Original Article
Turk J Endocrinol Metab. 2021;25:54-67

# Pheochromocytoma: 16 Years of Experience in a Single Center

## Feokromasitoma: Tek Merkezde 16 Yıllık Deneyim

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## Abstract

**Objective:** Reviewing the 16-year experience of pheochromocytoma in a tertiary referral center. **Material and Methods:** The demographics data and the results of clinical, biochemical, and radiological evaluations of 67 patients who received a diagnosis of pheochromocytoma between the years 2004 and 2020 were obtained retrospectively. **Results:** The mean age (±SD) of the patients at the time of diagnosis was 46 years (±16.1) with a slight female predominance. The percentage of patients diagnosed due to complaints was 50.8%, while 31.2% were diagnosed during the adrenal incidentaloma screening, and 18% were diagnosed during screening for hereditary conditions. Pre-existing hypertension was detected in 56.7% of the patients, while 11.9% of the patients were diagnosed to have hypertension at the time of diagnosis. Paroxysmal pattern was observed in 53.7% of the patients and was accompanied by the classical triad of palpitation (32.8%), headache (20.9%), and sweating (14.9%) as the leading symptoms. Median tumor size was 40 mm (range: 9-90 mm) and the lesion size correlated significantly ($p<0.001$) with the urinary catecholamine metabolite levels. The overall rate of hemodynamic instability in both perioperative and postoperative periods was 6%. Hereditary syndromes, including multiple endocrine neoplasia type 2A (MEN 2A), MEN 2B, von Hippel-Lindau (VHL), and neurofibromatosis type 1 (NF1), were diagnosed in 24% of these patients. Hereditary pheochromocytomas were diagnosed at younger ages, and bilateral lesions were more prevalent in hereditary pheochromocytomas ($p=0.003$ and $p<0.001$, respectively). In addition, patients with hereditary pheochromocytomas were more asymptomatic rather than sporadic ($p=0.016$). Metastasis was detected in 3% of these patients. **Conclusion:** Pheochromocytoma is a rare, life-threatening condition, and therefore, it is important to suspect and test for pheochromocytoma in patients with clinical suspicion. In addition, hereditary syndromes associated with pheochromocytomas should be considered while evaluating patients with pheochromocytoma. A life-long annual follow-up is recommended for the detection of recurrent or metastatic disease, and its evaluation, treatment, and follow-up should involve a multidisciplinary approach in experienced centers.

**Keywords:** Hereditary pheochromocytoma; sporadic pheochromocytoma; paroxysmal hypertension; multiple endocrine neoplasia type 2; von Hippel-Lindau disease

## Özet

**Amaç:** Üçüncü basamak bir üniversite hastanesinde, 16 yıllık feokromasitoma deneyiminin gözden geçirilmesi. **Gereç ve Yöntemler:** Bu araştırma, 2004-2020 yılları arasında feokromasitoma tanısı almış 67 hastanın değerlendirildiği retrospektif bir çalışma olup, hastaların demografik özellikleri ve klinik, biyokimyasal ve radyolojik değerlendirmelerine ilişkin sonuçlar araştırılmıştır. **Bulgular:** Araştırmada, feokromositoma tanısı konulan hastaların yaş ortalaması 46 (±16,1), kadın/erkek oranı 1,2, feokromositoma ile ilişkili yakınmalarla başvurup, bu tanının konulduğu hasta oranı ise %50,8'dir. Hastalara konulan tanıların %31,2'si rastlantısal adrenal kitle araştırılması sırasında, %18'i ise genetik geçişli sendromlar araştırılırken gerçekleştirilmiştir. Hastaların %56,7'sinde tanıdan önce de hipertansiyonun bilindiği, %11.9'unda ise hipertansiyonun tanı sırasında belirlendiği görülmüştür. Hastaların %53.7'sinde tansiyon yüksekliğinin ataklar halinde ortaya çıktığı saptanmıştır. Hastalarda ataklara en sık eşlik eden belirtilerin çarpıntı (%32,8), baş ağrısı (%20,9) ve terleme (%14,9) olduğu dikkati çekmektedir. Araştırmada, ortanca tümör boyutu 40 mm (9-90) saptanmış ve tümör boyutu ile idrar katekolamin metabolit düzeyleri arasında anlamlı korelasyon saptanmıştır ($p<0,001$). Cerrahi uygulanan hastalarda operasyon sırasında ve sonrasındaki takiplerde hemodinamik dengesizlik görülme sıklığı %6 olarak bulunmuştur. Hastaların %24'üne genetik geçişli sendromlar eşlik etmekte olup, bu sendromlar arasında multipl endokrin neoplazi tip 2A (MEN 2A), MEN 2B, von Hippel-Lindau (VHL) ve nörofibromatozis tip 1 (NF1) yer almaktadır. Öte yandan, kalıtsal feokromositomalı hastaların daha erken yaşlarda tanı aldıkları ve bu hastalarda adrenal lezyonların iki taraflı olma eğilimi gösterdikleri belirlenmiştir ($p=0,003$ ve $p<0,001$). Ayrıca, kalıtsal feokromositomalı hastaların, sporadik vakalara göre bulgu vermeden tanı aldıkları görülmüştür ($p=0,016$). Çalışmamızda, feokromositoma tanılı hastalarda metastaz oranının %3 olduğu saptanmıştır. **Sonuç:** Feokromositoma, ender görülmesine karşın yaşamı tehdit edebilen bir durumdur. Bu nedenle, klinik açıdan kuşku duyulan hastalarda feokromasitoma tanısını akla getirmek ve hastaları bu açıdan irdelemek büyük önem taşımaktadır. Ayrıca bu tanının konulduğu hastalarda altta yatan genetik sendromların da olabileceği özellikle dikkate alınmalıdır. Hastaların ömür boyu yıllık olarak takip edilmesi, nüks ve metastaz belirlemesi açısından ayrı bir önem taşımaktadır. Öte yandan, bu hastalıkla ilgili olarak değerlendirme, tedavi ve takip çalışmalarının, multidisipliner bir yaklaşımla deneyimli merkezlerde yapılmasına ayrı bir özen gösterilmelidir.

