ABSTRACT

Phaeochromocytomas are rare neuroendocrine tumours that produce symptoms through excess release of catecholamines. Treatment of choice is elective, complete surgical removal after pretreatment with α-adrenergic blocking drugs, to prevent dangerous haemodynamic fluctuations. In rare cases a ‘catecholamine crisis’ develops presenting with pulmonary oedema and circulatory shock. We report such a case of a patient with familial extra-adrenal phaeochromocytoma who successfully underwent emergency surgery. Pathophysiological mechanisms are discussed. Although pretreatment with α-adrenergic blocking drugs seems advisable in terms of morbidity and mortality, the concept is based on theory rather than clinical evidence. Surgical management of a catecholamine crisis is associated with high mortality rates. However, proof of better outcome by avoidance or discontinuation of emergency surgery is not available. Based on literature and on this case, we conclude that emergency surgery in phaeochromocytoma does not have to be structurally avoided and may be considered under life-threatening circumstances.

INTRODUCTION

Phaeochromocytomas (PCHC) are rare neuroendocrine tumours that arise from paraganglionic cells, either inside or outside the adrenals, and produce symptoms through excess release of catecholamines. Familial PCHC exists in syndromes such as multiple endocrine neoplasia (MEN) type 2A and 2B, Von Hippel Lindau disease (VHL) and type 1 neurofibromatosis (NF1). The term ‘phaeochromocytoma’ refers to the brown (Greek: phaios) colour of the cells that emerges after oxidation of catecholamines with chromium salts. Its use should be restricted to clinically overt tumours, whereas the term ‘paraganglioma’ is used for the tumour independent of the occurrence of disease. The adrenal form of PCHC is considered ‘classical’.1 The clinical picture is that of acute illness, predominantly appearing as paroxysms of headache, sweating, pallor, palpitations, hypertension and anxiety, or a more or less moderate form with sustained hypertension,1,2 representing less than 1% of all causes of hypertension.3 In rare cases its presence is unveiled by the dramatic and sudden onset of a ‘catecholamine crisis’, a medical emergency often leading to death. Under these circumstances the disease presents with signs mimicking an acute abdomen, or severe sepsis with circulatory shock and pulmonary oedema (POD).4-6 Since PCHC is a curable cause of hypertension and a potentially fatal disease, a high level of clinical suspicion is needed to establish early diagnosis. Elective, complete surgical removal is the treatment of choice. It is generally believed that surgery should be preceded by pharmacological control of effects of excessive adrenergic stimulation with α (and β) adrenergic receptor antagonists, as this has shown to be associated with low morbidity and mortality. Surgery in undiagnosed and unprepared severely ill patients, however, is associated with high morbidity and mortality rates and should therefore be avoided.6-7 We report a case of a patient with familial extra-adrenal PCHC, manifesting as acute onset POD and circulatory...
shock, who successfully underwent emergency surgery without pretreatment with α (and β) adrenergic receptor blocking drugs and fully recovered. Pathophysiological background and decision making are discussed.

