Pheochromocytoma in Italy: a multicentric retrospective study

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Abstract

Objective: To conduct an epidemiological study on pheochromocytoma in Italy.

Methods: Data on 284 patients with pheochromocytoma observed between 1978 and 1997 were collected from 18 Italian centers through a questionnaire reporting epidemiological, clinical, laboratory, radiological and surgical data.

Results: 53.6% of the patients were females and 46.4% were males. Thirty-two tumors were discovered as incidental adrenal masses. The most frequent referred symptoms were palpitations (58.1%), headache (51.9%), sweating (48.8%) and anxiety (35.3%). Their association was present only in 15.5% of patients. Paroxysmal symptoms were reported in 67.1% and hypertensive crises in 59.7% of patients. Normal blood pressure (systolic and diastolic) was present both in the supine and upright positions in 21.1% of patients. Among laboratory assays, urinary vanillylmandelic acid (VMA) was the most widely used (58.1%) and was the least sensitive (25% of false negative results). Basal plasma catecholamines were found to be normal in 11.3% of patients but were always elevated when sampled during a hypertensive paroxysm. A clonidine suppression test was performed in 38 patients with no adverse side effects. It gave a false negative response in 2 patients. A glucagon test was performed in 21 patients. It was interrupted for acute hypertension in 52.4% of patients. Only 5/21 patients were normotensive and had normal basal plasma catecholamines. In these patients the test gave a positive response in four (80%). CT (79.6%) and I-MIBG scintigraphy (68.5%) were the most widely used methods for tumor localization. CT sensitivity was 98.9% for intra-adrenal and 90.9% for extra-adrenal tumors. MIBG sensitivity was 88.5%. In the 261 patients who underwent surgery, the tumor was intra-adrenal in 89.4%, extra-adrenal in 8.5%, intra- and extra-adrenal in 2.1%, and bilateral in 11.0% of patients. Malignancy was reported in 9.9% of cases. Surgery caused remission of hypertension in 59.3%, improvement in 26.8%, and no changes in 13.9% of patients. In the last group the interval between initial symptoms and diagnosis was significantly longer.

Conclusions: The present study confirms that the clinical presentation of pheochromocytoma is variable and aspecific. Normotension is often present and often the tumor is discovered incidentally. An indication for the routine use of screening methods more sensitive than urinary VMA is strongly suggested. The clonidine test was found to be safe and should be preferred to the glucagon test which has to be restricted to very selected patients. CT and MIBG scintigraphy are almost always successful in localizing the tumor. Reversal of hypertension by surgery seems to depend on an early diagnosis.

Introduction

Pheochromocytoma (pheo) is a rare tumor arising from the chromaffin tissue. It causes hypertension in about 0.1% of hypertensive patients and presents itself with a highly variable clinical picture (1–7). 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 (8, 9).

Due to the great heterogeneity and the relatively low number of occurrences in many Italian series, in an attempt to standardize the diagnostic and therapeutic management of Italian patients with pheo, the National Italian Study Group on Adrenal Tumors, under the patronage of the Italian Endocrine Society, decided to perform a multicentric retrospective evaluation of patients with pheo.

The study included patients evaluated in 18 Italian centers over the last 20 years.

Patients and methods

Eighteen centers from all over Italy, belonging either to university departments or to major regional hospitals, participated in the study.
A questionnaire, previously approved by the participating units was distributed to obtain epidemiological, clinical, laboratory, radiological and surgical data on cases observed between 1978 and 1997.

The questionnaire included personal and familial data of the patients, the referred signs and symptoms, the approximate lag time between initial symptoms and diagnosis, systolic and diastolic blood pressure (BP) and heart rate (HR) in the supine and upright positions and, whenever possible, during a hypertensive crisis, echocardiographic evaluation, basal plasma and/or urinary levels of catecholamines (CA) or metabolites, plasma CA levels during dynamic tests (clonidine or glucagon), localization procedures, pre-surgical pharmacological treatment, surgical findings and blood pressure changes after surgery.

In 263 patients the diagnosis was confirmed at surgery. In the other 21 the presence of a pheo was ascertained by pathological laboratory findings and positive MIBG scintigraphy (10 patients) or positive adrenal sonography, CT or RMI (11 patients).

