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ORIGINAL ARTICLE

Pre- and peri-operative characteristics, complications and outcomes of patients with biochemically silent pheochromocytomas; a case series

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Abstract

Purpose: Pheochromocytomas are rare tumors and biochemically silent ones with normal catecholamine levels are even rarer. Up to date, biochemically inactive pheochromocytomas are poorly investigated. We aimed to systematically assess the pre- and peri-operative characteristics and the outcomes of patients with these tumors who had been treated and followed-up in 2 tertiary centers.

Methods: Clinical, laboratory and imaging data, treatment outcomes and follow-up of biochemically silent pheochromocytoma patients were recorded.

Results: Ten patients (5 men) [median age at diagnosis 52.5 years (24–72)] were included. Adrenal masses were incidentally discovered in all patients except from one who presented with pheochromocytoma-related manifestations. Twenty-four-hour urine metanephrine and normetanephrine levels were in the low-normal, normal and high-normal range in 4, 4 and 2 patients and in 1, 6 and 3 patients, respectively. Tumors were unilateral [median size 46 mm (17–125)] and high density on pre-contrast CT imaging or high signal intensity on T2-weighted MRI scans were found in all cases. Pre-operatively, 5 patients were treated with phenoxybenzamine [median total daily dose 70 mg (20–100)]. Intra-operatively, 4 patients developed hypertension requiring vasodilator administration and 8 developed hypotension; vasoconstrictors were required in 5 cases. One patient, not pre-operatively treated with phenoxybenzamine, developed Takotsubo cardiomyopathy. During a median 24-month (12–88) follow-up period, one patient had disease progression.

Conclusions: The majority (90%) of patients with biochemically silent pheochromocytomas developed hemodynamic instability during adrenal surgery. In patients with biochemically silent adrenal lesions and a high suspicion index for pheochromocytoma based on tumor imaging characteristics, pre-operative alpha-blockade treatment may be advisable.

Keywords Adrenals · Pheochromocytomas · Silent · Metanephrines · Normetanephrines · Hemodynamic instability

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Introduction

Pheochromocytomas (PCs) and sympathetic paragangliomas (sPGLs) are rare neuroendocrine tumors, arising from chromaffin cells of the sympathoadrenal system, which autonomously synthesize and secrete catecholamines and their metabolites. According to recent epidemiological studies, their incidence is 0.57–0.66 cases per 100,000 person-years [1, 2] and it has increased over the last 20 years due to more frequent use of abdominal imaging, increased awareness and rate of suspicion for these disorders on the part of the medical community, as well as mutation-based case detection testing. These factors have led to earlier detection and an increasing number of PCs being diagnosed on the basis of imaging and genetic testing as opposed to symptom-recognition/clinical presentation [3].

Although the vast majority of PCs are catecholamine-secreting, in extremely rare cases, these tumors may demonstrate no functional activity. Biochemically silent PCs are characterized by normal catecholamine levels due to either lack of catecholamine production or subtle synthesis and secretion within the established normal levels [4]. They are mostly asymptomatic and they are discovered either incidentally on abdominal imaging or due to space-occupying complications; when malignant, they may present with symptoms of metastatic disease [5].

Data on the characteristics of patients with biochemically silent PCs are scarce and the clinical behavior of these tumors is poorly investigated, mainly due to their rarity. The aim of the present study was to review the clinical, hormonal and imaging characteristics of patients with biochemically silent PCs from two Endocrine centers and to assess the pre-, intra- and post-operative management of these tumors and their outcomes.

Patients and methods

Study design and patients

This was a retrospective case series study from two Greek Endocrine centers. The records of adult patients diagnosed with biochemically silent PCs between 2014 and 2021 and followed-up in each participating center were reviewed and clinical, laboratory and imaging data, as well as treatment outcomes were recorded. The study was retrospective in nature and involved no intervention beyond routine patient care. Data were collected on a dedicated proforma.

Histologically proven PCs were defined as biochemically silent if pre-operative 24 h urine fractionated metanephrine (MN) and normetanephrine (NMN) levels, determined by high-pressure liquid chromatography, were below the upper limit of their respective reference range, measured on two different occasions in order to minimize the possibility of false negative results. For each patient, 24 h urine MN and NMN levels were defined as the average value of the two different measurements. The first and the fourth quartiles of the 24 h urine MN and NMN normal values were classified as low- and high-normal levels, respectively, while the second and third quartiles were classified as normal levels.

