

Original Article

Management of Pheochromocytoma: Report on 30 Cases

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ABSTRACT

Objective: To review the experience of the authors over the last 25 years in the management of pheochromocytoma.

Design: Retrospective and prospective study.

Setting: Teaching hospital.

Subjects: Thirty patients who presented with pheochromocytoma from 1974 to 2000.

Intervention: Surgical removal of the tumor.

Main outcome measures: Mortality, morbidity and recurrence.

Results: A total of 30 patients (24 females and 6 males) aged between 18-68 years were managed in our department. Of these, 26 patients had sporadic tumors,

one had MEN type II syndrome but without familial history, 29 patients (96,6%) presented with hypertension. Only one female patient presented with an incidentaloma. The diagnoses were confirmed biochemically in 25 patients. Tumor localization was done by CT scan (n=27), and ultrasonography (n=3). Scintigraphy was used for 6 patients. All but one patient had their tumors resected (n=29). Complications developed in 16,6% of the patients. There were no intra-operative or post-operative deaths.

Conclusion: Surgery for excision of pheochromocytoma is safe. Optimum results can be achieved with a multidisciplinary approach.

KEYWORDS: adrenal medulla, adrenalectomy, extra-adrenal phaeochromocytoma, hypertension, incidentaloma, pheochromocytoma.

INTRODUCTION

Pheochromocytoma is a catecholamine-producing tumor of neuroectodermal origin that is made up of chromaffin cells. Poll coined the term pheochromocytoma in 1905 when he described the dusky (Pheo) color (Chromo) of the cut surface of the tumor when exposed to dichromate^[1,2]. An overwhelming 90% of all cases arise from adrenal medulla where the biggest collection of chromaffin cells is found. Extra-adrenal pheochromocytoma (also called paragangliomas) is usually encountered intra-abdominally along the sympathetic chains or from the organs of Zuckerkandl^[3]. Intra-thoracic pheochromocytoma (<1%) is also related to the sympathetic chain^[1]. Other extra-adrenal sites are intrapericardial^[4,5], inter-atrial septum^[6], prostate^[7] and urinary bladder. Extra-adrenal pheochromocytoma can be the cause of high blood pressure in about 0.1-1% of all patients with hypertension^[8]. The first clinical description of the pheochromocytoma was by F. Frankel in 1886^[9,10] when a young female patient with a history of episodic attacks of headaches, palpitations and anxiety died suddenly. Post-mortem examination showed bilateral adrenal medulla tumors. The first

surgical excision of the pheochromocytoma was reported in 1927 by Roux^[10] who described removal of a suprarenal tumor in a patient with a two-year history of episodic vertigo and nausea. This feat was soon reported in USA by Mayo^[11]. The clinical syndrome is due to excess catecholamine secretion in a paroxysmal fashion. The most common symptoms are pounding severe headache, palpitations and inappropriate excessive perspiration. Other symptoms include anxiety, tremor, pallor, abdominal pain and weight loss. Hypertension is a common finding in these patients. In up to 50% of cases, the hypertension and symptoms are paroxysmal, with or without normotensive symptom-free intervals between attacks^[12,13]. Familial pheochromocytoma in association with medullary carcinoma of the thyroid and parathyroid gland hyperplasia or adenoma have been designated multiple endocrine neoplasia syndrome type II A (MEN IIA or Sipple's syndrome). MEN type IIB or III is the coexistence of pheochromocytoma and medullary thyroid carcinoma with gastrointestinal ganglioneuromatosis (benign mucosal neuromas in lips, tongue, buccal cavity), benign mucosal neuromas in eye lids conjunctiva and cornea, and marfanoid features^[14].