**Anahtar kelimeler:** Kalıtsal feokromasitoma; sporadik feokromasitoma; paroksismal hipertansiyon; multipl endokrin neoplazi tip 2; von Hippel-Lindau hastalığı

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Peer review under responsibility of Turkish Journal of Endocrinology and Metabolism.

**Received:** 18 Sep 2020 **Received in revised form:** 09 Nov 2020 **Accepted:** 27 Nov 2020 **Available online:** 11 Jan 2021



DOI:10.25179/tjem.2020-79054

## Introduction

Pheochromocytomas are rare tumors arising from the adrenomedullary chromaffin cells that originate from the neural crest (1). The reported annual incidence of pheochromocytomas is 2%-9.1% per million adults (2). Pheochromocytomas may either be sporadic or a component of hereditary syndromes such as multiple endocrine neoplasia type 2A and 2B (MEN 2A and MEN 2B), von Hippel-Lindau disease (VHL), and neurofibromatosis type 1 (NF-1); it may also be associated with the succinate dehydrogenase (SDHx) mutations (3,4). Sporadic pheochromocytomas are more common in the 3rd to 5th decades of life, while hereditary pheochromocytomas tend to occur at younger ages (3,5). The prevalence of pheochromocytomas in patients with hypertension is 0.1%-0.6%, and the incidence of pheochromocytomas in patients with adrenal incidentalomas is 5% (6-9).

Plasma free metanephrine or urinary fractioned metanephrine measurement is recommended to the patients for diagnosis in case of pheochromocytoma suspicion (10). The patients with biochemical evidence of pheochromocytoma should be subjected to computer tomography (CT) or magnetic resonance imaging (MRI) for localization (10). The nuclear imaging methods are useful for the functional evaluation and detection of metastatic disease. Laparoscopic adrenalectomy is suggested to most of the patients with adrenal pheochromocytomas after achieving adequate alpha blockage (2,10). Despite the availability of multiple histological algorithms for the prediction of the biological behavior and malignant potential of pheochromocytomas, no gold standard grading system exists to date. Even now, malignancy is being diagnosed through the detection of local invasion of the surrounding tissues and organs or distant metastases (11). Since all kinds of pheochromocytomas have a potential for malignancy, life-long annual biochemical evaluation is recommended for the detection of recurrent or metastatic disease in the patients (10).

The present retrospective study was aimed to present our experiences related to pheochromocytomas in 16 years of practice. The patients diagnosed with pheochromocytoma were investigated and the concomitance with genetic syndromes, their symptoms, signs, and biochemical characteristics was evaluated at the time of application as well as during follow-up. In addition, the treatment methods applied, the success rates of the applied treatment, and the recurrence rates in the patients were studied.

## Material and Methods

A total of 67 patients diagnosed with pheochromocytoma between January 2004 and July 2020 were included in the present study. Data regarding the demographic properties (age and gender), clinical history (presentation, medical history, complications, and family history), laboratory tests (24-hour urinary metanephrines and normetanephrines or plasma fractionated metanephrines and normetanephrines), imaging studies, surgical approaches, and pathological reports were obtained using paper charts and electronic records. Pheochromocytoma was diagnosed by measuring the 24-hour urine metabolites of catecholamines and searching for the detection of adrenal lesions in CT or MRI in the suspected patients. The 24-hour urine metanephrines and normetanephrines were measured using high-performance liquid chromatography (HPLC). CT without contrast and contrast-enhanced MRI were used as the primary imaging modalities. Lesion size was measured considering the largest dimension, and in bilateral cases, the size of the largest side was considered. In selected patients, nuclear imaging methods such as MIBG or PET CT were used. The patients with typical clinical signs and symptoms of pheochromocytoma, the patients with a history or a family history of genetic syndromes associated with pheochromocytoma, and those with adrenal incidentalomas were investigated for pheochromocytoma. Genetic tests were performed for the patients. Pheochromocytoma in the patients with negative genetic mutations and the patients with no suspicion of genetic syndromes and no available genetic test results were defined as sporadic. Laparoscopic adrenalectomy or adrenalectomy with open surgery was performed as the primary treatment approach, while other treatment options were considered in case of recurrent or metastatic disease. An 81-year-old female patient

who was clinically, biochemically, and radiologically diagnosed with pheochromocytoma refused to undergo surgery and is being followed-up with antihypertensive therapy, including the alpha blockers. The pathological specimens were examined by the experts in this field. All patients received at least 21 days of alpha blockage therapy (doxazosin), and a few patients received beta blockage after adequate alpha blockage therapy preoperatively. Beta blockage therapy was provided additionally in cases of persistent tachycardia, tachyarrhythmias, and persistent hypertension, despite adequate alpha blockage. Adequate fluid and salt intake were recommended to all patients during the preoperative period.