Imaging analysis, pre-, intra- and post-operative management and follow-up of the patients were based on clinical practice guidelines and the expert opinions of radiologists, endocrinologists, anesthesiologists and surgeons with experience in the management of patients with adrenal disorders at each participating center [6, 7]. Disease progression was diagnosed on the basis of radiological appearances. Follow-up period was defined from the time of surgery until the last imaging.

Intra-operative parameters

During adrenal surgery, hemodynamic parameters (blood pressure and heart rate), as well as blood glucose levels were monitored. Intra-operative data were obtained by review of anesthetic charts. Arrhythmias were considered when treatment with antiarrhythmic drug was required. Intra-operative hypertensive crisis was defined as SBP ≥ 200 mmHg and need for vasodilator therapy. Intra-operative hypotension was considered when mean arterial blood pressure <60 mmHg and/or treatment with vasoconstrictors or intravenous fluids (crystalloid and/or colloid) was required. Hemodynamic instability was defined as one or more episodes of hypertensive crisis or hypotension during adrenal surgery [8].

The above intra-operative parameters were also evaluated in 40 consecutive biochemically active PCs managed with adrenal surgery. All of these cases were pre-operatively treated with alpha-adrenergic receptors blockade.

Statistical analysis

Statistical analysis was performed using the SPSS software package (SPSS Inc., version 23, Chicago, USA). Median (min, max) values were used to express the results in all cases and the x^2-test was performed for the comparison of categorical variables. A two-tailed p value < 0.05 was considered statistically significant.

Results

Pre-operative characteristics of patients with biochemically silent PCs

Ten patients (5 men) were included in the study. Their pre-operative characteristics are shown in Table 1. The adrenal

Table 1 Pre-operative characteristics of patients diagnosed with biochemically silent pheochromocytoma

Characteristics	Values
Total number	10
Sex (males/females)	5/5
Median age at diagnosis (years) (range)	52.5 (24–72)
Median BMI at diagnosis (Kg/m^2) (range)	25.2 (16–34.2)
Incidental finding	9
Tumor lateralization (right/left)	7/3
Median maximum tumor size on imaging (mm) (range)	46 (17–125)
Median tumor density (Hounsfield units) (range) ($n = 8$)	35 (20–45)
Number of patients with low-normal, normal and high-normal 24 h urine metanephrine levels	4/4/2
Number of patients with low-normal, normal and high-normal 24 hurine normetanephrine levels	1/6/3
Number of patients treated with a-adrenergic receptors blockade	5
Median phenoxybenzamine daily dose (mg) (range)	70 (20–100)
Median phenoxybenzamine total cumulative dose (mg) (range)	490 (340–810)

masses were incidentally discovered in all patients except from one who presented with paroxysmal hypertension, palpitations and postural hypotension. Seven cases had a history of arterial hypertension.

Adrenal tumors were unilateral in all cases (7 on the right side) with a median maximum size on imaging of 46 mm (17–125). Increased tumor density on pre-contrast CT imaging (≥20 Hounsfield units) or high signal intensity on T2-weighted MRI scan was found in all cases; cystic and/or necrotic component was evident in 7 cases. ^{123}I-metaiodobenzylguanidine scintigraphy (MIBG) was performed in 4 cases and it was positive in all of them.

Regarding catecholamine secretion, 24 h urine MN and NMN levels were in the low-normal, normal and high-normal range in 4, 4 and 2 patients and in 1, 6 and 3 patients, respectively. All patients had normal renal function. Plasma free MN and NMN, as well as 24 h urine 3-methoxytyramine (3-MT) levels were not included in the diagnostic protocol of PCs/PGLs of both Endocrine centers, therefore they were not measured in any patient. Pre-operative serum chromogranin A (CgA) levels were measured only in one case and it was found 10-times higher the upper limit of normal.