CASE REPORT

A 31-year-old woman was admitted in an acutely ill condition to our emergency room. Half an hour earlier she had suddenly started to feel weak and vomited several times. As the weakness progressed rapidly, she had decided to seek immediate medical help. On arrival she complained of muscle weakness and vague abdominal pain. Blood pressure was 160/80 mmHg, pulse rate 100 beats/min and regular, and body temperature 36.5°C. In less than five minutes she became dyspnoeic and coughed up small amounts of bloodstained sputum. Blood pressure had dropped to 90/50 mmHg, pulse rate had increased to 130 beats/min and respiratory rate to 36 /min. The skin appeared normal, cardiac examination was unrevealing, but rales were heard throughout all lung fields. Examination of the abdomen was normal. The chest X-ray showed bilateral diffuse infiltration, compatible with oedema. Electrocardiography was normal. Arterial blood gas analysis, drawn while the patient was breathing oxygen at 10 l/min, showed pH 7.24, pCO₂ 40 mmHg, bicarbonate 17 mmol/l, base excess -9.8 mmol/l, pO₂ 67 mmHg and SO₂ 90%. The patient rapidly deteriorated into circulatory shock and respiratory failure and artificial ventilation was started while dopamine was given by vein, almost immediately followed by norepinephrine. At the same time blood cultures were drawn and broad-spectrum antibiotics were given intravenously. Additional history-taking revealed that the patient had been feeling well that morning and that she had been healthy until then, except for episodic vomiting when she was younger. At the time, gastroscopy had turned out to be normal. Erythrocyte sedimentation rate was 35 mm in the first hour, haemoglobin 6.1 mmol/l, white blood cell count 34 x 10⁹/l, differential count 94% neutrophils, platelet count 229 x 10⁹/l, sodium 144 mmol/l, potassium 3.1 mmol/l, creatinine 120 mmol/l, lactate 5.0 mmol/l and glucose 8.3 mmol/l. A specimen of urine tested for hCG was negative. Abdominal ultrasound revealed a round mass, 6 cm, retroperitoneally, caudally of the left kidney and another one, 4 cm, located ventrally of the sacrum. No abnormalities were detected in the adrenal glands, in the liver, nor in other abdominal organs. As an abdominal emergency was suspected, we decided to proceed to laparotomy. During the operation two tumours were found on the locations described above, but haemorrhage and/or rupture was absent. Both tumours were removed. During removal blood pressure remained low despite administration of high doses of dopamine and norepinephrine. Postoperatively oxygenation remained difficult. The patient needed high positive end-expiratory pressure (PEEP) up to 20 cm H₂O in a prone position. Nevertheless, her condition ameliorated very quickly and she spent a total of only three days on the intensive care unit. After discharge her blood pressure remained normal. She told us she had endured attacks of palpitations, nausea and vomiting that had begun when she was about thirteen years of age. They occurred during periods of exertional activity and usually faded when this was stopped. Subsequently, she systematically avoided situations that would precipitate such an attack. Histological examination of the specimens showed appearances typical of PCHC. There were no signs of haemorrhage or necrosis. In the blood sample drawn on arrival to the emergency room, before vasopressors were given, serum epinephrine and norepinephrine concentrations both exceeded the upper detection level of 10 nmol/l (normal <1.0) and 200 nmol/l (normal <10), respectively. Cultures of blood remained negative. Our patient left the hospital in good condition one week after the onset of her dramatic symptoms. There was no need for antihypertensive treatment. ¹³¹I-metaiodobenzyl guanidine (MIBG) scintigraphy showed no pathological accumulations of the tracer.

