimal atheroma of the coronary arteries. There was no evidence of myocardial infarction and no petechial haemorrhages were seen.

Case 2. A woman, aged 44, was admitted to Guy's Hospital in March 1964, for confirmation of a diagnosis of pheochromocytoma made at the Kent and Canterbury Hospital. She had been a known hypertensive for 11 years, with a one-year history of frontal headaches and panic attacks. A recent intravenous pyelogram had suggested a mass in the right kidney; a retrograde pyelogram and retro-peritoneal oxygen insufflation had shown that this mass was in fact in the right suprarenal gland. Urinary excretion of 3-methoxy 4-hydroxymandelic acid was found to be raised at 49.5 mg. per 24 hours, and catecholamine excretion was also considerably raised at 400 μ g. noradrenaline per 24 hours. Right adrenalectomy was carried out in April, the patient having been

put on a maintenance dose of phenoxybenzamine for 2 days. During exposure of the tumour the patient developed a supraventricular tachycardia of 160 a minute (Fig. 2B). A dose of 40 mg. pronethalol was given intravenously, with a fall in the pulse rate to 120 a minute. Removal of the tumour proved technically very difficult, as it was adherent to the inferior vena cava and liver. There was considerable blood loss and prolonged episodes of hypotension. Immediately after the operation the patient developed pulmonary oedema which responded poorly to digitalis, diuretics, and intravenous phentolamine. An electrocardiogram the day after operation (Fig. 2A) showed evidence of myocardial damage, with T wave inversion in standard leads I and II, and in V2 and V3, in addition to S-T depression in standard leads II and III, AFV and V4-V6. These changes were accompanied by a considerable rise in serum transaminases, which reached a maximum on the fourth post-operative day with a serum-glutamic oxaloacetic transaminase of 112 Karmen units/ml., and serum glutamic pyruvic transaminase of 268 Karmen units/ml. The patient developed a severe bronchopneumonia and died 15 days after operation.

FIG. 2.—Case 2.

(A) Myocardial damage.

(B) Paroxysmal supraventricular tachycardia, rate 160 a minute.

Findings at Necropsy. The tumour was locally malignant, having invaded the inferior vena cava. It had also invaded the liver but there were no distant metastases. Histology of the tumour removed at operation showed a phæochromocytoma with marked nuclear pleomorphism. The tumour weighed 113 g. and contained 2.15 mg. noradrenaline and 0.5 mg. adrenaline per g. soft tumour tissue. The heart appeared normal both macroscopically and histologically.

Case 3. This woman, aged 60 years, was admitted to the New Victoria Hospital, Kingston, in December 1962, in a state of peripheral circulatory failure. She had a pulse rate of 160 a minute with an unrecordable blood pressure. On December 20 she was transferred to the Brompton Hospital where she gave a history of two recent episodes of acute dyspnoea, accompanied by excessive sweating. She had been on digoxin 0.25 mg. twice daily since her first episode of acute dyspnoea, three months before. There was no previous history of hypertension. Her pulse rate on admission was 130 a minute, and her blood pressure 130/90 mm. Hg. She had a summation gallop rhythm. Shortly after admission, she developed a tachycardia of sudden onset, which was shown on electrocardiogram to be a paroxysmal nodal tachycardia of 200 a minute (Fig. 3). This was halved by carotid sinus pressure. She was taken off digoxin and started on pronethalol 100 mg. three times a day with a subsequent fall in the heart rate to between 100 and 120 a minute. Later that day, her

blood pressure was recorded as 160/120 mm. Hg. The patient died suddenly 6 days after admission, following an episode of peripheral circulatory failure, with a pulse rate of 120 a minute, and an unrecordable blood pressure.

Findings at Necropsy. There was a benign phæochromocytoma of the right adrenal gland. Examination of the heart revealed left ventricular hypertrophy. The coronary arteries were grossly atherosclerotic. Histological examination of the left ventricle showed ischaemic necrosis. A coronary artery included in the section had gross intimal thickening, resulting in partial occlusion of the lumen, but no evidence of recent thrombosis.

FIG. 3.—Case 3. Paroxysmal nodal tachycardia, rate 200 a minute.

DISCUSSION

The well-known clinical picture of paroxysmal hypertension occurring in cases of phæochromocytoma is mainly due to the vasoconstrictor effect of catecholamines on peripheral blood vessels. The central effects of catecholamines on the heart itself are less well recognized, but it seems possible that these are of much greater importance than the peripheral effects in determining prognosis. The patients described in this paper developed several severe cardiac complications, all of which can probably be attributed to the direct effect of catecholamines on cardiac muscle. These complications included ventricular fibrillation in Case 1, paroxysmal supraventricular tachycardia in all (accompanied by hypotension in Case 1 and Case 3), and myocardial damage, observed either clinically or at necropsy in each patient.