The study followed the ethical standards and adhered to the study protocol according to the international agreements (Helsinki Declaration revised in 2013). The study was approved by the Clinical Research Ethical Committee of Dokuz Eylül University on 21.10.2019; 2019/26-32.

### Statistical Analysis

Statistical analyses were performed using IBM SPSS for Mac Version 20 (IBM Corp. Released 2011, Armonk, NY). Numeric variables were expressed either as mean ±SD or as median (minimum-maximum) based on their distribution features. Categorical variables were evaluated with cross-table analysis and expressed numerically as a percentage. Mann-Whitney U test was used for pairwise comparison of the data that was not normally distributed, while Student's t-test was used for the pairwise comparison of normally distributed data. Spearman's correlation analysis was performed. $p<0.05$ was considered statistically significant.

## Results

### Demographic Information and Pheochromocytoma Evaluation

The present retrospective study included 67 patients with an initial diagnosis of pheochromocytoma, among which 66 patients had undergone one or more adrenal surgeries. The mean age (±SD) of the patients at the time of diagnosis of pheochromocytoma was 46 years (±16.1), and the female to male ratio was 1.2. The urinary catecholamine metabolite levels, biochemical parameters, and lesion characteristics in the patients are summarized in Table 1.

The median urinary metanephrine level was 633.9 ug/24 h (range: 28-18642), and the median urinary normetanephrine level was 1001 ug/24 h (range: 37.9-10071). Among the 50 patients with available urinary catecholamine levels, 18 patients (36%) exhibited predominantly increased urinary normetanephrine levels, ten patients (20%) had predominantly increased urinary metanephrine levels, 14 (28%) exhibited an increase in both urinary metanephrine and normetanephrine levels, and eight patients (16%) had normal levels. These urinary catecholamine metabolite levels correlated positively with the tumor size ($p<0.001$).

Table 1. Demographic and anthropometric characteristics, urinary catecholamine metabolite levels, biochemical parameters, localization, and lesion sizes of the patients at the time of diagnosis of pheochromocytoma.

| Parameter (reference range) | Value |
|---|---|
| Age (y) | 46 (±16.1) |
| Gender (F/M) | 37/30 (55.2%/44.8%) |
| Weight (kg) | 67.8 (±12.8) |
| BMI (kg/m$^2$) | 25.2 (±6.3) |
| Urinary Metanephrines (52-341ug/24 h) | 633.9 (28.2-18642) |
| Urinary Normetanephrines (88-444 ug/24 h) | 1001 (37.9-10071) |
| Size (mm) | 40 (9-90) |
| Localization (Left/Right/Bilateral) | 23/34/10 (34.3%/50.7%/14.9%) |

BMI: Body mass index; F: Female; M: Male; y: years.
Mean values (±SD) are provided for equally distributed variables while median (minimum-maximum) values are provided for unequally distributed variables. Nominal parameters are provided as number (percentage).

In all patients, CT and/or MRI were used for diagnosis, while MIBG and PET CT were used additionally for the lesions that required further characterization (29.9% and 9%, respectively). Imaging analysis of the patients revealed lesions other than adenomas that were suspects for pheochromocytomas. The median size of the adrenal lesions was 40 mm (range: 9-90 mm), with 57 patients (85.1%) having unilateral adrenal lesion and ten patients (14.9%) having bilateral pheochromocytoma (Table 1).

## Presentation Characteristics

Among the 61 patients whose presentation details could be obtained, pheochromocytoma diagnosis was provided on the basis of the clinical signs and symptoms in 31 patients (50.8%), while diagnosed during adrenal incidentaloma evaluation happened in 19 patients (31.2%). The remaining 11 patients (18%) were investigated either due to family histories of MEN, medullary thyroid cancer, VHL, and pheochromocytoma or due to their personal histories of familial syndromes or the diagnosis of diseases associated with the familial syndromes such as MTC (Table 2). Among these, eight patients had a family history of pheochromocytoma (7 had MEN2A and 1 had VHL), one patient had a family history of paraganglioma (her genetic analysis is non-applicable), and one patient with a family history of adrenal surgery died in a cerebrovascular event (his genetic analysis for hereditary syndromes was negative).
Hypertension pre-existed in 38 patients (56.7%), while eight patients (11.9%) received a diagnosis of hypertension at the

Table 2. Pheochromocytoma diagnosis histories of the patients.

| Detection history | Number of patients (%) |
|---|---|
| Investigation due to symptoms and signs | 31 (50.8%) |
| Incidentaloma screening | 19 (31.2%) |
| Screening due to family history of MEN | 4 (6.6%) |
| Screening due to diagnosis of MTC | 3 (4.9%) |
| Investigating due to history of NF1 | 2 (3.3%) |
| Screening due to family history of VHL | 1 (1.6%) |
| Screening due to family history of pheochromocytoma | 1 (1.6%) |
| Accompanying diseases and symptoms | |
| Existing hypertension | 38 (56.7%) |
| Preeclampsia/abortus | 2 (3%) |
| Hypertensive retinopathy | 2 (3%) |
| Hypertension diagnosed at the time of diagnosis | 8 (11.9%) |
| Paroxysmal pattern | 36 (53.7%) |
| Asymptomatic | 17 (25.4%) |
| Type 2 diabetes | 15 (22.4%) |
| Impaired fasting glucose and/or impaired glucose tolerance | 5 (7.5%) |
| Cardiovascular disease (angina, PTCA, MI, medical treatment) | 12 (17.9%) |
| Cardiomyopathy | 2 (3%) |
| Palpitation | 22 (32.8%) |
| Headache | 14 (20.9%) |
| Sweating | 10 (14.9%) |
| Weight loss | 4 (6%) |
| Pallor | 4 (6%) |
| Flushing | 4 (6%) |
| Fainting | 3 (4.5%) |
| Vomiting | 2 (3%) |
| Nervousness | 1 (1.5%) |
| Anxiety | 1 (1.5%) |
| Hematemesis | 1 (1.5%) |
| Chest pain | 1 (1.5%) |

