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Gender-related differences in the clinical presentation of malignant and benign pheochromocytoma

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Abstract Signs and symptoms associated with pheochromocytomas are predominantly caused by catecholamine excess, but tend to be highly variable and non-specific. In this study, we evaluated 23 male and 35 female pheochromocytoma patients for symptoms and signs of pheochromocytoma with special regard to gender-related differences in presentation. Total symptom score comparison between genders showed significant differences (12.0 vs. 7.8, *P*-value 0.0001). Female patients reported significantly more headache (80% vs. 52%), dizziness (83% vs. 39%), anxiety (85% vs. 50%), tremor (64% vs. 33%), weight change (88% vs. 43%), numbness (57% vs. 24%), and changes in energy level (89% vs. 64%). Females and males displayed comparable biochemical phenotypes (60% and 65% noradrenergic phenotype, respectively). Use of α- and/or β-blockade between males and females did not differ significantly. Subgroup analyses and multiple regression analysis revealed gender differences to be irrespective of benign or malignant disease, use of adrenoceptor-blockade, age and biochemical phenotype. We conclude female patients have significantly more self-reported pheochromocytoma signs and symptoms than male patients irrespective of biochemical phenotype and tumor presentation which may be related to distinct catecholamine receptor sensitivity. Clinicians should be aware of these complaints in female pheochromocytoma patients and offer adequate treatment if indicated.

Keywords Pheochromocytoma · Gender · Symptoms · Catecholamines

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Introduction

Pheochromocytomas are rare tumors arising either from chromaffin cells of medullary or extra-medullary tissue that synthesize, metabolize and secrete catecholamines. The diverse nature of catecholamine content and production of either predominantly norepinephrine (NE) or epinephrine (E) contribute to the variable clinical presentations [1, 2]. Catecholamines exert their effects through α- and β-adrenoceptors on various organs. Both catecholamines, but NE to a higher extent, stimulate β_1-adrenoceptors which will, for example, increase heart rate [2]. β_2-adrenoceptors are most potently stimulated by E which can lead to

hypotension and several metabolic effects and E is a stronger α_1-adrenoceptor agonist than NE [3]. Catecholamine concentrations at the effector sites are very important determinants of the final adrenoceptor-mediated response [2, 4, 5]. Adrenergic, predominately E-producing, tumors account for approximately 50% of adrenal tumors, the other half are primarily NE-producing [1]. Extra-adrenal tumors have been found to predominantly produce NE [6].

Although the majority of patients present with one or more symptoms related to catecholamine excess, the extent of catecholamine excess cannot be predicted by signs and symptoms alone, because of their variable and non-specific nature [6–9]. Desensitization of adrenoceptors (most likely due to long-term exposure to high circulating catecholamine levels) was demonstrated in a rat model of pheochromocytoma and might be an explanation for the reported lack of correlation between the level of catecholamine excess and symptoms [10].

Furthermore, gender differences in adrenergic receptor sensitivity have been reported. Studies have showed increased sensitivity to β_2-adrenergic receptor stimulation in women [11] and greater α_2-adrenoceptor-mediated effects in women have been suggested [12]. In addition, catecholamine-induced stress cardiomyopathy appears to be more prevalent in females, which is thought to be related to a gender-specific difference in adrenoceptor signaling in periods of excessive levels of catecholamines [13].

Pheochromocytomas are characterized by excessive levels of catecholamines, but specific gender-related differences in its presentation have not been described, so far. Therefore, we hypothesized that gender is an important determinant in the presentation of catecholamine excess-associated signs and symptoms in pheochromocytoma patients. Besides gender, we investigated biochemical phenotype, and benign versus malignant tumor behavior as possible determinants in pheochromocytoma-associated signs and symptoms.