When analyzing BP, patients were considered normotensive when their systolic BP values were below 140 mmHg and their diastolic BP values were below 90 mmHg. Hypertensive systolic records were divided into grade I for values between 140 and 159 mmHg, grade II for values between 160 and 179 mmHg and grade III for higher values. Hypertensive diastolic records were divided into grade I for values between 90 and 99 mmHg, grade II for values between 100 and 109 mmHg and grade III for higher values.

Measurements of CA or metabolites, in urine or plasma, were performed using different methods (Table 1). The results were classified as normal or abnormal according to the normality range referred to as normal by each center.

Clonidine tests were performed according to Bravo et al. (10). Plasma CA levels were measured in the supine position before and 120 and 180 min after oral administration of 300 μg clonidine.

In patients with normal basal plasma CA the response to the test was considered negative when a decrease of at least 50% was observed (11). In patients with elevated basal plasma CA the test was considered negative when a decrease into the normal range was observed (10, 12).

A glucagon test (13) was performed measuring plasma CA before and 1, 3, 5, and 10 min after i.v. administration of 1 mg glucagon. The response was considered positive when plasma epinephrine and/or plasma norepinephrine increased respectively to more than 2.5 or more than 1.5 times the upper values of their normal range. These criteria were derived from the evaluation of the CA response to glucagon in 60 essential hypertensive patients.

Data were transmitted either on paper support or using the Excel electronic spreadsheet and were collected in our center for the final elaboration.

**Statistical analysis**

Data are provided as means ± S.D. or as means plus range, as appropriate. When the data distribution deviated significantly from a normal one, the geometric mean was computed. Statistical comparisons were performed using either Student’s two-tailed t-test or chi-square test, as appropriate. Correlations were performed using linear regression analysis. A P value <0.05 was considered statistically significant.

**Results**

**Epidemiological and clinical data**

Data from 284 patients affected by a chromaffin tumor were analyzed. The patient group was composed of 53.6% female and 46.4% male patients with a mean age of 44 years (range 8–84 years) for females and 46 years (range 12–79 years) for males. Their body mass indexes were 23.1 (range 12.5–43.7) and 24.2 (range 18–33.0) respectively.

In 258 patients presenting symptoms, the mean interval between initial symptoms and diagnosis was 42 months, ranging from less than 1 month to 30 years.

Familial history for the presence of pheo was positive in 15% (39/260) and negative in 85% (221/260) of cases. When familial, the pheo was due to a MEN 2 syndrome in 30 patients (77%), to Von Hippel–Lindau in 4 patients (10%) and to neurofibromatosis in 5 patients (13%).

The presence of hypertension in first grade relatives of patients was found in 37.1% (86/232) of cases.

The frequency of the different symptoms is reported in Table 2. The most frequent were headache, palpitations, diaphoresis, and anxiety. The association of all these symptoms was found only in 15.5% of cases while the presence of at least three of them was found in 36.5% of cases.

<table>
<thead>
<tr>
<th>Table 1 Percentage distribution of laboratory methods used in the different Centers to measure CA or metabolites.</th>
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<tbody>
<tr>
<td>FL</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>urVMA</td>
</tr>
<tr>
<td>urCA</td>
</tr>
<tr>
<td>urNE</td>
</tr>
<tr>
<td>urE</td>
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<tr>
<td>pINE</td>
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<tr>
<td>pIE</td>
</tr>
</tbody>
</table>

FL, fluorimetric assay; HPLC, high pressure liquid chromatography; RE, radioenzymatic assay.
The presence of symptoms referred as paroxysmal by the patients was reported in 67.1% of cases (173/258).

**Cardiovascular picture**

The presence of hypertensive crises in their history was reported by 59.7% of patients (154/258). The absence of hypertension was reported by 28.5% (77/269) and its presence by 71.5% (192/269) of patients. In the group of patients with hypertension 61.5% classified it as continuous; the others as discontinuous.

Systolic and diastolic BP was measured in the supine position in 249 patients (212 with a sporadic pheo and 37 with a familial pheo) and in the upright position in 156 patients. The distribution of BP values is reported in Table 3. 24.5% of patients were found to be normotensive in the supine position and 35.3% in the upright position while 21.1% of patients were normotensive in both positions. Normal values (false negative results) were found in 25% of VMA assays (41/156), in 14% of urCA assays (12/86), in 21% of urNE assays (28/131), in 34% of urE assays (29/85), in 17% of pNE assays (24/139) and in 35% of pE assays (44/126).