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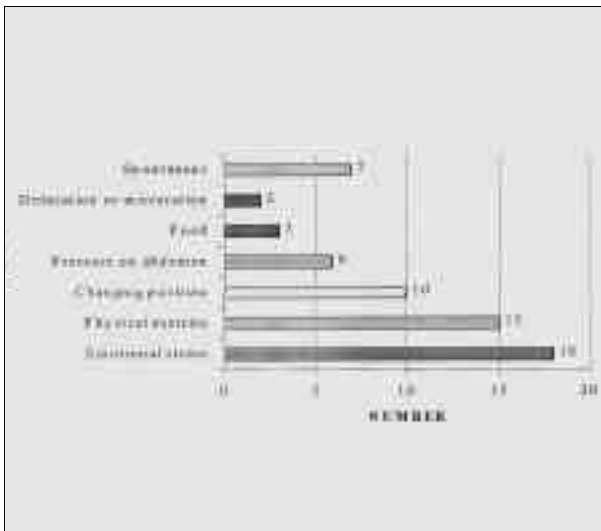


Fig. 1: Factors inducing paroxysms in 30 patients with pheochromocytoma

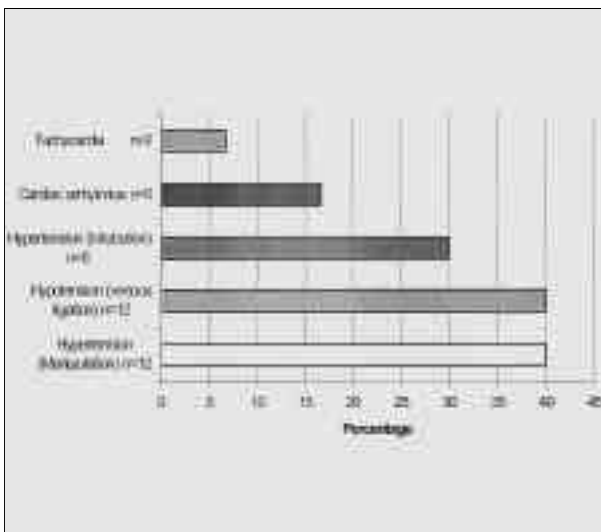


Fig. 2: Intra-operative changes during anesthesia of pheochromocytoma patients (n=30) operated between 1974-2000

Pheochromocytoma is also recorded as a first manifestation of von-Hippel-Lindau disease, an autosomal dominant disorder characterized by the development of hemangioblastomas in the cerebellum, spinal cord and retina, renal cell carcinoma and cysts, pancreatic cysts and pheochromocytoma^[15]. There is an increased prevalence of pheochromocytoma among patients with von-Recklinghausen's neuro-fibromatosis^[11,16,17]. A better understanding of the pathophysiology of this disease would result in an improvement in the outcome^[18]. Advances have also been made in the preoperative radiological and biochemical evaluation to localize these tumors.

We report a series of 30 patients with pheochromocytoma managed in the Third Chair and Department of Surgery, Karol Marcinkowski University School of Medicine in Poznań- Poland during the period from 1974 to 2000.



Fig. 3: CT scan of a large right side adrenal pheochromocytoma



Fig. 4: MRI showing a right adrenal pheochromocytoma (One year earlier the patient had a left radical nephrectomy due to a left adrenal malignant pheochromocytoma)

PATIENTS AND METHODS

Clinical features:

A total of 30 patients were referred to the authors' department for surgical management of pheochromocytoma. The group included 6 males and 24 females aged between 18-68 years with a mean age at diagnosis of 41 years. The mean duration of symptoms before the diagnosis was 30 months.

The classical triad of headaches, palpitations and diaphoresis was seen in 66% of patients (n=20). The main presenting symptoms are shown in Table 1. During paroxysms, the main symptoms were palpitations (n=24), headaches (n=24) and sweating (n=20).

Tumor localization tests:

CT scan localized the tumor in 27 patients (Fig. 3). MIBG was used in 6 patients to localize the tumor and MRI in 3 patients (Fig. 4).

Table 1

Clinical presenting features and their reporting frequencies in 30 patients with pheochromocytoma

Clinical Feature	No
Paroxysmal hypertension	26
Headache	26
Sweating	20
Palpitation	24
Sustained hypertension	22
Fatigue	16
Pallor	14
Tremor	10
Vomiting	9
Flushing	9
Abdominal pain	9
Anxiety	8
Nausea	6
Weight loss	4
Syncope	4
Angina pectoris	3
Myocardial infarction	2

Table 2

Immediate post-operative complications in a group of 30 patients operated for pheochromocytoma

Complications	No. of Patients
Pneumonia	1
Wound infection	1
Pneumonia and wound infection	1
Hemorrhage required re-operation	2
Pneumothorax	1
Total	5

Laboratory investigations:

Vanilylmandelic acid (VMA) levels in 24-hour urine collection were measured in all patients. The levels were elevated in 25 cases (sensitivity = 83%). It was normal in incidentaloma. Basal recumbent plasma catecholamines were measured in 12 patients. All showed elevated noradrenaline; 2 had elevated adrenaline and only one had elevated dopamine.