DISCUSSION

Although most clinicians recognise the classic symptoms of PCHC consisting of paroxysms of headache, palpitations, pallor, anxiety and hypertension, diagnosis appears to be far more difficult when less commonly encountered symptoms, such as nausea, abdominal discomfort, weakness and visual impairment occur. This is not surprising as the prevalence of the disease in the community is very low and its incidence is estimated between 1 to 8 per million.¹³,⁸,⁹ Unfamiliarity with the wide variety of symptoms can prove fatal when the tumour masquerades under the guise of POD or circulatory shock. Our patient’s illness presented dramatically so, initially without a history of the above-mentioned classical symptoms. The first step was to look for clinical disorders.
associated with the adult respiratory distress syndrome (ARDS), which can be defined by the occurrence of bilateral fluffy infiltrates on chest X-ray, severe hypoxaemia unresponsive to low-flow oxygen and a normal pulmonary capillary wedge pressure (PCWP). Sepsis was considered first, being the most common cause of ARDS. Although clinical features fitted this presumption, the acute onset and short course of the illness without appearance of petechiae, such as can be found in the Waterhouse-Friderichsen syndrome, and the lack of an immune-compromised medical history, made us doubt this. Secondly, rupture of an aortic aneurysm could be ruled out ultrasonographically. Finally, the question was raised whether the patient was suffering from an abdominal emergency: urine testing ruled out extra-uterine gravidity but both abdominal ultrasonography and CT scanning revealed two abdominal masses without signs of haemorrhage. These findings, combined with the history-taking of the patient’s sister, made us think of extra-adrenal PCHC as a possible cause. Our patient, who had developed acute POD and circulatory shock that had proceeded to cardiac arrest, was now depending on mechanical ventilation with PEEP and increasing doses of cardiotonic medication. Even though PCHC was already suspected at that time, we could not exclude the possibility of the patient harbouring an ischaemic or bleeding tumour of a different origin. Therefore, explorative laparotomy was performed. Two extraperitoneal tumours were found without signs of haemorrhage or rupture into the abdominal cavity. Nevertheless, it was agreed that both tumours, which had been clearly visualised by CT, should be removed given their surgical accessibility and, more importantly, given that it was too dangerous to supply drugs that could possibly lower the patient’s blood pressure further, while the diagnosis PCHC had not yet been made. No further problems were met during surgery. The postoperative period was difficult for a short period. POD and cardiovascular collapse have been reported as the sole manifestation of PCHC in naive patients, as well as in patients with established diagnosis. The pathophysiological background of POD and circulatory shock arising from catecholamine release is a debatable subject. It has been well recognised that high catecholamine levels can cause focal myocarditis in both humans and experimental animals. Foci of cellular necrosis that become fibrotic after prolonged exposure have been found on several occasions during autopsy. Cardiomyopathy, either dilated or hypertrophic, is also known to occur and downregulation of β-receptors and a net reduction of viable myofibrils have been proposed as causal factors. Although decreased myocardial function has been reported, its clinical significance should be doubted as some studies lack information about pulmonary capillary wedge pressure (PCWP) and some reports indicate that POD can exist without co-existing increased PCWP, thus suggesting a noncardiogenic origin. These observations are confirmed by a report of a patient with POD and normal left ventricular function. Interestingly, a parallel phenomenon has been described for neurogenic pulmonary oedema (NPO). As in PCHC-related POD, massive catecholamine release takes place immediately after brain injury. Strong evidence for the onset of an intense, generalised, but transient vasoconstriction leading to a shift of blood from high-resistance systemic circulation to low-resistance pulmonary circulation, preceded by an only momentarily depressed cardiac function, has been provided by several studies. Nevertheless, increases in left atrial and left ventricular end-diastolic pressure seem to be attributable to the augmented cardiac work rather than on intrinsic alterations in cardiac function. As massive infusion of epinephrine in dogs produced a pattern of haemodynamic response indistinguishable from that associated with NPO, it seems likely that indeed NPO and POD share a primarily noncardiogenic origin. As we have no data on our patient’s cardiac function during her catecholamine crisis, we can not deliver clinical evidence to support this. Fatal and near fatal periods of (transient) hypotension, with or without POD, have been observed in different situations, sometimes preceded by a hypertensive episode. Major discrepancy is known to exist between the largely increased blood pressure as measured in the aorta and the sometimes immeasurably low blood pressure as measured intra-arterially in the radial artery or with a sphygmomanometer. This observation reflects the extreme peripheral vasoconstriction mentioned above. In addition, plasma volume in patients with PCHC appears to be significantly reduced as a result of prolonged high levels of catecholamines and therefore prompt intravascular filling is needed in case of hypotension. Basically, three major problems threaten the PCHC patient when confronted with anaesthesia and surgery: uncontrolled hypertension, hypotension and arrhythmia. Anaesthesia and surgery seem to be precipitating factors. Various anaesthetic agents, especially those with sympathicomimetic properties, can interfere with high circulating concentrations of catecholamines. Although halothane suppresses catecholamine release, it may sensitise the myocardium to the effects of catecholamines, promoting arrhythmia. Suxamethonium may stimulate the sympathetic ganglion and involuntary fasciculations may squeeze the tumour. Peritoneal insufflation of air and tumour manipulation during (laparoscopic) surgery can evoke release of catecholamines, thus promoting a crisis. Hypertensive crises during surgery can be controlled by the
use of phentolamine, a short-acting nonselective \( \alpha \)-blocking drug. Based on the afore mentioned about extreme peripheral vasoconstriction during a catecholamine crisis, it seems very likely that this condition can be treated with the same agent.\(^3\) However, no clinical reports emphasising this could be found. Naturally, a balanced choice of anaesthetics and employment of an experienced surgeon minimises the chance of calamity.

