

CLINICAL STUDY

Circumstances of discovery of phaeochromocytoma: a retrospective study of 41 consecutive patients

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Abstract

Objective: Phaeochromocytoma is a rare tumour of the chromaffin cells, the diagnosis of which is based on an assay of metanephrines and treatment is surgical excision of the tumour. It is usually discovered due to a rich and varied symptomatology or classic paroxysmal hypertension. The main purpose of this study was to specify the exact circumstances of discovery of the phaeochromocytomas operated on in our university hospital between 1990 and 2002.

Design and methods: Forty-one consecutive and complete case reports of patients who had surgery for phaeochromocytoma were analysed retrospectively. This series includes 10 patients with a genetic disorder predisposing to phaeochromocytoma.

Results: The association of headaches and palpitations with sweating was found in only 24% of cases (10/41). Blood pressure anomalies led to the discovery of phaeochromocytoma in only 51% of cases (21/41) and 59% (24/41) of all the patients suffered from hypertension. In almost half the cases (20/41), the tumour was discovered by an imaging method (ultrasonography, CT scan or MRI) which had been performed for reasons unrelated to a blood pressure abnormality.

Conclusions: Phaeochromocytoma, the symptoms of which are not very specific and during which hypertension is present in only half the patients, is a disease that remains rare. Its incidence could be increasing because of changes in the method of detection. Indeed, in our study, different imaging techniques led to its incidental discovery in half of the cases.

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Introduction

Phaeochromocytoma is a rare tumour (approximately one hypertensive subject in 1000) of the chromaffin cells which secrete catecholamines and/or their metabolites (1). In 90% of cases it arises from the adrenal medulla but it may also be revealed in chromaffin cells of sympathetic paraganglia located throughout the body, from the neck to the bladder. Its prevalence is identical in both sexes and its incidence maximal between the ages of 40 and 60. It varies in size but rarely exceeds 60 mm along the long axis. It is bilateral in 10% of cases (20% in children) and usually (90%) benign. However, regardless of its histological aspect, the tumour cannot be assumed to be benign at the time of diagnosis. Extra-adrenal phaeochromocytomas, also called paragangliomas, are more often malignant (more than 30%) (2). In 20–30% of the cases, phaeochromocytoma is part of a genetic disease with

autosomal dominant inheritance: multiple endocrine neoplasia (MEN) type 2, Von Hippel–Lindau's disease (VHL), or neurofibromatosis type 1 (NF1, Von Recklinghausen's disease) (3, 4).

Hormonal diagnosis is based on the measurements of urinary or plasma catecholamines or the catecholamine metabolites metanephrines. The treatment of choice is surgical excision of the tumour. Although the prognosis for patients who have surgery for benign phaeochromocytoma is identical to that of healthy patients, the prognosis in cases of malignant phaeochromocytoma is poor. Hypertension, the classic condition leading to the discovery of phaeochromocytoma, may be cured after surgical excision but persists in one-third of the patients who undergo surgery.

The purpose of this study was to determine the circumstances of discovery of phaeochromocytoma in 41 consecutive cases operated at the Grenoble University Hospital between 1990 and 2002.

Subjects and methods

We have retrospectively studied the files of all patients who underwent surgery for pheochromocytoma at Grenoble University Hospital between 1990 and 2002. The cases were identified from the files of the Department of Pathology and included patients followed in the departments of cardiology, endocrinology, internal medicine and other departments of our hospital. The completeness of the case report forms drawn up by a senior physician was verified prior to their inclusion. For the purposes of this study, medical records on the first consultation were analysed to establish how diagnosis was made. Detailed personal and family history, physical examination, biochemical analysis and imaging were also reviewed at the time the tumour was detected. Two incomplete case report forms (exact circumstances of discovery of pheochromocytoma were missing) were not included and only 41 of 43 cases were analysed. Clinical blood pressure (BP) measurements were recorded on therapy. The following assay methods were used: photometry for total urinary metanephrines and urinary vanillylmandelic acid (VMA); fluorimetry for total urinary catecholamines; and HPLC for plasma metadrenaline, normetadrenaline and catecholamines (5). Urinary analyses were performed at Grenoble University Hospital and plasma analysis at Lyon University Hospital. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA). The mean and standard deviation were calculated for each numerical variable.