Preoperative preparation:

We started the pre-operative receptor blockade with phenoxybenzamine in increasing divided doses, from 5 to 80 mg per day between 10 to 20 days to achieve good blood pressure control. In four patients, propranolol (20-50 mg/day) had to be added for 3-5 days before the operation because of tachycardia. Recently, we began giving phenoxybenzamine on the morning of operation. The mean blood pressure on induction of anesthesia was 138/86mmHg.

Expansion of blood volume with intravenous fluids before the operation and generous replacement of blood lost during operation time greatly reduced postoperative hypotension.

RESULTS

Of the 29 patients with hypertension, 26 patients (86%) had intermittent rises in blood pressure. Fig. 1 shows the provocation factors, which induced the hypertensive paroxysms in 30 patients. In this series, one young male patient was diagnosed preoperatively in another hospital as renal tumor. An operation was planned. During induction of anesthesia, an episode of hypertensive crisis was recorded (up to 300/200mmHg). The operation was postponed and the patient was re-investigated and re-operated later. In three women, two of them being siblings, the symptoms started during early pregnancy. A total of four members of their family were operated for pheochromocytoma, and a fifth for Addison's disease. Both of these ladies were fully diagnosed and operated after delivery. The third pregnant lady was operated during the second trimester and went on to deliver safely at full term.

There was one female patient with incidentaloma, proved to be MEN type IIB. She was operated for pheochromocytoma and thyroid medullary carcinoma on separate occasions. There were four familial cases (13%) and none of them had MEN syndrome. MEN was excluded in those patients by measuring serum and urinary calcium levels, serum levels of PTH, serum phosphate and calcitonin. This was followed by thyroid and parathyroid USG, technetium scanning of parathyroid gland and fine needle aspiration cytology of thyroid. One patient suffered a cerebrovascular accident (CVA) before pheochromocytoma was diagnosed.

Anesthesia and intra-operative management:

The mean blood pressure just before anesthesia was 138/86 mmHg. Nine patients (30%) had raised blood pressure at intubation (blood pressure greater than 168/102mmHg). Episode of raised blood pressure (up to 200/120 mmHg) was noted during tumor manipulation and was seen in 12 patients (40%). The intra-operative rise of blood pressure was controlled by intravenous infusion of phentolamine (alpha-adrenergic blocker) in all cases, except in two, where sodium nitroprusside was used. Five cases (16.6%) had cardiac arrhythmia for which lidocaine was needed. In two cases, propranolol used to control tachycardia (Fig. 3).

A fall in blood pressure (mean 60/40 mmHg), mainly after suprarenal vein ligation, was noticed in 12 patients (40%). Intravenous fluids (Ringer's lactate or Dextran) and blood replacement were used aggressively in anticipation of the hypotension and potential vasodilatation that developed during tumor removal. Inotropic agents as adrenaline, phenylephrine and dopamine were used in hypotension, either during or after operation.

Operative management:

Laparotomy was performed in all cases. Only one tumor was un-resectable. The surgical approach was carried out through a flank incision in 18 cases, bilateral subcostal incision in 4 cases, unilateral subcostal incision in one case, midline incision in one case and paramedian incision in 6 cases. Total unilateral adrenalectomy was performed for intra-adrenal pheochromocytoma in 21 cases, total bilateral adrenalectomy in 4, tumor excision with partial adrenalectomy in 4 and tumor debulking in one inoperable tumor. Additional surgical procedures were performed in seven patients after resection of their pheochromocytoma. Bilateral adrenal tumors were found in three patients (10%). The tumor size ranged from 1 to 15 cm.