An alteration in either pNE or pE measured in basal conditions was present in 88.7% of patients (126/142). In 11 patients plasma for CA measurement was drawn during a hypertensive paroxysm; a pathological increase in CA concentrations was found in each of them (100%), including 4 patients with normal basal plasma CA.

No correlation was found between BP values and basal plasma CA concentrations in 111 patients. In patients whose basal pNE and pE were both elevated normotension was nonetheless present in 17/66 (25.7%). When only one plasma CA was elevated, normotension was more frequent in patients with an E-secreting pheo (4/8 = 50.0%) than in patients with an NE-secreting pheo (3/25 = 12.0%) (P < 0.0002). Among the 12 patients with normal basal plasma CA, 5 were normotensive and 7 had grade I hypertension.

**Laboratory results**

In 284 patients the most widely used laboratory methods for the diagnosis of pheo were: urinary vanillymandelic acid (VMA) 58.1%; total urinary catecholamines (urCA) 30.3%; urinary norepinephrine (urNE) 46.1%; urinary epinephrine (urE) 29.9%; plasma norepinephrine (pNE) 48.9% and plasma epinephrine (pE) 44.4%.

HR measured in the supine position (249 patients) was lower than 80 beats/min in 60.5%, between 80 and 100 beats/min in 34.4% and higher than 100 beats/min in 5.1% of patients. HR measured in the upright position (156 patients) was lower than 100 beats/min in 80.8%, between 100 and 110 beats/min in 13.1% and higher than 110 beats/min in 6.1% of patients.

BP was also measured during a hypertensive paroxysm in 101 patients: the mean systolic increase was 72.1 mmHg (range 200–4) and the mean diastolic increase was 32.0 mmHg (range 100–5).

Cardiac evaluation was performed in 110 patients by echocardiography: in 68.2% cardiac dimensions and functions were normal.

### Table 2

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Distribution (%)</th>
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<tbody>
<tr>
<td>Palpitations</td>
<td>58.1</td>
</tr>
<tr>
<td>Headache</td>
<td>51.9</td>
</tr>
<tr>
<td>Sweating</td>
<td>48.8</td>
</tr>
<tr>
<td>Anxiety</td>
<td>35.3</td>
</tr>
<tr>
<td>Tremors</td>
<td>25.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>22.4</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>16.6</td>
</tr>
<tr>
<td>Vertigo</td>
<td>16.5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>16.1</td>
</tr>
<tr>
<td>Parasthesiae</td>
<td>11.9</td>
</tr>
<tr>
<td>Chest pain</td>
<td>11.8</td>
</tr>
<tr>
<td>Diarrhoea/constipation</td>
<td>10.6</td>
</tr>
<tr>
<td>Fainting</td>
<td>5.1</td>
</tr>
<tr>
<td>Fever</td>
<td>2.0</td>
</tr>
</tbody>
</table>

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### Table 3

<table>
<thead>
<tr>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>supine</td>
<td>supine</td>
<td>upright</td>
<td>upright</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>249</td>
<td>249</td>
<td>156</td>
</tr>
<tr>
<td>Normotensive</td>
<td>31.3%</td>
<td>36.5%</td>
<td>44.2%</td>
</tr>
<tr>
<td>Hypertension grade I</td>
<td>28.9%</td>
<td>22.9%</td>
<td>30.8%</td>
</tr>
<tr>
<td>Hypertension grade II</td>
<td>18.9%</td>
<td>23.3%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Hypertension grade III</td>
<td>20.9%</td>
<td>17.3%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>
A clonidine suppression test was performed in 38 patients. Basal plasma CA levels were normal in 7 and elevated in 31 patients.

In the group with normal basal values, clonidine did not suppress plasma NE in 7/7 patients (no false negatives). In the group with elevated basal CA, 20 patients showed abnormal NE and E, 10 patients abnormal NE and normal E and 1 patient abnormal E and normal NE. In the 30 patients with abnormal basal NE, clonidine did not suppress plasma NE after 120 and 180 min in 26 patients while it suppressed plasma NE in 1 patient after 120 min, in 1 patient after 180 min and in 2 patients after 120 and 180 min respectively (2 suspicious and 2 false negative responses). In the patient with abnormal basal E clonidine did not suppress plasma E (no false negative).