Of these cardiac complications, ventricular fibrillation has apparently not been recorded before in a case of phæochromocytoma. On the other hand, there are many reported instances in which the patient has died suddenly and unexpectedly. In a large proportion of these, the mode of death, with sudden onset of acute pulmonary oedema or of generalized epileptic convulsions, is consistent with death from ventricular fibrillation. The undoubted occurrence of ventricular fibrillation in Case 1 can probably be attributed to a high level of circulating catecholamines, since intravenous injection of high doses of these is known to cause ventricular fibrillation in experimental animals. The intravenous injection of digoxin may have played a part in the second episode of ventricular fibrillation, but digitalis is unlikely to have been an important factor in the first episode, since the patient had received no intravenous digitalis at that time, though she was receiving digoxin 0.25 mg. thrice daily by mouth.

All three patients developed a supraventricular tachycardia while under observation. In Cases 1 and 3 this was accompanied by episodes of hypotension. It is reasonable to attribute the hypotension to the supraventricular tachycardia, since any arrhythmia with such a high ventricular rate almost invariably leads to a fall in blood pressure, as a result of inadequate ventricular filling. This clinical picture of shock, or paroxysmal hypotension, has been described in several cases of phæochromocytoma (Evans, 1937; Jelliffe, 1952; Baird and Cohen, 1954; Henry, 1954; Gjøl, Dybkær, and Funder, 1957; Terry, Tobin, and O'Connor, 1958; Horn, 1959; Seward, 1961; French and Campagna, 1961; Richmond, Frazer, and Millar, 1961; Hamrin, 1962, etc.), but it does not appear to have been

described before in association with the cardiogram of paroxysmal tachycardia.

Two of the patients developed cardiographic evidence of diffuse myocardial damage, accompanied by a marked rise in serum transaminase levels. In Case 1, a cardiogram in March 1963 about four hours after the repair of uterine prolapse (Fig. 1A) showed severe widespread myocardial anoxia, with notable S-T depression in standard leads, and in AVF and V2-V6. The T waves were upright in the above leads in this record, but five days later (Fig. 1B) the record showed widespread T wave inversion, in addition to S-T segment depression, maximal in V3-V5, suggesting diffuse myocardial damage in addition to anoxia. In Case 2 also there was evidence of myocardial damage in a tracing taken on the first post-operative day, with widespread T wave inversion in addition to S-T segment depression (Fig. 2A). Similar appearances have been described before in phæochromocytoma by Jelliffe (1952). In addition, myocardial infarction has been described by Wilkins *et al.* (1950), Priest (1952), Boldt, Flexner, and Ortnier (1957), Gjøl *et al.* (1957), Horn (1959), Mattman (1961), Pelkonen and Pitkänen (1963). The myocardial damage in the two patients described here was accompanied by a rise in the transaminase levels. In Case 1 the SGOT rose to 2300 Karmen units per ml., and the SGPT to 2800 Karmen units per ml. In Case 2 the corresponding figures were 112 and 268 units. It might be argued that these results could be attributed to the previous abdominal operations. Serum transaminase levels have been studied after operation by several authors. Normal levels of SGOT were found after operation on repeated measurements in 12 patients who had had abdominal operations, not on the biliary tract, by Nickell and Allbritten (1957), and in 10 patients who had had hysterectomy by Fisk, Thomas, and Maurukas (1958). Ayres and Williard (1960) studied the same enzyme changes in 266 post-operative patients. If biliary tract operations are excluded (49 patients), only 4 patients had a level above 100 units, one of these being a patient with massive hepatic metastases. Only one patient had a level above 200 units, and he had protracted fatal shock. Prolonged hypotension might provide an explanation in Case 2, but the very high levels in Case 1 did not follow any clinically recognizable shock. Necropsy in these three patients showed no macroscopic myocardial damage or infarction. Histological examination of the myocardium in Case 2 showed no abnormality, while in Case 3 there was ischaemic necrosis in the left ventricular wall, accompanied by coronary atheroma, but no evidence of recent thrombosis.