DISCUSSION

Hypertension of a sustained or paroxysmal nature remains the most consistent manifestation in pheochromocytoma^[8,19-22]. Pheochromocytoma should be considered in young hypertensive patients, diabetic patients with hypertension and patients with hypertensive crisis during labor or anesthesia. One of the most important factors in pheochromocytoma identification is the clinical suspicion. Some cases were detected on the basis of family screening or discovered incidentally during investigation for other complaints. Leading features that directed the physician towards pheochromocytoma were hypertension labile or stable, paroxysms of headache, sweating, palpitation, anxiety, chest pain or abdominal pain. In this study, the most useful diagnostic test was the detection of high levels of catecholamine metabolites in 24-hour urine collection^[10,23].

Tumor localization is essential before surgery. Both U/S and CT-scan were shown to be accurate in localizing the tumor^[24,25]. MRI is more expensive but if available would accurately locate the tumor^[26,27]. MIBG-scan is valuable only if there is a relative increase in the uptake and sequestration of the radiolabelled guanethidine analogue by chromaffin cells inside the tumour. It may be used in the detection of bilateral or extra-adrenal pheochromocytoma before surgery. Some drugs such as labetalol, sympathomimetics and tricyclic antidepressants, interfere with MIBG uptake^[17]. During the period of investigations, hypertension control by calcium-channel blockers is advised because it may prolong the radionuclide half-life^[17].

The preoperative control of hypertension by phenoxybenzamine, a non-competitive alpha-1 antagonist given in carefully titrated and increasing doses, was our choice. The mean dose of phenoxybenzamine required to achieve adequate control of blood pressure in 80% of our patients was

25mg/day for about 15 to 18 days. In 4 patients, propranolol, in addition to phenoxybenzamine, was used to control tachycardia and hypertension. The continued use of alpha-blockers up to the pre-medication time is vital to avoid severe rise in blood pressure during induction of anesthesia. The surgical approach may be transperitoneal (through midline, paramedian or subcostal incision) or extraperitoneal through posterolateral incision. The transperitoneal approach permitted intraoperative assessment of the opposite adrenal gland, examination of potential sites of paragangliomas and liver examination for metastases. Another advantage is that other intra-abdominal pathology such as cholelithiasis, can be dealt with^[28]. The careful preoperative tumor localization and reliable information about the stage of the disease, allowed us to use the posterolateral extraperitoneal approach across the 12th rib after its excision.

By this approach, the post-operative convalescence is improved, and there is less pain and greater comfort in respiration. This approach has a lower incidence of post-operative ileus^[13]. There is a risk of hypertensive crisis during surgical manipulation of tumor due to excessive catecholamine release. Severe hypotension can occur immediately after suprarenal vein ligation. The preoperative preparation with alpha adrenergic blockers, adequate intravenous volume repletion, and careful intra-operative cardiovascular monitoring can decrease the surgical morbidity as noted previously^[29,30]. Laparoscopic adrenalectomy is emerging as a safe method for tumor removal^[31]. A total of five of our patients had serious post-operative morbidity (Table 2). The morbidity in current literature ranges from 8.7 to 27%^[8,32,33]. The only mortality in this series was a patient who died due to recurrence of malignant pheochromocytoma in the opposite side 24 months after the surgery. Undiagnosed pheochromocytoma is associated with 0.02-2% of operative or post-operative complications which can lead to death^[35]. In cases of inoperable malignant pheochromocytoma, medical treatment is advised to control the symptoms.

Few malignant pheochromocytomas are radio-sensitive. Radioactive ¹³¹I-MIBG is used for metastatic pheochromocytoma. In more than 70-90% of the patients, the blood pressure came back to normal after surgery^[17,31,36]. Our long-term follow-up data indicates that 25 patients were free of symptoms whereas 4 patients still required anti-hypertensive medication for persistent stable hypertension. Their urinary 24-hour VMA levels were all within the normal range. Biochemical and radiological assessment did not detect recurrent

pheochromocytoma and all remain under regular follow-up. Pheochromocytoma continues to be an interesting and challenging neuroendocrine neoplasm for the physician, radiologist, anesthetist, and the surgeon.

CONCLUSION

Surgery for pheochromocytoma is safe provided that pre-operative localization is successful and that adequate pre-operative preparation is made.

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