Results

The characteristics of the 41 patients selected are shown in Table 1. They were aged between 14 and 79. Eleven patients had a family history of hypertension (27%) and two suffered from refractory hypertension (5%). Ambulatory BP monitoring (ABPM) was performed in 12 patients (29%) with a mean daytime BP of 142 ± 21 for systolic BP (SBP) and 92 ± 15 mmHg for diastolic BP (DBP). A hypertensive peak, defined for both clinical and ambulatory measurements as a sudden elevation in SBP by more than 50% of the

preceding measurement, was detected clinically in 49% of the patients and in 67% of the subjects when using ABPM. Nineteen patients (46%) were being treated for hypertension at the time of pheochromocytoma diagnosis, and had suffered from hypertension for an average of 54 ± 45 months (maximum = 10 years). In the treated patients, the average period of anti-hypertensive drugs was 35 ± 35 months and the average number of anti-hypertensive medication was 2.2 ± 0.4 . Seven patients (17%) had NF1; two related patients (5%) suffered from MEN type 2A with a mutation in the RET gene at codon 634. One patient (2%) with a bilateral pheochromocytoma proved to carry a missense germinal neomutation in the gene for VHL.

Table 2 reports the clinical symptoms and signs of patients before surgery for pheochromocytoma. The different ways of detecting the tumours are given in Table 3. BP anomalies led to the discovery of pheochromocytoma in 51% of cases (21/41): paroxysmal, symptomatic, refractory or gravidic hypertension. Hypertension, defined by a clinical SBP ≥ 140 mmHg and/or a clinical DBP ≥ 90 mmHg and/or current anti-hypertensive treatment (6), was found in 59% (24/41) of the patients. Hypertension was grade 1 (SBP between 140 and 159 mmHg and/or DBP between 90 and 99 mmHg) in nine of the 24 (37.5%) hypertensive subjects, grade 2 (SBP between 160 and 179 mmHg and/or DBP between 100 and 109 mmHg) in nine cases (37.5%) and grade 3 (SBP > 180 mmHg and/or DBP > 110 mmHg) in six of the 24 (25%) patients. Among the 19 treated patients, 15 (79%) had a persistent hypertension. Orthostatic hypotension was defined as a fall in BP 1 min after standing, by more than 20 mmHg for the SBP and more than 10 mmHg for the DBP. Twelve subjects (29%) did not display either signs of the triad or orthostatic hypotension. Of the patients whose pheochromocytoma was discovered during an imaging examination, 35% were hypertensive.

The results of preoperative hormonal assays are given in Table 4. All of the patients had at least one abnormal hormonal assay. Only two patients out of

Table 1 Characteristics of the 41 patients who had surgery for a pheochromocytoma.

Variables	Mean \pm SD
Gender (men/women)	16/25
Age (years)	46 ± 16
Body mass index (kg/m ²)	23 ± 4
Cardiovascular heredity (yes/no)	11/30
Clinical SBP (mmHg)	142 ± 21
Clinical DBP (mmHg)	87 ± 14
Clinical heart rate (b.p.m.)	76 ± 14
Glucose level (mmol/l)	6.9 ± 3.0

Table 2 Symptoms and clinical signs of the 41 patients before surgery for pheochromocytoma.