A glucagon stimulation test was performed in 21 patients. The test was improperly performed in 7 patients (33.3%) who showed elevated basal BP values. In the 14 normotensive patients, basal plasma CA was abnormal in 9 patients. The test was interrupted for a hypertensive crisis in 5/7 (71.4%) hypertensive and in 6/14 (42.8%) normotensive patients. In the 5 normotensive patients with normal basal plasma CA the test was interrupted in 1/5 patients (20%). It gave a positive response in 4/5 patients (80%).

Localization procedures

The most widely used radiological tool for localization of pheo was CT (226/284; 79.6%). MR was performed in 39/284 patients (13.7%) and scintigraphy with I-MIBG in 174/254 patients (68.5%) observed after 1983. The tracer used was 131I-MIBG in 66.1% and 123I-MIBG in 33.9% of cases. The sensitivity of CT was 98.9% for intra-adrenal pheo and 90.9% for extra-adrenal pheo. The overall sensitivity of I-MIBG scintigraphy was 88.5% (154/174) with no statistical differences between the two different tracers (131I-MIBG 87.8% and 123I-MIBG 89.8% respectively).

In the 263 patients who underwent surgery, the distribution of the localization studies was as follows: abdominal sonography was performed in 69.2%, CT scan in 84.4%, MR in 13.7%, and MIBG scintigraphy in 62.3% of patients.

Before surgery, localization studies were carried out as follows: 79 (30%) patients underwent only one radiological procedure (sonography or CT scan or MR); 161 (61.2%) underwent MIBG scintigraphy and one radiological procedure (among these patients, 144 had a CT scan); 3 (1.2%) underwent only MIBG scintigraphy; in 20 (7.6%) no localization procedures were reported.

Pre-surgery medical treatment

Medical treatment before surgery was recorded in 170 patients. Alpha-blockers were administered to 106 of them, 82 as monotherapy, the others in association with other drugs. Beta-blockers were given to 27 patients, labetalol to 56, calcium antagonists to 21 and ACE-inhibitors to 6.

Surgical findings

In the 263 patients who underwent surgery the tumor was intra-adrenal in 89.4% of patients (235/263), extra-adrenal in 8.5% (22/263) and intra- and extra-adrenal in 2.1% (6/263). When intra-adrenal, the tumor was bilateral in 11.0% (26/235) and monolateral in 89% (209/235); when monolateral, it was located in the right adrenal in 57% (134 patients) and in the left adrenal in 32% (75 patients) (P<0.0001).

Extra-adrenal tumors were more common in patients younger than 20 years (3/17; 17.6%) compared with patients aged 20–60 years (22/187; 11.8%) and with patients older than 60 years (3/49; 6.1%).

Malignancy, as judged by local infiltration or the presence of metastases, was referred in 9.9% of patients (26/263). Malignancy was more frequent in extra-adrenal (9/28; 32.1%) than in intra-adrenal pheos (17/235; 7.2%).

Complications during surgery affected 3.4% of patients.

Blood pressure changes after surgery

The effects of tumor removal on BP were evaluated in 108 patients who were hypertensive before surgery. After surgery, 64 patients (59.3%) became normotensive while 44 (40.7%) remained hypertensive. Nevertheless, in this last group a decrease in BP sufficient to determine a change of hypertensive class was recorded in 26 patients for systolic values and in 25 patients for diastolic values. In 15 patients (13.9%) no significant decrease in BP was recorded after surgery.

In this last group the time lag between initial symptoms and diagnosis was significantly longer (geometric mean 40.9 months) than in the group of patients who became normotensive after surgery (geometric mean 16.9 months) (P<0.02).

Discussion

The present retrospective study confirms the wide variability of the clinical picture in patients with pheo and the difficulties in reaching a correct diagnosis. The presence of a paroxysmal event which, although specific, has always been considered a hallmark of pheo, has been reported by only 2/3 of the patients.

In agreement with other authors (2, 4, 6, 7), the most frequent symptoms were headache, sweating, palpitation and anxiety but their frequency was rather low and even rarer was the association of three (36.5%) or four (15.5%) of them. Therefore, in view of the very
The 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 (42 months) between initial symptoms and diagnosis and why, quite often, the pheo is discovered as an incidental adrenal mass (32 patients, 11.2% in the present study) or at autopsy.

