Clinicopathological Analysis of Pheochromocytoma: A Retrospective Study

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Abstract

Pheochromocytoma is a rare tumor of chromaffin tissues most commonly arising from the adrenal medulla. We retrospectively reviewed the records of 34 patients with pheochromocytoma who underwent surgical treatment between 1971 and 2006. Fourteen patients (41.2%) were females and twenty (58.8%) were males. The most frequent symptoms were Hypertension (97%) and palpitation (38.2%). Seven patients had an extra-adrenal tumor and in one patients the tumor occurred in the urinary bladder. Nine patients (26.5%) had persistent hypertension, 11 patients (32.4%) had paroxysmal hypertension and 13 patients (38.2%) had persistent with paroxysms. The 24-h urinary total metanephrines and vanillylmandelic acid (VMA) were the most sensitive biochemical tests for the diagnosis of pheochromocytoma. One of our patients was found to be associated with hereditary pheochromocytoma syndrome. All hypertensive patients were preoperatively treated with phenoxybenzamine and propranolol. All underwent explorative laparotomy and adrenelectomy. All patients were followed up with 24-h urinary VMA levels and CT scan of abdomen regularly.

Introduction

Pheochromocytomas are most commonly tumours of adrenal medullary origin and are a rare catecholamine-producing tumor of neuroectodermal origin arising from chromaffin cells. Incidence is around 1 to 2 per million population. 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). Pheochromocytoma by definition produces and secretes catecholamines. Similar tumours that do not secrete active substances of any kind are called non functioning paragangliomas. The hallmark clinical manifestation of pheochromocytoma is hypertension accompanied with various signs and symptoms in excess of catecholamines or other bioactive substances. The early diagnosis of pheochromocytoma is important not only because it offers the possibility of curing hypertension but also because unrecognised pheochromocytoma is a potentially lethal condition. The aim of this article is to analyse the clinical finding, diagnostical values of the laboratory tests and possibilities of morphological localizing techniques in a series of 34 patients with surgically proven pheochromocytoma.

Pheochromocytoma is 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. Other extra-adrenal sites are intrapericardial (4.5) inter-atrial septum (6), prostate(7) and urinary bladder.

The first clinical description of pheochromocytoma was by F. Frankel in 1886 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 who described removal of a suprarenal tumor in a patient with a two-year history of episodic vertigo and nausea(8,9).

Familial pheochromocytoma in association with medullary carcinoma of the thyroid and parathyroid gland hyperplasia or adenoma have been designated as multiple endocrine neoplasia syndrome type II A (MEN IIA or Sipple's syndrome) .MEN type IIB 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 conjuctiva and cornea, and marfanoid features. 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. There is also an increased prevalence of pheochromocytoma among patients with von-Recklinghausen's disease (10).

Pheochromocytomas account for 0.1% of all patients with hypertension and can present with a highly variable clinical picture. These two characteristics
(rarity and variability) render these tumors very difficult to diagnose so that many of them are discovered incidentally during radiological examinations (especially of the abdomen) or at autopsy.

Materials and Methods

This is a retrospective study of all patients diagnosed to have pheochromocytoma from 1971 to 2007. Medical records were used for collecting data including demographic data, clinical symptoms, familial disease, pre- or post-operative urinary concentrations of VMA, localization procedures, preoperative pharmacological treatment, surgical findings, operative and histopathological reports and follow up status were recorded and analyzed. Inpatient records were used for collecting data of the immediate postoperative period (until discharge or 40 days – whichever is later) and the outpatient records for additional information including follow up. The median period of follow up is two years.

Discussion

The present study showed wide variability in symptoms as compared to other studies (11,12). The presence of a paroxysmal event which, although aspecific, has always been considered as a hallmark, has been reported in 11 out of 34 patients in our study. In contrast to other studies (13), the most frequent symptoms were abdominal pain and hypertension while frequency of other symptoms was rather low. Therefore, in view of the very low sensitivity of any symptom or of any association of them, the clinical suspicion is often extremely difficult. This difficulty can explain the long mean time lag between initial symptoms and diagnosis and why, quite often, pheochromocytoma is discovered as an incidental adrenal mass or at autopsy. Therefore, the most frequent reason for suspecting pheochromocytoma is hypertension, especially if paroxysmal or resistant, especially if accompanied by an adrenal mass.

One of our patients was associated with the familial form of pheochromocytoma. Though one of our patients were incidentally discovered, data from previous studies confirm that pheochromocytomas have to be taken into account in the differential diagnosis of adrenal incidentalomas and that the absence of hypertension does not rule out the presence of a pheochromocytoma (14).

The biochemical method used for the diagnosis of pheochromocytoma in our study was 24-h urinary VMA levels. This finding is in agreement with the data reported in the literature,(15,16,17) but use of more sensitive assays such as urinary and plasma free metanephrines should be considered for better sensitivity and specificity. Results indicate similarly high sensitivity of plasma total or free or urinary metanephrines for the diagnosis of pheochromocytoma. All three measurements provide clearly better clues to detect this tumor compared with the classical determination of plasma catecholamines (18) To date, none of these tests appear to be able to detect pheochromocytoma before the others at an earlier time of tumor development.(19) A normal value of any of these does not exclude the presence of a pheochromocytoma. Recent studies indicate plasma free metanephrines as the most sensitive diagnostic index. (20)

Localization of the tumor relies mainly on CT scan of abdomen(21). Nevertheless, due to the frequency of incidental adrenal masses, MIBG scintigraphy should also be performed before surgery. In the present study, CT scan of abdomen was used in all cases for localization with 100% sensitivity while MIBG scan was used in one patient who had negative VMA and UCA. In our study, 7 out of 34 tumors were extra-adrenal, which is in line with most recent studies in which ectopic tumors comprise 10 to 29% of the adult pheochromocytomas. The 10% rule is no longer applied (22) the higher rate may well reflect increased disease awareness and improved tumor localizing facility since the last century. None of Our tumors showed evidence of malignancy as judged by local infiltration or presence of metastasis.