Variables	Percentage (yes/no)
Headaches	49 (20/21)
Palpitations	46 (19/22)
Sweating	49 (20/21)
Headaches + palpitations + sweating	24 (10/31)
Absence of symptoms	29 (12/41)
Hypertension	59 (24/41)
Orthostatic hypotension	15 (6/35)
Clinical BP peak	49 (20/21)
ABPM peak	67 (8/4)
Acute pulmonary oedema	2 (1/40)

Table 3 Circumstances of discovery of 41 cases before surgery for pheochromocytoma.

	Percentage (%)	Presence (41)
Hypertension	51	21
Paroxysmal HT		11
Aetiological report of HT		9
Gravidic HT		1
Imaging for pain examination	29	12
Abdominal pain		7
Nephretic colic		1
Urinary infection		2
Hepatic colic		1
Lumbar pain		1
Imaging for various pathologies	20	8
Uterine fibroma		1
Elevated transaminases		1
Bone metastases		1
Hypereosinophilia		1
Pregnancy monitoring		1
MEN 2A*		2
Von Recklinghausen's disease*		1

HT, hypertension.

*After finding elevated level of metanephrines.

29 (7%) had a normal level of urinary metanephrines, six (21%) had up to twice the normal level and 21 (72%) had more than twice the normal level. Plasma metanephrines were normal in 21% of cases (4/19) and urinary VMA in 12% of patients (3/24). Fifty-four per cent (22/41) of patients had fasting glucose levels higher than 6.0 mmol/l.

Thirty-nine patients (95%) had at least one adrenal tumour, in one case associated with a coeliac paraganglioma and in another case with a vertebral neurofibroma. Twenty-one of the adrenal tumours were on the right side, 15 on the left and three were bilateral. The other two subjects suffered from an inter-aortocaval paraganglioma. Metastases were detected at the time of diagnosis in two of the 41 patients. All of the patients were given a preoperative computerized tomography (CT) scan or magnetic resonance imaging (MRI). Total body scan by metaiodobenzylguanidine was performed in 15 patients. This exam was concordant with surgical findings in 14 cases (one bilateral adrenal fixation detected by this method but a unilateral tumour found during the surgery). From 1990 to

1996, the surgical approach was a laparotomy in all cases (21/21), whereas from 1997 to 2002, 11 of the 20 patients (55%) underwent a laparoscopic approach. Six (15%) of the patients encountered intra- or peri-operative complications: eventration, peritonitis, sub-hepatic haematoma, catheter subclavian thrombophlebitis, duodenal ulcer bleeding and acute pulmonary oedema. There was no mortality.

Table 5 shows the comparison of patients' characteristics and tumour data according to the circumstances of detection of the pheochromocytoma. When the tumour was detected because of hypertension abnormality, the plasma normetadrenaline level was higher ($P = 0.006$) and there was a tendency towards higher SBP ($P = 0.123$), urinary VMA level ($P = 0.158$) and tumour weight ($P = 0.054$).

Discussion

Hypertension and pheochromocytoma

Pheochromocytoma is a disease which is often evoked but rarely found. The most characteristic clinical sign of this pathology and the one most frequently reported in the literature (in almost 90% of cases) is hypertension, which may be only paroxysmal but is usually permanent, stable or with paroxysms, sometimes even malignant (7–9). This hypertension, which shows extreme variation between levels, usually resists anti-hypertensive drugs apart from α -blockers.

In our study, hypertension led to the discovery of pheochromocytoma in only 51% of patients, and in half these cases because of its evocative paroxysmal character. When the reason for discovering the pheochromocytoma was permanent hypertension, it was symptomatic, severe, resisting treatment, or gravidic. We found only six patients (15%) with severe (grade 3) hypertension. This low prevalence is explained by the use of anti-hypertensive drugs in 19 of the 24 hypertensives and the high prevalence of paroxysmal hypertension with only 59% suffering from permanent clinical hypertension before surgery. Moreover, we found a very high prevalence of uncontrolled hypertension in spite of an average number of anti-hypertensive medication of 2.2. This is well

Table 4 Preoperative hormonal data and tumour weight for the 41 patients suffering from pheochromocytoma.