Patients and methods

This study included 58 biochemically diagnosed pheochromocytoma patients (23 male and 35 female) who were admitted at the National Institutes of Health (NIH) and completed standardized questionnaires. The following signs and symptoms were assessed: blood pressure and heart rate at referral, headache, sweating, palpitations, anxiety or nervousness, tremors (hands/arms, feet/legs, or other), pain (chest, abdomen, back, or other), numbness, nausea/vomiting, weakness/fatigue, changes in energy level, weight change, warmth or heat intolerance, visual disturbances, dizziness, change in bowel function, pallor or flushing, and seizure. Symptoms were self-reported by answering yes or no preceding initial diagnosis. The most updated version of the questionnaire is available (by request) through our Clinical Trials Database website. Appropriate Institutional Review Boards approved the studies and all patients gave informed consent.

Biochemical testing

All patients were diagnosed with biochemically active pheochromocytoma on initial presentation with urinary or plasma catecholamines and/or metanephrines above the upper reference limit respective of institutional guidelines. Upon referral to NIH, biochemical testing was confirmed and included measurements of plasma concentrations of free metanephrines, normetanephrine (NMN) and metanephrine (MN), and catecholamines, NE and E determined by liquid chromatography with electrochemical detection as previously described [14]. Patients were classified as either having noradrenergic or adrenergic phenotype, according to the criteria published previously by Eisenhofer et al. [1]. In addition to biochemical testing, diagnostic evaluation included the use of conventional radiological imaging.

Analysis of data

Symptoms and signs were analyzed comparing gender, age, tumor behavior (non-metastatic and metastatic), and biochemical profile (noradrenergic and adrenergic). Male and female responses to the same questions were compared using chi square. A total symptom score, calculated as a ratio of the total number of affirmative responses out of the possible symptoms, was calculated for each patient. Total symptom scores were further analyzed in a multiple regression model with gender, tumor behavior, biochemical phenotype, use of adrenoceptor blockade at referral, and age as independent variables. Differences in blood pressure, heart rate, catecholamine concentrations, and metanephrine concentrations were assessed by unpaired *T*-test and a two-tailed *P*-value of less than 0.05 was considered significant.

Results

A total of 58 pheochromocytoma patients completed the questionnaire described. Our cohort consisted of 35 female and 23 male patients, with no significant differences in age (46.3 ± 12.5 (±SD) vs. 44.8 ± 16.5 years), mean arterial pressure (96 ± 18 (±SD) vs. 98 ± 12, $P = 0.6875$), heart rate (82 ± 14 (± SD) vs. 81 ± 14, $P = 0.8073$), or use of adrenoceptor blockade (55.9% vs. 47.6%, $P = 0.6887$) at referral admission. Multiple regression analysis with tumor behavior, biochemical phenotype, and use of adrenoceptor blockade and age as independent variables identified only

Table 1 Clinical presentation of pheochromocytoma

	All patients	Gender	
		Male	Female
n	58	23	35
Avg. age (years, ±SD)	45.7 (±14.1)	44.8 (±16.5)	46.3 (±12.5)
Signs & symptoms			
Palpitations	74% [43/58]	65% [15/23]	80% [28/35]
Sweating	72% [42/58]	61% [14/23]	80% [28/35]
Palor or flushing	70% [40/57]	61% [14/23]	76% [26/34]
Headache	69% [40/58]	52% [12/23]	**80% [28/35]***
Dizziness	66% [38/58]	39% [9/23]	**83% [29/35]*****
Anxiety	71% [40/56]	50% [11/22]	**85% [29/34]****
Panic attack	29% [17/58]	22% [5/23]	34% [12/35]
Tremor	53% [27/51]	33% [6/18]	**64% [21/33]***
Pain	75% [47/55]	60% [12/20]	83% [29/35]
Nausea	38% [22/58]	30% [7/23]	43% [15/35]
Weakness	79% [46/58]	74% [17/23]	83% [29/35]
Weight change	70% [38/54]	43% [9/21]	**88% [29/33]*****
Warmth	65% [35/54]	52% [11/21]	73% [24/33]
Visual disturbances	50% [29/58]	35% [8/23]	60% [21/35]
Constipation	50% [27/54]	48% [10/21]	52% [17/33]
Numbness	45% [25/56]	24% [5/21]	**57% [20/35]***
Seizure	11% [6/56]	4% [1/23]	15% [5/33]
Change in energy	79% [45/57]	64% [14/22]	**89% [31/35]***
Triad (%)	48 [28/58]	39 [9/23]	54 [19/35]
Avg. total symptoms [TSS]	10.4	7.8	**12.0*****
Blood pressure (mmHg)			
Systolic	134	136	134
Diastolic	79	80	78
Mean arterial pressure (mmHg, ±SD)	97 (±16)	98 (±12)	96 (±18)
Heart rate (BPM, ±SD)	82 (±14)	81 (±14)	82 (±14)