Pre-operative alpha-adrenergic receptors blockade with phenoxybenzamine at a median total daily dose of 70 mg (20–100) was administered in 5 patients; four of them had positive pre-operative ^{123}I-MIBG scan, while in the fifth one there was a high index of suspicion for PC based on imaging characteristics of the tumor. In two of them, terazocin was also offered, before phenoxybenzamine initiation, at a daily dose of 2 mg and 5 mg, respectively. Phenoxybenzamine was discontinued 24 h before the adrenal surgery. The median duration of alpha-adrenergic receptors blockade was 14 days (9–32).

Individual patients' characteristics at diagnosis along with their intra- and post-operative management and follow-up are shown in Table 2.

Intra-operative characteristics

Nine patients (90%) had one or more episodes of intra-operative hemodynamic instability, most commonly hypotension followed by hypertensive crisis (Table 2). Laparoscopic adrenalectomy was performed in 6 patients (cases 1, 2, 4–7) and open adrenalectomy in the remaining 4 ones.

Hypotension after adrenal vein ligation was developed in 8 patients (4 of them had not been treated pre-operatively with alpha-adrenergic receptor blockade). Normalization of blood pressure required use of vasoconstrictors (phenylephrine or noradrenaline) in 5 patients (pre-operative alpha-adrenergic receptors blockers were not offered in 3 of them), while in the other 3 only intravenous crystalloid and/or colloid fluids were administered. It should be mentioned that hypotension was of short duration and was successfully treated before extubation in all patients apart from one (case 7, Table 2), who had not been pre-operatively treated with phenoxybenzamine or terazocin, and who developed Takotsubo cardiomyopathy during surgery requiring admission in the cardiac intensive care unit.

Intra-operative hypertensive crisis requiring glyceryl trinitrate administration developed in 4 patients despite pre-operative treatment with alpha-adrenergic receptors blockade in 2 of them (Table 2). None of the patients developed intra-operative arrhythmias or hypoglycemia. Further statistical analysis between the two subgroups of biochemically silent PCs (treated *vs* non-treated with alpha-adrenergic blockade) was not performed due to small sample size.

Evaluation of the intra-operative characteristics of 40 consecutive patients with secreting PCs, who were pre-operatively treated with alpha-adrenergic blockade, revealed hypertensive crises and hypotensive episodes in 57.5% (23/40) and 37.5% (15/40) of them, respectively; none of the patients developed intra-operative arrhythmias or hypoglycemia.

After comparing patients with silent PCs, who were offered pre-operative treatment with phenoxybenzamine, *vs* secreting ones, no statistically significant difference in the rates of hypertensive crisis ($p = 0.64$) and hypotension ($p = 0.14$) was found between the two groups. Same findings were also observed when patients with silent PCs, not pre-operatively managed with alpha-adrenergic receptors

Table 2 Individual patients' characteristics at diagnosis along with their intra- and post-operative management and follow-up

Parameters/Cases	1	2	3	4	5	6	7	8	9	10
Sex	F	M	M	M	F	F	F	F	M	M
Age at diagnosis (years)	72	47	57	24	71	37	46	63	65	48
Hypertension	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Manifestations	No Incidental finding	No Incidental finding	No Incidental finding	No Incidental finding	Paroxysmal hypertension Palpitations Postural hypotension	No Incidental finding	No Incidental finding	No Incidental finding	No Incidental finding	No Incidental finding
Maximum tumor size on imaging (mm)	20	17	95	60	50	51	38	44	43	125
Pre-operative 24 h uMN levels	LN	LN	N	N	N	LN	N	HN	HN	LN
Pre-operative 24 h uNMN levels	HN	N	N	N	N	N	HN	HN	N	LN
Attenuation*	45 HU T2 hyper-intense	44 HU T2 hyper-intense	25 HU	T2 hyperintense	38 HU	T2 hyperintense	20 HU	23 HU	32 HU	42 HU
Cystic component/ necrosis	No	No	Extensive necrosis	Comprising 50% of tumor	Extensive necrosis	Extensive cystic component	Focal cystic component	Extensive necrosis	No	Focal necrosis
^{123}I - MIBG	Positive	Positive	Positive	ND	Positive	ND	ND	ND	ND	ND
Pre-operative use of alpha-blockers	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
Phenoxybenzamine Max daily dose (mg)	70	70	30	100	20	NA	NA	NA	NA	NA
Phenoxybenzamine Total cummulative dose (mg)	490	390	340	810	550	NA	NA	NA	NA	NA
Alpha-blocker treatment duration (days)	23	9	14	10	32	NA	NA	NA	NA	NA
Intra-operative hypertensive crisis	Yes	No	Yes	No	No	No	Yes	Yes	No	No
Intra-operative hypotension	No	Yes	Yes	Yes	Yes	Yes	Yes Takotsubo cardiomyopathy	Yes	No	Yes
Histology PASS score	6	2	9	7	6	6	5	6	7	7
Follow-up (months)	24	12	72	24	12	24	16	55	63	88
Hypertension during follow-up	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes

Table 2 (continued)

Post-operative 24 h uMN levels	LN	LN	N	N	N	LN	N	LN	LN	N	
Post-operative 24 h uNMN levels	N	LN	LN	HN	N	LN	LN	HN	LN	N	
Disease progression	No	No	No	No	No	No	No	No	No	Yes	88 mo after initial surgery

(*F* female, *M* male, *uMN* urine metanephine/ *uNMN* urine normetanephine, *LN* low-normal, *N* normal, *HN* high-normal, *ND* not done, *HU* Hounsfield units, *MIBG* metaiodobenzylguanidine scintigraphy, *NA* not applicable)

*CT image attenuation is given as pre-contrast HU

blockade, were compared with non-silent ones [hypertensive crisis ($p = 0.64$) and hypotension ($p = 0.14$)]. With regard to intra-operative hypoglycemia and arrhythmias, no comparison between biochemically silent and non-silent PCs was performed given that none of the patients in both groups developed any episodes.

Post-operative outcomes and follow-up

Complete tumor excision was achieved in all cases. Apart from the patient who developed Takotsubo cardiomyopathy, none of the other patients developed any episodes of hemodynamic instability during the post-operative period and there was no need for further administration of vasoconstrictors. Histology was diagnostic for PC in all patients and PASS score was ≥4 in all but one cases (2–9) (Table 2).

Testing for genetic syndromes known to be associated with PC was individually considered in each patient. Taking into account that PCs were unilateral in all cases and that, at the time at diagnosis, none of the patients had any syndromic or malignant features and no positive family history for any hereditary syndromes associated with PC, genetic testing was performed only in one patient (case 4, Table 2) due to young age. Genotyping of *SDHB, VHL, RET* was negative.

Median follow-up from the time of adrenal surgery until last imaging was 24 months (12–88). Post-operative 24 h urine MN and NMN levels were in the low-normal, normal and high-normal range in 5, 5, and 0 patients and in 5, 3 and 2 patients, respectively. During this period, disease progression was observed in one patient, 88 months after his initial surgery. A 2.9 cm right retroperitoneal para-aortic histologically-proven metastasis was detected with no local recurrence in the adrenal bed. At the time of disease progression 24 h urine MN and NMN levels were again normal.

In the only patient who pre-operatively presented with PC-related symptoms, adrenal surgery led to the resolution of all symptoms, as well as normalization of blood pressure levels.

Discussion

To our knowledge, this is the first case series systematically reviewing the clinical and imaging characteristics of patients with biochemically silent PCs and assessing their pre-, intra- and post-operative management and outcomes. We found that patients with biochemically silent PCs were in the vast majority asymptomatic and incidentally diagnosed (90%) due to lesions suspicious for PC on CT or MRI imaging. Importantly, 90% of the patients experienced at least one episode of hemodynamic instability during adrenal surgery, despite their tumors being biochemically inactive.

Biochemically silent PCs are very rare and published literature assessing the characteristics and the management of patients with this condition is extremely limited. We performed a literature search of Pubmed (up to 31/Dec/2021) using the term 'silent pheochromocytoma' and we identified only 12 reports [[3, 9–19], including 22 patients in total] assessing patients with histology-proven PCs and negative 24 h urine and/or plasma MN and NMN. Their pre-operative characteristics and management, as well as their intra-operative behavior and outcomes are presented in Table 3.