Variables	Mean \pm SD	n	Normal values	Median (range)
Urinary metanephrines (μ mol/24 h)	36.5 \pm 32.4	29	< 4.2	31.6 (2.8–99.3)
Urinary VMA (μ mol/24 h)	79.8 \pm 63.7	24	< 30.3	55.8 (26.1–244)
Plasma metadrenaline (pg/ml)	5852 \pm 7685	19	< 1500	1818 (178–25 824)
Plasma normetadrenaline (pg/ml)	23 529 \pm 30 499	19	< 4000	5069 (811–97 638)
Urinary catecholamines (nmol/24 h)	8058 \pm 7965	24	< 1200	4945 (621–27 061)
Plasma catecholamines (pg/ml)	85	1	< 40	85 (85)
Tumour weight (g)	103 \pm 148			37 (4.9–661)

Table 5 Comparison of data according to the circumstances of discovery of the 41 operated cases of phaeochromocytoma.

Variables	BP abnormality (n = 21)	Other circumstance (n = 20)
Gender (men/women)	12/9	4/16
Age (years)	45±19	47±13
Clinical SBP (mmHg)	147±22	137±18
Clinical DBP (mmHg)	89±17	85±9
Clinical heart rate (b.p.m.)	78±16	74±11
Glucose level (mmol/l)	6.8±3.1	6.9±3.0
Headaches + palpitations + sweating (Y/N)	7/21	3/20
High BP level (Y/N)	17/21	7/20
Treated hypertension (Y/N)	15/21	4/20
Urinary metanephrines (µmol/24 h)	43.1±32.9 (n = 14)	30.3±31.9 (n = 15)
Urinary VMA (µmol/24 h)	98.4±73.2 (n = 12)	61.2±48.6 (n = 12)
Plasma metadrenaline (pg/ml)	7264±8320 (n = 7)	4954±7523 (n = 11)
Plasma normetadrenaline (pg/ml)	44 470±35 892 (n = 8)	8298±12 907 (n = 11)
Tumour weight (g)	58±60	150±195

Y, yes; N, no.

described in secondary hypertension, especially in phaeochromocytoma. Hypertension is far from constant during phaeochromocytoma and its absence should not be a reason for rejecting a clinical diagnosis. Asymptomatic or slightly symptomatic characteristics and absence of hypertension in a patient suffering from phaeochromocytoma is usually explained by a tumour secreting very little catecholamines and with a discontinuous pattern. Thus, in our study, we found a significant lower plasma normetadrenaline level in patients for which the discovery of the tumour was not a BP abnormality. The ABPM performed over 24 h at the time of the metanephrine assay usually revealed hypertensive peaks more frequently than did clinical examination and is therefore more useful in revealing a paroxysmal rise in arterial pressure.

Apart from hypertension, clinical examination is usually normal in patients suffering from phaeochromocytoma. Some authors have found that hypertension linked to phaeochromocytoma is often associated with orthostatic hypotension explained by the down-regulation of α -adrenergic receptors (10, 11). This hypotension was only detected in six of our 41 patients. This low rate (15%) of orthostatic hypotension in our study could also be due to moderate secretion of catecholamines.

Other symptoms and clinical signs

Phaeochromocytoma must be evoked when intense pulsing headache, profuse sweating and palpitations are associated (12). The sensitivity and specificity of this triad are high (13) but it may be present during an attack of hypertension in the absence of a phaeochromocytoma or in perimenopausal women. Its presence seems to be more important in detecting phaeochromocytoma when it is linked to orthostatic hypotension. In our study, each element of this triad

was only present in half the patients and only 24% displayed all three symptoms. These findings are also reported in other studies (8, 9).

In the present study, only two patients displayed acute pulmonary oedema but this did not lead to discovery of the tumour. This complication can be due to a very high BP level or can be secondary to adrenergic myocarditis with, on echocardiography, frequent association of left ventricular hypertrophy and ventricular dilation (14).