Patient's responses to survey for symptoms are compared considering gender. Significantly higher affirmative responses are in bold and indicated by asterisk (*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$; chi square). The triad includes positive responses for all three: palpitations, sweating, and headache. Total symptom score (TSS) was calculated by total affirmative responses over total questions (*** $P < 0.001$, unpaired *T*-test)

gender as an independent predictor of total symptom scores (β 0.464, $P < 0.0001$).

Symptoms

In general, females reported more signs and symptoms than males, as reflected by a higher total symptom score between females and males (12.0 vs. 7.8, $P = 0.0001$ Table 1). Significant differences between females and males patients were found for headache (80% vs. 52%, $P = 0.0250$), dizziness (83% vs. 39%, $P = 0.0005$), anxiety (85% vs. 50%, $P = 0.0042$), tremor (64% vs. 33%, $P = 0.0382$), weight change (88% vs. 43%, $P = 0.0004$), numbness (57% vs. 24%, $P = 0.0151$), and change in energy level (89% vs. 64%, $P = 0.0245$).

Biochemical phenotype

The levels of catecholamines and free metanephrines did not significantly differ between males and females. A noradrenergic phenotype was found in 60% of females and 65% of males in our cohort, an adrenergic biochemical phenotype was found in 40% and 35%, respectively. No patients had a primarily dopamine secreting phenotype. In the comparison between patients with noradrenergic and adrenergic biochemical phenotype, only tremor was found to be associated with E excess (74% vs. 41%, $P = 0.0222$), all other symptoms did not differ significantly. Correction for the biochemical phenotype did not change the significant gender differences in total symptom scores (Table 2).

Benign and malignant disease

Out of the 58 patients, 28 patients (19 females, 9 males) had non-metastatic pheochromocytoma, whereas 30 patients (16 females, 14 males) developed metastases. Comparing female versus male total symptom scores in subgroups of malignant and benign tumor behavior separately, similar gender differences (11.8 vs. 6.9 and 12.3 vs. 9.2, respectively) were found. Females with benign disease

Table 2 Gender and role of biochemical phenotype and tumor presentation

	Total	Male	Female	
Gender and biochemical phenotype				
Noradrenergic	36 patients (average TSS 10.0)	15 patients (average TSS 8.2)	21 patients (average TSS 11.2)	$*P = 0.0115$
Adrenergic	22 patients (average TSS 11.0)	8 patients (average TSS 7.1)	14 patients (average TSS 13.2)	$**P = 0.0050$
	$P = 0.3803$	$P = 0.5279$	$P = 0.1330$	
Gender and tumor presentation				
Malignant	30 patients (average TSS 9.5)	14 patients (average TSS 6.9)	16 patients (average TSS 11.8)	$**P = 0.0011$
Benign	28 patients (average TSS 11.3)	9 patients (average TSS 9.2)	19 patients (average TSS 12.3)	$P = 0.0687$
	$P = 0.1136$	$P = 0.1595$	$P = 0.6963$	

Comparison of total symptom scores (TSS) in patients with pheochromocytoma (** $P < 0.01$, * $P < 0.05$; unpaired t-test)

significantly reported weight change (88% vs. 38%, $P = 0.0084$) more frequently. Females with malignant disease also significantly reported more sweating (81% vs. 43%, $P = 0.0294$), headache (88% vs. 43%, $P = 0.0096$), dizziness (88% vs. 21%, $P = 0.0002$), anxiety (73% vs. 36%, $P = 0.0417$), tremor (53% vs. 17%, $P = 0.0499$), and weight change (88% vs. 46%, $P = 0.0166$) than male patients in this subgroup. Tumor presentation of benign or malignant disease did not change the greater total symptom score response in females (Table 2).