In patients with an established diagnosis, preoperative preparation with \( \alpha \)-adrenergic receptor blocking agents is widely accepted as the foundation for successful surgical treatment, as it is believed to minimise morbidity and mortality due to sudden haemodynamic changes. The concept of pretreatment has been developed since 1965, when the anaesthetic management of 92 surgical patients with PCHC was reviewed.\(^3\) Several retrospective studies have been published since then, emphasising the structural need for preoperative pharmacological treatment.\(^6\) Perry and co-workers, who reviewed another 33 patients in 1972, based their conclusions on the occurrence of less hypotension during surgery in pretreated patients, although this did not result in administration of significantly more vaspressors and fluids, nor in increased mortality in non-pretreated patients. However, several other studies failed to demonstrate the advantage of pretreatment.\(^3\) Scott and colleagues, who had already reviewed the cases of 27 patients with PCHC in 1965, found their surgical outcomes to be largely dependent on prompt recognition of symptoms and good-planning of operative removal. Pretreatment with \( \alpha \)-blockade was not used in any of the cases.\(^3\) Deoreo and associates postulated that preoperative adrenergic blockade is neither advantageous nor necessary as they described their experience with 46 non-pretreated patients operated on between 1952 and 1973.\(^3\) More recently, Boutros et al. and Uchaker et al. reviewed the surgical outcome of 63 and 127 cases, respectively. They found that using no preoperative medication was as effective as using \( \alpha \)-blockade and explained their findings by suggesting that recent advances in anaesthetic and monitoring techniques, along with the use of faster-acting vasoactive agents, have improved the management of sudden changes in intraoperative haemodynamics.\(^4\) It may, however, be important to realise that to date, the concept of \( \alpha \)-adrenergic blocking drugs has a theoretical basis rather than one founded on clinical evidence, since prospective controlled studies of large groups of PCHC patients are lacking.

A definitive statement regarding management of a so-called catecholamine crisis, without or with POD and circulatory shock, as in our patient, is even more difficult to make. Several reviews that involve autopsy-proven cases of patients with PCHC emphasise the hazardous and lethal course of unrecognised and untreated PCHC. St. John Sutton and co-workers described 54 autopsy-proven cases of clinically unsuspected PCHC and found that 27% of them had died from hypertensive or hypotensive crises precipitated by, or occurring during, minor operations for unrelated pathology.\(^3\) Scott et al. reported 27 cases, 16 of which, clinically diagnosed as having PCHC, were successfully operated. From the remaining 11 cases harbouring clinically unsuspected PCHC, four operations were eventually fatal and were thought to be directly related to the tumour.\(^3\) Platts et al. did a survey of 62 PCHC related deaths and found that 16 patients died from anaesthesia and surgery (table 1).\(^4\) In addition, a number of case reports have demonstrated surgery in unsuspected PCHC to be a situation associated with high mortality.\(^4\) Consequently, it is generally believed that surgery should be discontinued whenever PCHC is suspected and that emergency resection is never indicated. It seems, however, important to underline that fatalities tended to occur in unsuspected PCHC and that some studies were only concerned with patients who had died and had had a complete autopsy. Nevertheless, nine cases of emergency resection in non-pretreated patients with a good outcome have been described, six of which are outlined in table 2.

### Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Number of Cases</th>
<th>Period</th>
<th>Number of Deaths During Surgery in Unrecognised PCHC (N = Operations)</th>
<th>Number of Deaths During Surgery in Recognised PCHC (N = Operations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John Sutton et al., 1981(^8)</td>
<td>Retrospective; autopsy proven PCHC/paraganglioma</td>
<td>54</td>
<td>1928-1977</td>
<td>6 (11)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Scott et al., 1965(^3)</td>
<td>Retrospective; cases of PCHC/paraganglioma</td>
<td>27</td>
<td>1950-1975</td>
<td>4 (4)</td>
<td>0 (16)</td>
</tr>
<tr>
<td>Platts et al., 1995(^4)</td>
<td>Retrospective; deaths with PCHC/paraganglioma</td>
<td>62</td>
<td>1981-1989</td>
<td>9 (9)</td>
<td>7 (46)</td>
</tr>
</tbody>
</table>
Table 2
Overview of case reports of successful emergency surgery in preoperatively undiagnosed PCHC (in the first three cases PCHC was unexpected)

<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>CASE</th>
<th>SIGNS AND SYMPTOMS</th>
<th>MEDICATION DURING SURGERY</th>
<th>FINDINGS DURING OPERATION</th>
<th>OUTCOME</th>
<th>HISTOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huston JR, et al., 1965[^1]</td>
<td>Woman, 20 years</td>
<td>Sudden onset pain</td>
<td>Levateronol tartrate, plasma saline</td>
<td>No increase in blood pressure while removing the tumour</td>
<td>Direct postoperative dependency on levateronol tartrate, phenylephrine</td>
<td>PCHC of left adrenal gland, major part advanced necrosis</td>
</tr>
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<td></td>
<td>Previously asymptomatic mentally retarded, resident of a mental institution</td>
<td>Shock, blood pressure 60/40 mmHg, pulse 160 bpm, cold and clammy skin, paralytic ileus</td>
<td>Direct postoperative</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>White blood cell count 23 10^9/l</td>
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<tr>
<td>Greaves DJ, et al., 1989[^7]</td>
<td>Man, 22 years</td>
<td>Acute collapse, blood pressure 110/60 mmHg, pulse 130 bpm, pale sweaty back</td>
<td>Ketamine, suxamethonium, vecuronium, 50% nitrous oxide in oxygen and diamorphine</td>
<td>Normal duodenum and pancreas Vascular tumour 10 cm diameter over bifurcation of the aorta, suspected to be an extra-adrenal PCHC</td>
<td>Immediately after resection drop in blood pressure, adrenaline and isoprenaline</td>
<td>Extra medullary PCHC of the organ of Zuckerkandl</td>
</tr>
<tr>
<td></td>
<td>Abdominal trauma</td>
<td>Pale sweaty back</td>
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<tr>
<td></td>
<td></td>
<td>Amylase elevated</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>After five hours ARDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>May EE, et al., 2000[^6]</td>
<td>Woman, 34 years</td>
<td>Eight pregnancies and six deliveries, hypertension during last pregnancy Fall on ice with sudden onset right flank pain and upper quadrant of abdomen</td>
<td>Nitroprusside and esmolol initially Not otherwise specified</td>
<td>Retroperitoneal haematoma right with a soft necrotic right adrenal mass 6 cm diameter</td>
<td>Inotropic medication for nine days Uncomplicated pulmonary course after ARDS, three days mechanical ventilation Ejection fraction 70% Lengthy convalescence time</td>
<td>Oedematous, haemorrhagic, partly necrotic PCHC of the right adrenal gland</td>
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<tr>
<td></td>
<td></td>
<td>Blood pressure 190/110 mmHg, pulse 62 bpm</td>
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<tr>
<td></td>
<td></td>
<td>Then sudden fall in systolic pressure max. 60 mmHg, pain CT and angiography: right pararenal haematoma, active bleeding, coil embolised, hypertension and tachycardia</td>
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<td></td>
<td></td>
<td>Clinical diagnosis of PCHC ARDS</td>
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<tr>
<td>Newell KA, et al., 1988[^3]</td>
<td>Woman, 62 years</td>
<td>Poorly controlled hypertension, diabetes mellitus, congestive heart failure, intermittent headache and backache Presentation with syncope, blood pressure 285/140 mmHg, fluctuating nadir 60/0 mmHg. PCHC suspected and confirmed</td>
<td>Deterioration with MOF, DIC, high fever, β-blocking agents, inotropics and broad-spectrum antibiotics</td>
<td>Broad spectrum antibiotics Supportive care with inotropic medication</td>
<td>Protracted postoperative course. Restoration of organ function but remaining quadriplegia and dysarthria</td>
<td>PCHC of right adrenal gland with foci of recent tumour necrosis</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Broad spectrum antibiotics</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Supportive care with inotropic medication</td>
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</tbody>
</table>
The three remaining cases (and abstracts) are written in Russian and French and are therefore not included. In two of the outlined cases PCHC was not suspected until surgery.45-49 Apparently, emergency surgery in PCHC can be successful. Based on the afore-mentioned cases and on our own case, it seems to us that it would be more rational to suppose that the optimal surgical approach for clinically suspected PCHC in emergency situations should be tailored to the circumstances. Under life-threatening conditions due to a PCHC catecholamine crisis, when stabilisation of the patient followed by pretreatment with β-blocking drugs does not seem to be a realistic option, emergency resection of the tumour(s) should not have to be structurally avoided. Early recognition of the hazards of PCHC is of major importance in this respect and, naturally, complete resection has to be achieved. Preoperative localisation of the tumour(s) by CT or MRI is therefore indispensable. Both CT scanning and magnetic resonance imaging (MRI) are highly sensitive (98 to 100%). Specificity depends on inclusion of patients with previous biochemically confirmed PCHC and has recently been reported as high as 98.4%. With T2-weighted MRI intensity of adrenal PCHC enhances, in contrast to liver tissue. It may also be superior to CT scanning in demonstrating primary extra-adrenal and metastatic tumours.50 Naturally, the positive predictive value will depend on the level of suspicion.