Historically, genetic factors were believed to be implicated in only 10% of phaeochromocytoma, but recent data suggest that germline mutations may be detected in approximately 25% of unselected cases. The most frequent causes of genetic predisposition for phaeochromocytoma are VHL, MEN type 2, the newly delineated phaeochromocytoma–paraganglioma syndrome and, less commonly, NF1 (3). In our study, phaeochromocytoma had been diagnosed by systematic screening with metanephrine in two patients previously known to be affected by MEN 2A and in one patient suffering from NF1. In the other six patients with NF1, diagnosis of phaeochromocytoma was made only when the patients became hypertensive. Similarly, diagnosis of VHL was made after paroxysmal hypertension led to the diagnosis of a bilateral phaeochromocytoma in a 14-year-old boy with no other manifestation of VHL and no family history. Genetic analysis of leukocyte DNA identified a germinal missense neomutation of the VHL gene consistent with VHL type 2C.

Biological diagnosis

In phaeochromocytoma, there is an intermittent or permanent increase in the excretion of catecholamines and their metabolites, metanephrines. These compounds can be assayed in plasma or urine. Phaeochromocytomas secreting dopamine are exceptional.

A urinary metanephrine assay is currently the standard examination for pheochromocytoma diagnosis. Its sensitivity and specificity approach 100% when HPLC is used (15, 16). This was found in our study where 93% of urinary metanephrines assays were pathological.

In addition, fasting hyperglycaemia is common in pheochromocytoma because of insulin resistance due to desensitization of β -adrenergic receptors and inhibition of insulin secretion by the activation of α -adrenergic receptors. Thus, half the patients in our study had a blood glucose level higher than 6.0 mmol/l.

Role of imaging in diagnosis

When an abnormally high level of excretion of metanephrines is recorded, the tumour must be located. CT scan or MRI detect one or more tumours in most cases, specify their anatomical relations and detect metastases. On the other hand, these same imaging techniques along with ultrasonography may find an abnormal mass which could be a pheochromocytoma (17). Imaging is increasingly used in medical practice and for many indications. It is therefore not surprising, among the methods of detecting pheochromocytoma, to find a high percentage of pathologies which led to abdominal, pelvic or retroperitoneal imaging being performed. Thus, in our study, 49% of pheochromocytomas were discovered by ultrasound, CT scan or MRI. The reason for performing these examinations was initially a painful abdominal or lumbar syndrome. These data are very close to those published by Noshiro *et al.*, who had found that of 46 patients suffering from pheochromocytoma diagnosed between 1986 and 1995, in 19 cases (41%) the tumour was discovered quite accidentally by imaging prescribed for other causes (liver dysfunction, upper abdominal pain, health check, weight loss, lumbar pain, abdominal discomfort, and hepatomegaly) (9). In a study performed at the Mayo Clinic, only 15 of 150 patients with a pheochromocytoma were discovered serendipitously by abdominal CT (18). In our series, the high prevalence of patients with pheochromocytoma discovered by imaging might be due to the 'comprehensive' nature of this series which included all patients operated for pheochromocytoma in our university hospital and not only patients explored in cardiologist or endocrine units. It has also already been demonstrated that any adrenal mass must lead to a search for pheochromocytoma, even in the absence of hypertension. Interestingly, in our study, tumour weight was three times higher in subjects with incidental discovery of pheochromocytoma (150 vs 58 g, $P = 0.056$). This should be explained by the low rate of tumoral secretion despite the size of the pheochromocytoma, and by the fact that the larger the tumour, the easier it is to detect using imaging.

Conclusions

In conclusion, pheochromocytoma is a pathology that remains rare but its incidence could increase following changes in the methods used to detect it. Indeed, various imaging techniques led, in our study, to its incidental discovery in half the cases. Its symptomatology is not very specific and hypertension is present in only half the patients.

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