Very few comparisons have been made between the cardiographic appearances in phæochromocytoma and those induced by the intravenous injection of catecholamines. It is well recognized that high levels of both adrenaline and noradrenaline can cause a wide range of cardiac arrhythmias, including ventricular fibrillation. Sjöstrand (1951) described S-T segment and T wave depression, together with a positive after potential (prominent "U" wave) following the T wave, on intravenous infusion of adrenaline in man. Cannon and Sjöstrand (1952) described similar appearances in 7 out of 8 cases of phæochromocytoma, though they could only be clearly seen in 4. Similar S-T segment and T wave changes can be seen in Fig. 1A, 1B, and 2A, and in addition the presence of a positive after potential is very well shown in Fig. 1A. The electrocardiogram of myocardial infarction, described in other cases of phæochromocytoma, may be due to higher levels of circulating adrenaline, since large doses given in error to humans have been followed by S-T elevation and T wave inversion (Nordenfelt, 1941, 1942; McGinty and Baer, 1947) and in some cases by deep Q waves (Mattioli, 1948). S-T segment elevation with T wave inversion has been observed experimentally in animals by Milles and Smith (1937) and by Douglas, Gelfand, and Shookhoff (1937) and in these, histological examination at necropsy has revealed myocarditis (Gruber, Olch, and Blades, 1933). Nahas, Manion, and Brunson (1959) have observed hæmorrhagic myocarditis and severe oedema of the cardiac valves at necropsy in humans following the use of noradrenaline as well as adrenaline, even in therapeutic doses. They produced similar changes experimentally in the intact animal by the infusion of noradrenaline and in the heart-lung preparation by the infusion of both adrenaline and noradrenaline. They also observed similar lesions in a case of phæochromocytoma, as did Rothermich (1952). The diffuse myocardial damage seen in the present two cases and the myocardial infarction seen in other instances of phæochromocytoma, may thus be caused by the action of circulating catecholamines upon heart muscle.

The electrocardiogram in phæochromocytoma is non-specific, but widespread myocardial damage in the absence of chest pain, or in the presence of an otherwise unexplained paroxysmal tachycardia, especially in conjunction with hypertension, should suggest the possibility of a phæochromocytoma. Thus, our Cases 1 and 2 presented with paroxysmal tachycardia. In a known case of phæochromocytoma, cardiography may help to elucidate an unusual feature such as hypotension.

These cardiac complications of phæochromo-

cytoma may be of considerable importance in treatment. The bad prognosis in this malady is emphasized by the fact that all our three patients died. The classical adrenergic blocking drugs, such as phenoxybenzamine and phentolamine, do not effectively antagonize the myocardial responses to catecholamines (Nickerson, 1959). An explanation of this is provided by the proposition of Ahlquist (1948) that there is a dual adrenergic receptor mechanism, vascular effects being due to stimulation of alpha receptors, and cardiac effects due to stimulation of beta receptors. The introduction of specific beta-adrenergic blocking agents, such as pronethalol and propranolol, raises the possibility of preventing these cardiac complications of phæochromocytoma. Pronethalol has been shown to prevent most of the cardiac effects of infused catecholamines in experimental animals (Black and Stephenson, 1962), and in human volunteers (Dornhorst and Robinson, 1962). In Cases 2 and 3 described in this paper, supraventricular tachycardias were quickly controlled by pronethalol. The prophylactic use of beta-adrenergic blocking agents might also be expected to prevent ventricular fibrillation and myocardial damage. Against this, in Case 3 the patient died after being put on a regular maintenance dose of pronethalol. It is possible that she may have already sustained severe myocardial damage. In view of the very bad prognosis of these complications, it is suggested that the diagnosis of phæochromocytoma should be regarded as an urgent indication to start prophylactic maintenance treatment with beta-adrenergic blocking agents, pending surgical removal of the tumour.

SUMMARY

Three patients with phæochromocytoma are described, all of whom developed severe cardiac complications. These complications included paroxysmal supraventricular tachycardia (accompanied by hypotension in two patients), ventricular fibrillation, and diffuse myocardial damage. In two of the patients paroxysmal supraventricular tachycardia responded to treatment with a beta-adrenergic blocking agent. The only finding at necropsy was ischaemic necrosis of the left ventricular wall, in one case, on histological examination.

Cardiac complications may occur much more frequently in this condition than is generally realized. It is suggested ventricular fibrillation may be the cause of sudden unexpected death, and that a very fast paroxysmal tachycardia may be the cause of the paroxysmal hypotension that has been reported. The role of beta-adrenergic blocking agents in this treatment of phæochromocytoma is discussed.

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