Patients with secreting PCs may present with a broad spectrum of symptoms including the classic triad of headaches, palpitations, and sweating, as well as symptoms of anxiety and panic attacks, cardiomyopathy or even heart failure [20]. In biochemically silent PCs, one would expect patients to be asymptomatic. Despite this being the case in the vast majority of our patients (90%) and of those published in the literature (Table 3), four patients in the study by Gruber et al. and one of ours presented with PC-related symptoms [3]. Whether these patients had periodically-secreting PCs or their MN and NMN levels were falsely normal cannot be elucidated. It should be noted, however, that in our case, 24 h urine MN and NMN levels were well within the normal range (not even in the high-normal) on 3 different occasions, when the patient was symptomatic.

Detection of biochemically silent PCs is mostly incidental [10, 11, 13, 15–17, 19] or on the basis of germline-mutation testing [3, 9, 18]. In all published cases (including ours), tumors were unilateral, apart from 2 patients in whom bilateral biochemically silent PCs have been described; one patient had multiple endocrine neoplasia type 2 A (MEN2A) [3], while in the other no genetic testing was performed [17]. Tumors had an unenhanced CT density >20 Hounsfield units [3, 11], while in others hyperintensity on T2-weighted MRI images was reported [3, 19]; cystic changes and necrosis were also common [13, 15–17, 19]. These findings are in accordance with the imaging features of our patients.

The management of biochemically silent PCs is challenging. In secreting PCs, pre-operative alpha-adrenergic receptors blockade, for the prevention of intra-operative hypertension, tachycardia, and hemodynamic instability, and blood volume restoration, in order to decrease the risk of protracted hypotension as a result of sudden vasodilation during surgery, are recommended [21]. However, the pre-operative use of alpha-adrenergic receptors blockers is currently challenged mainly due to the post-operative sustained hypotension that can manifest as a complication of these agents [22, 23]. Although unexpected, malignant hypertension during adrenal surgery has been described in some [11, 16, 17] but not all [9, 13, 15, 19] patients with biochemically inactive PCs, as well as hypotensive episodes after adrenal vein ligation [16, 17]; none of these patients were pre-operatively treated with alpha-adrenergic receptor blockers. In our series, 90% of the patients developed intra-operative hemodynamic instability. Hypotension presented in 8 patients (half of them were treated with pre-operative alpha-adrenergic receptors blockers) and hypertensive crises in 4 patients, despite pre-operative treatment with adrenergic blockade in 2 of them. Notably, in one case, intra-operative hemodynamic instability was very severe and the patient developed Takotsubo cardiomyopathy. Although not elucidated yet, a possible mechanism for the intra-operative behaviour of biochemically silent PCs is that they might harbor significant intra-tumoral catecholamine reserve which is discharged during surgical tumor manipulations [22]. Interestingly, we did not identify any statistically significant differences in the rate of intra-operative hemodynamic instability (hypotension or hypertensive crisis) when we compared biochemically silent who were offered pre-operative treatment with non-silent PCs. However, these findings should be interpreted with caution given the small number of patients with biochemically silent PCs pre-operatively managed with or without alpha-adrenergic blockade.

Follow-up of patients with biochemically silent PCs is usually individualized and due to the scarce relevant literature, there is a lack of evidence-based recommendations. According to the 2016 ESE pheochromocytoma guidelines, these patients should be followed-up for disease progression with imaging every 1–2 years [24]; the authors, however, acknowledge that this time interval is arbitrary due the absence of observational or randomized studies on non-functioning PCs. Only one of our patients had disease progression during a 24-month median period of follow-up. He developed a right retroperitoneal para-aortic metastasis 88 months after his initial surgery. Metastatic disease progression of a biochemically silent PC has been also reported in a *SDHD* mutation carrier, who developed mediastinal and infrahilar lymph node metastases 4 months after surgery and a lytic vertebral bone metastasis 3 years later [18]. In addition, 7 patients with metastatic PCs (2 with *SDHB* mutations and 5 with apparently sporadic tumors) and normal 24 h urine MN and NMN levels [14], as well as a case of apparently sporadic biochemically silent PC who presented with metastatic disease at diagnosis [3] have been reported. CgA was measured in the pre- and post-operative state only in 3 patients (one in our series and in two case reports [13, 19], therefore, robust conclusions about the validity and reliability of CgA as an alternative biochemical marker for the monitoring of patients with biochemically silent PCs is not possible.