As compared to other studies(23) preoperative preparation formed an important part of management in our study. All hypertensive patients received phenoxybenzamine and propranolol before the operation. Arterial line placement and preoperative correction of intravascular volume was done in all patients.

The effects of surgery on BP were documented in our study by the disappearance of hypertension in about 60% of patients. BP did not change significantly after surgery in 40% of our patients with hypertension indicating, as suggested by others, the presence of other causes of hypertension or nonreversible catecholamine-induced structural changes in the cardiovascular system or delay in diagnosis(24)
Reference

Illustrations

Illustration 1

[Figure-1] Sex ratio

Illustration 2

[Figure-2] Distribution of extraadrenal pheochromocytoma
Illustration 3

[Figure-3] Duration of symptoms at the time of presentation

![Illustration 3](image1)

Illustration 4

[Figure-4] Intraoperative picture

![Illustration 4](image2)
Illustration 5

[Figure-5] Cut section of the specimen
Illustration 6

Results

Demographic data
This study includes 34 patients of surgically proven pheochromocytoma. We retrospectively reviewed the records of 34 patients with pheochromocytoma who underwent surgical treatment between 1971 and 2006. Fourteen patients (41.2%) were females and twenty (58.8%) were males.[Figure-1]

Clinical presentation
The most frequent symptoms were Hypertension (97%) and palpitation (38.2%). The various patterns of hypertension among the patients in our study are shown in the table.

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent hypertension-</td>
<td>09</td>
<td>nil</td>
</tr>
<tr>
<td>Paroxysms</td>
<td>07</td>
<td>04</td>
</tr>
<tr>
<td>Persistent with paroxysms</td>
<td>04</td>
<td>09</td>
</tr>
<tr>
<td>Hypotension</td>
<td>nil</td>
<td>01</td>
</tr>
</tbody>
</table>
Nine patients (26.5%) had persistent hypertension, 11 patients (32.4%) had paroxysmal hypertension and 13 patients (38.2%) had persistent with paroxysms. The average duration of symptoms at the time of diagnosis is around two years [Figure-3]

<table>
<thead>
<tr>
<th>Associated symptoms</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitation</td>
<td>13</td>
</tr>
<tr>
<td>Sweating</td>
<td>10</td>
</tr>
<tr>
<td>Chest pain</td>
<td>04</td>
</tr>
<tr>
<td>Black out</td>
<td>01</td>
</tr>
<tr>
<td>Head ache</td>
<td>09</td>
</tr>
<tr>
<td>convulsions</td>
<td>02</td>
</tr>
<tr>
<td>Weight loss</td>
<td>07</td>
</tr>
</tbody>
</table>
Biochemical and pathological evaluation

The 24-h urinary total metanephrines and vanillylmandelic acid (VMA) were used to diagnosis pheochromocytoma. Among the 34 patients, 32 patients (94%) were positive and 02 patients (6%) showed negative results for urinary VMA. A lab value of VMA more than 8mg/24 hours urine sample is considered as positive. A lab value of UCA of more than 150ug/24 urine sample is considered as positive test. In this study, 30 patients (88.2%) were positive for UCA and 04 patients (11.8%). were negative for UCA test. In one patient both VMA and UCA were negative and MIBG scan was done to confirm the diagnosis of pheochromocytoma.

<table>
<thead>
<tr>
<th>Results of Biochemical studies</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both VMA &amp; UCA elevated</td>
<td>24 (69.6%)</td>
</tr>
<tr>
<td>Normal VMA* &amp; UCA elevated</td>
<td>2 (5.8%)</td>
</tr>
<tr>
<td>Elevated VMA &amp; Normal UCA</td>
<td>7 (20.3%)</td>
</tr>
<tr>
<td>Normal VMA* &amp; Normal UCA</td>
<td>1 (2.9%)</td>
</tr>
</tbody>
</table>
Localization procedure

In our study CT scan is used as a predominant tool to localize the tumour. Eight of the patient had tumor on the left side and nineteen of them had the tumor on the right side and seven in the extra adrenal sites. The distribution of the extradrenal pheochromocytoma in our study is shown[Figure-2]

<table>
<thead>
<tr>
<th>Extra adrenal Location</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Close to kidney</td>
<td>02</td>
<td>01</td>
</tr>
<tr>
<td>Superior to the pancreas</td>
<td>01</td>
<td>01</td>
</tr>
<tr>
<td>Below the renal vein</td>
<td>01</td>
<td>01</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td></td>
<td>01</td>
</tr>
</tbody>
</table>

Preoperative preparation

All hypertensive patients received phenoxybenzamine and propranolol before the operation. Arterial line placement and preoperative correction of intravascular volume was done in all patients.

Intraoperative events

All our patients underwent open laparotomy. Midline incision with lateral extension was used in all cases. Adrenal vein was ligated first and minimal handling of tumor was done in all cases.[Figure-4]
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