MEN: Multiple endocrine neoplasia; MTC: Medullary thyroid cancer; NF1: Neurofibromatosis type 1; VHL: von Hippel-Lindau; PTCA: Percutaneous transluminal coronary angioplasty; MI: Myocardial infarction.

time of pheochromocytoma diagnosis. A paroxysmal pattern was observed in 36 patients (53.7%). The most common symptoms accompanying paroxysmal hypertension were palpitation, headache, and sweating. Detailed information regarding the symptoms at the initial presentation is summarized in Table 2. The accompanying malignancies in the patients with sporadic pheochromocytoma were papillary thyroid cancer in one patient and breast cancer in one patient at the time of diagnosis. Two patients were diagnosed with malignancies during follow-up (bladder cancer in one patient; papillary thyroid cancer and basal cell carcinoma in one patient).

### Accompanying Adrenal Cortex Evaluation

In eight patients (11.9%), low-dose dexamethasone suppression test (DST) was unable to suppress cortisol (>1.8 mcg/dL), while three patients with cortisol levels higher than 5 mcg/dL after 1 mg DST received steroid coverage during the surgery as well as for a short time after the surgery. We have previously reported a patient's case with the diagnosis of CRH producing pheochromocytoma (12). Postoperative ACTH levels and cortisol values after DST were normalized in these three patients.

### Surgical Approach and Complications

All patients had successful surgery and were discharged from the hospital. Among these patients, one patient experienced intraoperative hypertension approaching 200 mmHg systolic pressure, and another experienced severe hypotension in the postoperative period; both were treated successfully. Moreover, one patient was readmitted to the endocrinology clinic on postoperative Day 7 with a complaint of hypotension and a history of syncope. Her blood pressure was 70/40 mmHg. She was hospitalized, treated with intravenous isotonic fluid and increased oral salt intake, and discharged from the hospital after three days. Adrenal insufficiency was excluded, and she did not report any complaints afterward.

Ten patients had bilateral adrenalectomy, either in one session or in separate surgeries during follow-up. Nine patients had genetic syndromes associated with pheochromocytomas, while the genetic test results of one patient (with a family history of paraganglioma) were non-applicable (Table 3). Two

Table 3. Pathological diagnosis, surgery types, and outcomes of the patients.

| **Operation features** | |
|---|---|
| Type of surgery Laparoscopic/Open surgery* | 45/11 (80.4%/19.6%) |
| Perioperative/Postoperative hemodynamic instability** | 4 (6%) |
| Pathological diagnosis (n=66) | Number of patients (%) |
| Pheochromocytoma | 60 (91%) |
| Composite pheochromocytoma (+ganglioneuroma) | 3 (4.5%) |
| Adrenal medullary hyperplasia | 2 (3%) |
| Necrosis | 1 (1.5%) |
| PASS score*** | 4 (0-17) |
| PASS <4 | 15 (42.9%) |
| PASS ≥4 | 20 (57.1%) |
| Outcome | |
| Median follow-up (y) | 3 (0.3-14) |
| Remission | 47 (71.2%) |
| Missed follow-ups | 15 (22.7%) |
| Metastatic disease | 2 (3%) |
| Recent operation | 2 (3%) |
| Deceased | 1 (1.5%) |
| Being followed-up without surgery | 1 (1.5%) |

PASS: Pheochromocytoma of the Adrenal gland Scaled Score.
*n=56; **n=50; ***n=35.

patients with unilateral pheochromocytoma had non-functional stable, benign adrenal lesions on the contralateral adrenal gland.

### Pathological Evaluation

Pathological diagnoses of the patients are summarized in Table 3. Among the patients who underwent surgery, 60 patients had pheochromocytoma, three patients had composite pheochromocytoma (+ganglioneuroma), two patients had medullary hyperplasia, and one patient had necrosis. The median PASS score of the patients was 4 (range: 0-17). Laparoscopic surgery was preferred over open surgery (Table 3).

### Outcomes of the Patients

Our median follow-up time after the surgeries performed in our hospital was three years (range: 0.3-14). The follow-up characteristics of the patients are summarized in Table 3. The detailed information regarding the hereditary syndromes of the patients and their families, along with the outcomes, is provided in Table 4. Forty-seven patients are being followed-up in remission, while 15 patients missed their follow-ups. Among the two patients with metastatic disease, one patient had MEN2A, and the metastasis was detected one year after the surgery (Table 4, MEN2A, Family 2, patient 1). She had multiple metastatic lesions in the lung, liver, and bone, as well as retroperitoneal implants and local recurrence. She is currently being followed-up by the medical oncology and nuclear medicine teams. The other patient with metastatic pheochromocytoma had no family history or diagnosis of a hereditary syndrome. He was diagnosed with lytic bone metastasis four years after the surgery with no local recurrence and is currently receiving chemotherapy. One patient with the diagnosis of MEN2A died one year after bilateral adrenalectomy due to severe upper respiratory infection and adrenal insufficiency despite receiving adequate steroid replacement therapy and warnings regarding stress conditions (Table 4, MEN2A, Family 5, patient 1).