In conclusion, PCHC can produce life-threatening symptoms such as acute POD and circulatory shock, which may not be recognised as such. As in NPO, POD seems to emerge after a sudden fluid shift to the pulmonary vasculature and appears to have a primarily noncardiogenic origin. Treatment of choice is elective, complete surgical removal. Preoperative treatment with β-blocking agents – and in cases of arrhythmia with α-blocking agents – seems advisable in terms of morbidity and mortality, but we have to realise that the concept has a theoretical basis rather than one founded on clinical evidence. Emergency surgery in patients with life-threatening symptoms is generally dissuaded. Although it is certainly not without danger, it has proved to be successful in several cases and our case can be added to that category. The final outcome is probably also influenced by the level of clinical suspicion and by the anaesthetic and surgical technique used. Based on literature and on our own experience, we feel that emergency tumour resection in PCHC does not have to be structurally avoided and may be considered under certain circumstances.

Newell KA, et al.48 50 year hypertension, lactic phentolamin, adrenal gland quickly, in right-sided adrenal (article in German) 18 months, blood pressure octreotide, tumour histological adrenal gland

Lamberts R, Woman, et al.49 66 years headache, diarrhoea, adrenaline, disturbances while weakness, haemorrhagic (article in German) 18 months, blood pressure octreotide, tumour histological adrenal gland

ARDS = adult respiratory distress syndrome, DIC = disseminated intravascular coagulation, MOF = multiple organ failure, PCHC = phaeochromocytoma.
ACKNOWLEDGEMENTS

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REFERENCES