The pathogenetic mechanisms for the functional inactivity of biochemical silent PCs are not completely understood and several theories have been proposed. One hypothesis is that these tumors do not secrete catecholamines but instead

Table 3 Pre-operative characteristics and management, intra-operative complications and outcomes of patients with biochemically silent pheochromocytomas in the published literature

Patient number	Study	Sex	Age at diagnosis (years)	PC-related symptoms	Tumor size on imaging (mm) max)	Side	Imaging characteristics	Pre-op alpha-blockers	Hemodynamic instability during surgery	Disease progression	Genetic testing
1	Montebello et al. [19]	F	55	Incidentaloma	54	R	Partly solid and partly cystic 29% relative washout T2 hyperintense	No	No	NR	Negative for *FH, KIF1B, MAX, NF1, PRKAR1A, RET, SDHA, DHAF2, SDHB, SDHD, TMEM127, VHL*
2	Kumar et al. [16]	M	35	Incidentaloma	132	L	Cystic with thick intermediated intensity walls and thin septations	No	Yes Hypertensive episodes requiring vasodilators and bradycardia Hypotension settled with fluids	No	Not performed
3	Gruber et al. [3]	F	24	Palpitations Tremors Anxiety	4	L History of R silent PC	MIBG avid	NR	NR	No	MEN2A
4	Gruber et al. [3]	F	29	Headache Palpitations	13	R	T2 hyperintense	NR	NR	No	VHL
5	Gruber et al. [3]	F	41	Anxiety Palpitations Diaphoresis	23	L	T2 hyperintense	NR	NR	No	None
6	Gruber et al. [3]	M	57	Incidentaloma	11	L	Pre-contrast CT density 28 HU	NR	Metastatic disease at diagnosis - no surgery	Stable	None
7	Gruber et al. [3]	F	27	MEN2A case detection testing	10	L	Pre-contrast CT density 46 HU	NR	NR	No	MEN2A
8	Gruber et al. [3]	M	30	Palpitations Anxiety	15	R	T2 hyperintense	NR	NR	No	MEN2A
9	Gruber et al. [3]	F	65	MEN2A case detection testing	19	L	Pre-contrast CT density 30 HU	NR	NR	No	MEN2A
10	El-Doueihi et al. [17]	F	28	Incidentaloma	R: 58 L: 44	Bilateral	Internal necrosis in both tumors	No	L adrenalectomy No R adrenalectomy Yes Hypertensive episode requiring vasodilators Hypotension requiring vasoconstrictors	NR	Not performed
11	Dreijerink et al. [18]	M	46	*SDHD* mutation detection testing	140	Unilateral	NR	NR	NR	Yes Mediastinal and infrahilar lymph nodes and bone metastases	*SDHD* mutation carrier

Table 3 (continued)

Patient number	Study	Sex	Age at diagnosis (years)	PC-related symptoms	Tumor size on imaging (mm) max)	Side	Imaging characteristics	Pre-op alpha-blockers	Hemodynamic instability during surgery	Disease progression	Genetic testing
12	Dreijerink et al. [18]	F	48	*SDHD* mutation detection testing	NR	Unilateral	NR	NR	NR	NR	*SDHD* mutation carrier
13	Petramala et al. [15]	F	61	Incidentaloma	44	R	Focal cystic area	No	No	No	Not performed
14	Sundahl et al. [13]	F	54	Incidentaloma	12	R	Multilocular, cystic mass with septations	No	No	No	Negative testing for *SDHB, SDHD, VHL*
15	Heavner et al. [12]	F	49	NR	35	Unilateral	NR	NR	NR	NR	NR
16	Heavner et al. [12]	M	37	NR	150	Unilateral	NR	NR	NR	NR	NR
17	Heavner et al. [12]	F	73	NR	17	Unilateral	NR	NR	NR	NR	NR
18	Heavner et al. [12]	M	20	NR	13	Unilateral	NR	NR	NR	NR	NR
19	Heavner et al. [12]	M	34	NR	68	Unilateral	NR	NR	NR	NR	NR
20	Kota et al. [11]	F	30	Incidentaloma	76	R	Pre-contrast CT density: 35 HU	No	Yes Hypertensive episode led to surgery interruption	No	Not performed
21	Tütüncü et al. [10]	NR	NR	Incidentaloma	50	Unilateral	NR	NR	NR	NR	NR
22	Aprill et al. [9]	M	27	VHL case detection testing	20	L	MIBG non avid	No	No	NR	VHL