### Characteristics of Hereditary and Sporadic Pheochromocytomas

Sixteen of the patients had accompanying hereditary syndromes, including MEN2A, MEN2B, VHL, and NF1. None of our patients had SDHx mutations. Among the 67 patients included in the present study, ten patients had MEN2A (14.9%), one patient had MEN2B (1.5%), three patients had VHL (4.5%), and two patients had NF1 (3%). The genetic analysis of one patient with possible hereditary syndromes was non-applicable; she was, therefore, excluded from the comparative analyses. The mean age of the patients with hereditary syndromes at the time of diagnosis (36±11.3 years) was significantly less ($p=0.003$) than the mean age of those with sporadic pheochromocytomas (49.4±16.3 years). The patients with sporadic pheochromocytomas tended to be more asymptomatic ($p=0.016$) rather than sporadic. Hereditary pheochromocytomas tended to be bilateral ($p<0.001$) (Table 5). Although statistically insignificant ($p=0.064$), the median lesion size of sporadic pheochromocytomas was observed to be larger than that of hereditary pheochromocytomas (Table 5).

## Discussion

In the present study, we have comprehensively reviewed our experience in the diagnosis, treatment, and follow-up of pheochromocytomas in a tertiary center during the period between 2004 and 2020. Our results concerning the initial presentations of the patients are rather different from those in the literature. Falhammar et al. (13) reviewed 98 cases in their study, in which diagnoses of pheochromocytomas were obtained mostly due to the investigation for incidentalomas (64%), followed by clinical suspicion of pheochromocytoma (32%) and screening for a family history of MEN2A (4%), respectively. In the present study, most of the patients (50.8%) were diagnosed due to suspicious symptoms of pheochromocytoma, while 31.2% of the patients were diagnosed during the incidentaloma screening. The remaining 18% of the patients were diagnosed while investigating for possible hereditary syndromes. This difference might be due to the use of more aggressive approaches for identifying the cause of secondary hypertension and the increased awareness of pheochromocytoma during the past years.

CT and MRI are generally accepted to be sufficient for the diagnosis of pheochromo-

Table 4. Detailed information regarding the patients and their families with hereditary syndromes.

| Age at diagnosis/Current age (y)/ Genetic mutation | HT and symptoms | Concomitant diseases | Urine catecholamine metabolites Size and localization | Treatment and outcome for pheochromocytoma |
|---|---|---|---|---|
| | | MEN 2A | | |
| Family 1 | | | | |
| Patient 1 (index) | Paroxysmal HT | MTC PHPT | M: N/A | Bilateral adrenalectomy |
| 33/43 | Palpitation Sweating | | NM: N/A | Bilateral pheochromocytoma |
| | | | Right: 20 mm | PASS: N/A |
| | | | Left: 65 mm | Remission (11y follow-up) |
| Patient 2 47/58 | Screening due to family history | MTC | M:2800 ug/24 h | Bilateral adrenalectomy |
| No symptoms | | PHPT | NM: 2629 ug/24 h | Bilateral pheochromocytoma |
| | | | Right: 43 mm | PASS: N/A |
| | | | Left: 46 mm | Remission (11y follow-up) |
| Patient 3 | HT | MTC | M: 462 ug/24 h | Bilateral adrenalectomy |
| 53/60 | Paroxysmal HT | PHPT | NM: 231 ug/24 h | Bilateral pheochromocytoma |
| | Palpitation Nervousness | Type 2 DM | Right: 15 mm | PASS: N/A |
| | | | Left: 9 mm | Remission (8y follow-up) |
| Patient 4 | Paroxysmal HT Palpitation | MTC | M: 673 ug/24 h | Unilateral adrenalectomy |
| 27/29 | | | NM: 1916 ug/24 h | Pheochromocytoma |
| | | | Left: 30 mm | PASS: 5 |
| | | | | Remission (2y follow-up) |
| Family 2 | | | | |
| Patient 1 (index) | Paroxysmal HT | MTC | M: N/A | Unilateral adrenalectomy |
| 46/58 | Pallor | Type 2 DM | NM: N/A | Pheochromocytoma |
| | Fainting | | Right: N/A | PASS: N/A |
| | Headache | | | Metastatic disease (1y after surgery) |
| | Palpitation | | | Total follow-up 12 years |
| | High glucose | | | Medical oncology and nuclear medicine |
| Patient 2 | Screening due to family history | MTC | M: 708 | Bilateral adrenalectomy |
| 30/38 | Hypertension | PHPT | NM: 1186 | (2 years apart) |
| *RET c.1901G>A* | Pallor | | Left: 25 mm | Bilateral pheochromocytoma |
| | Fainting | | MIBG: left | PASS: N/A |
| | Headache | | 2 years later | Remission (9y after second surgery) |
| | | | Right: 25 mm | |
| | | | MIBG: right | |

*continued* →

Table 4. Detailed information regarding the patients and their families with hereditary syndromes *(contunied)*.