Therefore, the most frequent reasons for suspecting a pheo are hypertension, especially if paroxysmal or resistant, and the presence of an adrenal mass, especially if accompanied by hypertension.

It is interesting to point out the increasing incidence of the incidentally discovered pheos. In fact, while 40.6% were diagnosed in the 15 years between 1978 and 1992, the majority of them (59.4%) were diagnosed in the last 5 years (between 1993 and 1997). Among the patients with an incidentally discovered pheo, 12 (37.5%) were hypertensive and 20 (62.5%) were normotensive. These data confirm that pheos have to be taken into account in the differential diagnosis of adrenal incidentalomas (14, 15) and that the absence of hypertension does not rule out the presence of a pheo. It is likely that in the future an increasing number of pheos will be discovered as an incidental adrenal mass.

In our study 21.1% of patients were normotensive both in the supine and upright positions. When present, hypertension was mostly mild (Table 2) and in 61.5% of cases it was referred to as discontinuous. These data may, at least in part, explain the finding of normal echocardiographic patterns in 68.2% of patients.

Hypertensive crises were registered in 101 patients and were characterized by great variability. The mean and peak increase were respectively 72 and 200 mmHg for systolic BP and 32 and 100 mmHg for diastolic BP. Quite surprisingly, no fatal event was reported during paroxysmal hypertension.

The laboratory results show that the most widely used method for the diagnosis of pheo (urinary VMA) is the least sensitive. This finding is in agreement with the data reported in the literature (5, 6, 16) and should be interpreted as a strong indication to the laboratories for the use of more sensitive assays such as urinary CA or, even better, metanephrines.

Our data confirm that plasma CA values are a very sensitive diagnostic tool when samples are drawn during a hypertensive paroxysm. Outside of this, a normal value does not exclude the presence of a pheo. Recent papers indicate plasma metanephrines as the most sensitive diagnostic index (17, 18).

Our data also confirm that the clonidine suppression test is a useful tool in the diagnosis of pheo (10, 19). In fact, it gave a false negative response in 2/38 patients. It is worth mentioning that, in the present study, the test gave useful information also in patients with normal basal plasma CA, where it suggested an abnormal regulation of CA secretion. No adverse reaction was reported during the test.

On the other hand, the glucagon stimulation test must be performed in accurately selected patients because of its potentially dangerous effects. From our data only normotensive patients with normal basal values of CA should be tested with glucagon; all the others should first undergo a clonidine suppression test.

Localization of the tumor relies mainly on CT/MR (20–22). Nevertheless, due to the frequency of incidental adrenal masses, MIBG scintigraphy (23, 24) should also be performed before surgery. In fact, in at least 3 patients an association of an extra-adrenal pheo with an incidental adrenocortical mass has been reported.

In the present study, surgical findings are in close agreement with those reported in the literature. In fact, the 9/1 ratio was confirmed for the localization (intra-extra-adrenal), the number (mono- or bilateral), and the biology of the tumor (benign or malignant) (25). In agreement with some authors, the right adrenal gland was significantly more affected than the left one (6).

The effects of surgery on BP are documented by the disappearance of hypertension in about 60% of patients and by an improvement in about 26% of patients. BP did not change significantly after surgery in only 14% of the patients indicating, as suggested by others (26), the presence of other causes of hypertension or non-reversible CA-induced structural changes in the cardiovascular system.

In conclusion, our study confirms the great variability of the clinical picture of pheo. Large numbers of affected patients are normotensive. This finding, besides making the diagnosis very difficult, may explain why many tumors are discovered as incidental adrenal masses.

To confirm the diagnosis the use of one or more sensitive assays (urinary metanephrines, plasma CA, plasma metanephrines) may be necessary. Dynamic tests are seldom required and, while the clonidine suppression test gives useful information without risk for the patient, the use of the potentially dangerous glucagon stimulation test should be restricted to suspected patients who are normotensive and have negative basal measurements.

As already stated, presurgical localization relies on CT and MIBG scintigraphy.

As a final remark, surgery cures hypertension in 60% and ameliorates it in 26% of the patients. Delay in the diagnosis seems to be responsible for the irreversibility of hypertension after surgery.

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