Discussion

In the present study we, for the first time, report gender-related differences in signs and symptoms associated with catecholamine excess in pheochromocytoma patients, using health-related questionnaires. Female patients reported significantly more symptoms of headache, dizziness, anxiety, tremor, weight change, numbness, and changes in energy level than males. Gender differences were found to be independent of biochemical phenotype, use of adrenoceptor blockade and the presence of malignant disease. We believe clinicians should be aware of these complaints in female pheochromocytoma patients and offer adequate treatment if indicated.

Distinct physiological features of male and female sympathoadrenal function have been previously reported [15]. Gender differences have been observed for adrenoceptor responsiveness, with women having greater α_2- and β_2-adrenergic receptor sensitivity than men [12]. Furthermore, in animal studies female rats exhibited greater α_2-adrenergic receptor protein levels than their male counterparts [16]. In our study, we found female pheochromocytoma patients to display significantly more catecholamine excess-associated signs and symptoms than male patients, irrespective of the biochemical phenotype. In accordance, a recent report revealed increased incidence of catecholamine excess-associated cardiomyopathy in female patients [13]. Because on average females and males had a similar degree of catecholamine elevation and comparable biochemical phenotypes, this does not explain the reported differences between genders. Estrogens have been shown to affect neuronal excitation in the central nervous system; however, the role of estrogen leading to different perception of peripheral stimuli is unclear [17]. Although in our study estrogens were not routinely measured, we did compare pre- and postmenopausal age as a predictive variable in multiple regression and gender remained the only significant predictor of total symptom scores in multiple regression analysis. Because our study focused on clinical complaints only, future studies are needed to reveal the exact underlying pathophysiology. However, we speculate that catecholamine receptor sensitivity could be associated with gender and might contribute to these differences. Moreover, differences in receptor polymorphisms, second messenger systems, and transporters associated with gender have been described [18–21].

Gender differences in signs and symptoms have been previously described in cancer patients [22–24]. Because these studies reported that women express more signs and symptoms than males, which is in line with our observations, it is possible that women report more disease-related complaints due to the presence of cancer itself. However, since we used a questionnaire focusing on complaints known to be associated with catecholamine excess and no differences between benign and malignant disease were found, we speculate this could be a disease-specific phenomenon. How does it transfer to clinical practice? Since women with pheochromocytoma report more commonly headache, dizziness, anxiety, tremor, weight change, numbness, and changes in energy level than men, clinicians should be aware of these findings and approach women in a different way. This means women with pheochromocytoma may need better or more careful evaluation of these symptoms and treatment should be adjusted differently than in males. Conversely, because men with this tumor appear to have less severe clinical manifestations, the

examining physician may be less likely to order the appropriate tests to establish pheochromocytoma in male patients. In the evaluation of patients, especially male, one needs to consider the diagnosis of pheochromocytoma even in the absence of the typical clinical manifestations. Such a gender-specific approach may be necessary for other endocrine tumors where excessive hormone levels may differently affect various organ systems. This is one of the first reports suggesting gender-specific evaluation of endocrine cancer patients.

One of the shortcomings of this study is the use of self-reported questionnaires. Patients were asked to complete these upon admittance at the NIH for symptoms experienced prior to initial diagnosis. Most patients were referred from elsewhere with different stages of disease, duration of follow-up, and treatment prior to referral. However, we only included patients with biochemically and histologically confirmed pheochromocytoma and furthermore studied patients in a clinical setting, thus reflecting clinical practice in a tertiary referral center. In addition, we compared age, blood pressure, medication use, and the levels of catecholamines with their respective metabolites and did not find significant differences between male and female subgroups.

In conclusion, our data indicate that female patients with pheochromocytoma report more catecholamine excess-associated complaints than male patients. Gender differences were found in the clinical presentation of both benign and malignant pheochromocytomas, and in both noradrenergic and adrenergic phenotypes. Thus, these complaints might be associated with gender-specific catecholamine receptor sensitivity, which needs to be investigated in future studies. Clinicians should be aware of gender differences in clinical presentation of pheochromocytoma, especially in complaints more often presented in women where additional treatment or care might be beneficial.

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