| Age at diagnosis/Current age (y)/ Genetic mutation | HT and symptoms | Concomitant diseases | Urine catecholamine metabolites Size and localization | Treatment and outcome for pheochromocytoma |
|---|---|---|---|---|
| Family 3 | | | | |
| Patient 1<br>40/46<br>RETc611y<br>(index) | Investigated for MEN due to MTC<br>No symptoms | MTC | M: 79 ug/24 h<br>NM: 77 ug/24 h<br>Left: 16 mm | Unilateral adrenalectomy<br>Pheochromocytoma<br>PASS: 4<br>Remission (6y follow-up) |
| Family 4 | | | | |
| Patient 1<br>45/49<br>RETp.cys634arg<br>(index) | Investigated for MEN due to MTC<br>No symptoms | MTC<br>PHPT | M: 537 ug/24 h<br>NM: 109 ug/24 h<br>Right: 35 mm<br>Left: 25 mm | Bilateral adrenalectomy<br>Pheochromocytoma/composite pheochromocytoma (+ganglioneuroma)<br>PASS: 1/4<br>Remission (4y follow-up) |
| Family 5 | | | | |
| Patient 1<br>34/35 ex<br>N/A | HT<br>Paroxysmal HT<br>Palpitation | MTC<br>PHPT | M: 3018 ug/24 h<br>N: 929 ug/24 h<br>Right: 60 mm<br>Left: 65 mm | Bilateral adrenalectomy<br>Bilateral pheochromocytoma<br>PASS: 6<br>Deceased (1 y after surgery) |
| Family 6 | | | | |
| Patient 1<br>42/55 | Screening due to family history<br>No symptoms | MTC | N/A<br>Right: 25 mm<br>Left: 50 mm | Bilateral adrenalectomy<br>Bilateral pheochromocytoma<br>PASS: N/A<br>Remission (13y follow-up) |
| | | **MEN 2B** | | |
| Family 1 | | | | |
| Patient 1<br>26/29<br>RETM918T<br>(index) | Investigated for MEN due to MTC<br>No symptoms | MTC<br>Marfanoid habitus<br>Lingual ganglioneuroma | M: 129 ug/24 h<br>NM: 62 ug/24 h<br>Right: 9 mm | Unilateral adrenalectomy Pheochromocytoma<br>PASS: 0<br>Remission (3y follow-up) |

*continued* →

Table 4. Detailed information regarding the patients and their families with hereditary syndromes *(contunied)*.

| Age at diagnosis/Current age (y)/ Genetic mutation | HT and symptoms | Concomitant diseases | Urine catecholamine metabolites Size and localization | Treatment and outcome for pheochromocytoma |
|---|---|---|---|---|
| | | **VHL** | | |
| Family 1 | | | | |
| Patient 1<br>22/49 | Detected during pregnancy<br>(Intrauterine ex)<br>Paroxysmal HT | Autoimmune thyroid disease | M: 28.19 ug/24 h<br>NM: 333 ug/24 h (before second op)<br>R: 25 mm<br>L: 18 mm<br>MIBG: left adrenal active | Bilateral partial adrenalectomy<br>Steroid replacement: only during pregnancy<br>Local recurrence (24y after)<br>Left unilateral adrenalectomy<br>Pheochromocytoma<br>PASS:2<br>3y follow-up after second surgery |
| Patient 2<br>10y/24y<br>VHL<br>VHL c.695 G>A<br>(index) | Screening due to history of retinal angioma and family history of pheochromocytoma<br>No symptoms | Retinal angioma | N/A<br>Bilateral<br>Size: N/A | Bilateral adrenalectomy<br>Invasive pheochromocytoma<br>PASS: N/A<br>Remission (14y follow-up) |
| Family 2 | | | | |
| Patient 1<br>32/34 | Screening due to family history<br>No symptoms | Intracranial lesion<br>Spinal hemangioblastoma<br>Clear cell RCC<br>Pancreatic serous cystadenoma | M: 42 ug/24 h<br>NM: 505 ug/24 h<br>Left: 33 mm<br>MIBG: Left | Unilateral adrenalectomy<br>Hematoma and medullary hyperplasia<br>PASS: N/A<br>Remission (2y follow-up) |
| | | **NF1** | | |
| Family 1 | | | | |
| Patient 1<br>46/52 | Incidentaloma<br>No symptoms | Subcutaneous neurofibromas | M: 766 ug/24 h<br>NM:1547 ug/24 h<br>Right: 70 mm<br>1y after op.<br>Left: 20 | Unilateral adrenalectomy<br>Adrenal medullary tumor, composite pheochromocytoma (+ganglioneuroma)<br>PASS: 7<br>Remission (6y follow-up)<br>Left adrenal lesion: stable |
| Family 2 | | | | |
| Patient 1<br>43/49 | Paroxysmal HT<br>Headache<br>Diagnosis of NF | Schwannoma (mediastinal and in the extremity)<br>Neurofibromas<br>Café-au -lait | M: 709 ug/24 h<br>NM: 718 ug/24 h<br>Left: 44 mm | Unilateral adrenalectomy<br>Pheochromocytoma<br>PASS: 4<br>Remission (7y follow-up) |

HT: Hypertension; M: Metanephrines; MEN 2A: Multiple endocrine neoplasia type 2A; MEN 2B: Multiple endocrine neoplasia type 2B; MIBG: Metaiodobenzylguanidine; MTC: Medullary thyroid cancer; N/A: Non-applicable; NF: Neurofibromatosis; NM: Normetanephrines; PASS: Pheochromocytoma of the adrenal gland scaled score; PHPT: Primary hyperparathyroidism; RCC: Renal cell carcinoma; VHL: von Hippel-Lindau; y: Year.