PC pheochromocytoma, *F* female, *M* male, *R* right/ *L* left, *MIBG* metaiodobenzylguanidine scintigraphy, *HU* Hounsfield units, *MEN2A* multiple endocrine neoplasia type 2A, *VHL* Von Hippel-Lindau syndrome, *NR* not reported)

The study by Turkova et al. is not included in the table because it does not provide the vast majority of the above information.

they metabolize them to inactive compounds [5, 11, 19]. Alternatively, defective catecholamine synthesis due to the absence of tyrosine hydroxylase may be the underlying cause of the biochemical silent phenotype of these tumors. However, this mechanism has only been described in patients with *SDHB* mutations and biochemically silent abdominal sPGLs [25]. Other potential hypotheses include periodically-secreting PCs (during paroxysmal attacks) [10, 11, 14, 19] and tumors consisting of a small amount of functioning tissue due to cystic component, necrosis and/or hemorrhage [5, 11, 16, 19]. In our series, cystic and/or necrotic component on imaging comprising ≥50% of tumor was evident in 5 patients.

Biochemically silent PCs have been associated mainly with *SDHB* mutations [5, 14, 24]. However, this type of tumors has also been identified in other hereditary syndromes, such as Von Hippel-Lindau syndrome [3, 9], MEN2A [3], and in *SDHD* mutation carriers [18], as well as in apparently sporadic cases [3, 14, 19]. In accordance with the 2014 pheochromocytoma guidelines issued by the Endocrine Society [21], genetic testing was considered in our patients only in those with young age, presence of syndromic or malignant features and positive family history for any hereditary syndromes associated with PC. Only one patient fulfilled these criteria (case 4, Table 2) in whom genotyping of *SDHB*, *VHL*, *RET* was negative.

Overall, patients with biochemically silent PC represent a perplexing clinical scenario. Given the increased intra-operative risk of hemodynamic instability of these patients (as our study demonstrated), a pre-operative diagnosis is crucial. In cases of biochemically inactive adrenal lesions and a high index of suspicion for PC, based on imaging (unenhanced CT density >20 Hounsfield units, hyperintensity on T2-weighted MRI images, cystic changes and necrosis), functional imaging with either ^{123}I-MIBG or 6-18F-fluorodopamine positron emission tomography scans should be considered. In these patients, pre-operative alpha-adrenergic blockade may be advisable irrespective of the presence of hypertension. Optimal target blood pressure and heart rate during treatment cannot be established given the absence of relevant evidence. However, staying in line with those proposed in the 2014 Endocrine Society guidelines [21] for the secreting PCs seems prudent.

Limitations of our study include its retrospective design (although prospective studies on this topic may not be practically feasible given the rarity of biochemically silent PCs), the small sample size which did not allow statistical analysis of our findings and that pre-operative 3-MT determination was not performed in our patients because it was not included in our diagnostic protocol of PCs/PGLs. The strength of our study is the systematic evaluation of pre-, intra- and post-operative management, complications and outcomes of patients with these tumors.

In conclusion, our study has systematically assessed for the first time the characteristics of patients with biochemically silent PCs and showed that they carry a substantial risk of hypertension, hypotension and cardiac events during adrenal surgery. Our findings underline the importance of a pre-operative diagnosis of these rare tumors and the need for such patients to be managed by endocrine, anesthesiology and adrenal surgery teams specialized and experienced on the management of patients with PCs. Further studies are needed in order to elucidate the pathophysiology of biochemically silent PCs and to identify potential predictive factors of intra-operative hemodynamic complications that will facilitate the development of valuable evidence-based management protocols.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethics approval The study was registered with and approved by the 'G. Gennimatas' General Hospital of Athens ethics committee and its reporting conforms to the Guidelines for Good Clinical Practice, Declaration of Helsinki.

Informed consent Informed consent was obtained from all patients participating in the study.

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