Table 5. Comparison of the characteristics of hereditary and sporadic pheochromocytomas.**

| | Hereditary pheochromocytoma | Sporadic Pheochromocytoma | p value |
|---|---|---|---|
| Age (y) | 36 (±11.3) | 49.4 (±16.3) | 0.003 |
| F/M | 9/7 | 27/23 | 1 |
| Asymptomatic/Symptomatic | 8/8 | 9/41 | 0.016 |
| Bilateral/Unilateral adrenalectomy | 9/7 | 0/49 | p<0.001 |
| Urinary Metanephrines | 605 (28-3018) | 600.4 (34.8-18642) | 0.588 |
| Urinary Normetanephrines | 612 (62-2629) | 1200 (37.9-10071) | 0.117 |
| Lesion size | 31.5 (9-70) | 40 (18-90) | 0.064 |

F: Female; M: Male; y: Years.

cytomas owing to characteristic appearances and contrast-enhancement profiles (14). These typical findings were observed in all our patients who had radiological imaging reported to be suspicious for pheochromocytoma or consistent with the non-adenoma adrenal lesion. Although MIBG and PET CT are not recommended for diagnosis in routine use, they are used for the evaluation of functionality and metastatic disease, respectively (14). In the present study, CT and/or MRI were sufficient for diagnosis for most of the patients, while nuclear imaging methods had to be used additionally for 37.3% of the patients. In our study, tumor size was significantly correlated with the urinary catecholamine levels, similar to other studies, while the median size of the lesions in our study (40 mm) was slightly smaller than that reported (49 mm) in previous studies (13,15). The smaller tumor size in our study could be attributed to the relatively higher number of patients investigated for genetic syndromes.

As the patients with clinical suspicion constituted the dominant portion of clinical presentation, 56.7% of the patients had pre-existing hypertension, while 11.9% of the patients were diagnosed with hypertension at the time of pheochromocytoma diagnosis. Two patients were diagnosed with pheochromocytoma while being investigated for preeclampsia and abortus. Hypertension exhibited a paroxysmal pattern in 53.7% of the patients. The major accompanying symptoms of the hypertension episodes were palpitation, headache, and sweating, consistent with the classical triad of pheochromocytoma (16).

Pheochromocytoma incidence during pregnancy was <0.2 per 10,000 pregnancies (17). It is generally stated that the diagnosis of pheochromocytoma during pregnancies might go unnoticed due to the rarity of this disease and because its symptoms generally mimic the other forms of hypertension observed during pregnancy, such as preeclampsia and gestational hypertension (17). Two of our patients had a history of abortus and preeclampsia at the time of presentation. It is important to consider pheochromocytoma in pregnant women with hypertension as this disease may cause significant morbidity and mortality to both fetus and mother. Since the screening of all pregnant women with hypertension is not a cost-effective approach, it is recommended to screen the pregnant women with resistant hypertension, those having adrenal mass, and the ones with classical signs and symptoms of pheochromocytoma (17).

Despite improvements in preoperative preparation with alpha blockage (and subsequent beta blockage if required) and adequate fluid intake, both perioperative and postoperative complications can occur in patients with pheochromocytoma. Laparoscopic surgery is our preferred surgical approach, and the intraoperative and postoperative complications observed are low in our institution. A study concerning 100 patients with pheochromocytoma reported 27.3% hemodynamic instability in the perioperative period (18). The overall rate of he-

modynamic instability in perioperative and postoperative periods in our patients was 6%. General anesthesia, along with sympathetic blockage, is the preferred method for anesthesia. Adequate preoperative preparation, appropriate anesthesia administration, laparoscopic approach, and the experienced team could be the possible reasons for a low frequency of intraoperative severe hypertension. Tumor manipulation during the resection of pheochromocytoma is thought to be the most probable reason for perioperative hypertension (19). Prolonged hypotension after tumor removal might be due to chronically low circulating levels of plasma volume, an abrupt decrease in the plasma catecholamine levels, downregulation of adrenoreceptors, increased blood loss, and cardiogenic or septic shock (19,20). Larger tumor size and higher urinary catecholamine metabolite levels are reported as the predictors of prolonged hypotension requiring postoperative catecholamine support (20).

Low dose DST was unable to suppress cortisol levels in 11.9% of the patients, while three patients had cortisol levels higher than 5 mcg/dL after 1 mg DST. Among the latter, one patient had accompanying obvious Cushing syndrome and was diagnosed with ectopic CRH secretion from the pheochromocytoma, as previously reported (12). In addition, the ACTH levels of the remaining two patients were not suppressed. Despite normalization of both ACTH levels and cortisol suppression after DST, we were unable to explain the causality as ACTH, and CRH staining of the pathology specimens could not be performed. When considering the patients with DST values compatible with subclinical Cushing syndrome, there are possible reasons for such results. First, the abnormal test results, particularly in patients with subclinical Cushing, may be interpreted as false-positive results as there are several common sources of error for DST's. Acute stress and illness, conditions elevating the serum corticosteroid-binding globulin (CBG) levels, and drugs causing variations in dexamethasone metabolism through cytochrome 3A4 (CYP3A4) are reported to cause false-positive results (21). In addition, increased cortisol secretion could accompany the pheochromocytomas via several different mechanisms, one of which is the increased catecholamine secretion that causes increased cortisol secretion via activation of aberrant adrenal beta-adrenergic receptors (22). Furthermore, cytokines such as tumor necrosis factor-alpha, interleukin-1 (IL-1), and interleukin-6 (IL-6) are reported to activate the hypothalamic-pituitary-adrenal (HPA) axis (23). There are also studies demonstrating cytokine production from pheochromocytomas resulting in increased cortisol production from the adrenal cells (24,25). Corticomedullary mixed tumors causing both pheochromocytoma and subclinical Cushing syndrome are also reported (26).

The pathological reports of two patients stated adrenal medullary hyperplasia, and three patients stated composite pheochromocytoma, both of which are rare conditions reported to be associated with hereditary conditions, although sporadic cases are also reported (27-31). One of our patients with adrenal medullary hyperplasia was diagnosed with VHL, and the other patient was a sporadic case with negative genetic test results. To the best of our knowledge, our patient is the first one to have been diagnosed with both VHL and adrenal medullary hyperplasia. On the other hand, among the three patients with composite pheochromocytoma, two had hereditary syndromes (MEN2A and NF1). Medullary hyperplasia is considered a precursor of pheochromocytoma, while composite pheochromocytoma is clinically and radiologically indistinguishable from pheochromocytoma and these cases are, therefore, recommended to be managed similar to pheochromocytomas (32-34).

The risk of pheochromocytoma was reported to be 50% in MEN2A and MEN2B, 10-20% in VHL, and 1-3% in NF-1 (35,36). Although pheochromocytomas in NF-1 are generally benign and unilateral, bilateral, recurrent, or malignant pheochromocytomas may also be detected (36). Our patients with NF-1 had unilateral lesions and are being followed-up regularly after adrenalectomy in remission. Pheochromocytomas in MEN2 and VHL tend to be bilateral and generally occur at younger ages compared to sporadic pheochromocytomas (37,38). In our study, most of the patients with bilateral adrenal lesions had hereditary syndromes. Heredi-

tary pheochromocytomas in our study tended to occur at younger ages, and the adrenal lesions tended to be smaller. The mean age of our patients with hereditary syndromes at the time of diagnosis was significantly lower than that of the sporadic cases. Although the median lesion size in our patients with hereditary syndromes tended to be smaller than that in the sporadic cases, the difference was not statistically significant. Hereditary pheochromocytomas were more asymptomatic rather than sporadic. These observations could be attributed to the early detection of the lesions because of the screening in hereditary syndrome-diagnosed families. Pheochromocytomas are generally diagnosed after medullary thyroid cancer in patients with MEN2, as in our study (38). Pheochromocytomas in VHL are generally asymptomatic, while the pheochromocytomas in MEN are generally associated with paroxysmal hypertension, which was partially true for our study as well (38).

### Study Limitations

The retrospective pattern of our study generated multiple limitations. Missing data for certain patients, such as symptom durations, urinary catecholamine metabolite levels, PASS scores, and types of surgeries, and the patients missing their follow-ups were the main limitations. In addition, not all patients had genetic testing results, and the lack of routine genetic screening reduced the reliability of sporadic cases as the sporadic case definition was generally based on no clinical suspicion for a hereditary syndrome. In addition, the sample size was relatively small, and the data were obtained from a single institution.

## CONCLUSION

In conclusion, our study group may be defined as a small cohort of pheochromocytoma as it represents the general features and the accompanying hereditary syndromes of the disease. Pheochromocytoma should be suspected in the hypertensive patients with resistant hypertension, hypertension with a paroxysmal pattern, or secondary hypertension. In addition, as generally observed in hereditary syndrome cases, investigating the patients diagnosed with pheochromocytoma for possible hereditary diseases and screening for pheochromocytoma in the patients with hereditary diseases are important. Owing to the lesser understanding of the malignant potential of these tumors, life-long annual follow-up is recommended for the detection of recurrent or metastatic disease. Since pheochromocytoma is a rare condition that could be life-threatening, its evaluation, treatment, and follow-up should involve a multidisciplinary approach in experienced centers.

## Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

## Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

## Authorship Contributions

Idea/Concept: Serkan Yener, Mustafa Seçil, Ömer Demir, Kutsal Yörükoğlu, Mehmet Ali Koçdor; Design: Serkan Yener, Mustafa Seçil, Ömer Demir, Kutsal Yörükoğlu, Mehmet Ali Koçdor; Control/Supervision: Serkan Yener, Mustafa Seçil, Ömer Demir, Kutsal Yörükoğlu, Mehmet Ali Koçdor; Data Collection and/or Processing: Başak Özgen Saydam, Süleyman Cem Adıyaman, Ozan Bozkurt; Analysis and/or Interpretation: Başak Özgen Saydam, Süleyman Cem Adıyaman, Ozan Bozkurt, Serkan Yener; Literature Review: Başak Özgen Saydam, Süleyman Cem Adıyaman, Ozan Bozkurt; Writing the Article: Başak Özgen Saydam, Süleyman Cem Adıyaman, Ozan Bozkurt; Critical Review: Başak Özgen Saydam, Süleyman Cem Adıyaman; Materials:Süleyman Cem Adıyaman, Başak Özgen Saydam.

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