

Clinical course and management of adrenal endocrine hypertension: A single-center experience

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Objectives. Endocrine etiologies of secondary hypertension (HTN) are frequent and increasingly diagnosed according to the learned societies. Adrenal causes as primary aldosteronism (PA), pheochromocytomas (PHEO), and ACTH-independent Cushing's syndrome (CS) are widely described separately regarding their clinical, biochemical, and morphological aspects and only a few studies have developed the particular aspect of associated HTN. For this reason, we conducted a retrospective observational descriptive study at a tertiary referral center.

Subjects. Fifty-five subjects were included (PA: 52.8%, PHEO: 29.1%, and CS: 18.1%). We found a slight female preponderance (60%). The average age of participants was 47.0±14.9 years. First-degree family history of HTN was described in up to two thirds of cases. Regarding HTN characteristics, subjects with PA presented significantly younger age at diagnosis and had more severe and resistant profile and required higher number of antihypertensive drugs. HTN-mediated organ damage (HMOD) was mainly cardiovascular and ocular. Patients with PHEO were significantly older at diagnosis and had more severe and paroxysmal HTN. Patients with CS had less severe HTN and less HMOD. Specific treatments were indicated in all cases aiming complete remission of HTN. Subjects with PA were treated medically with mineralocorticoid receptor antagonists in 72.4% of cases and HTN remission was achieved in only 21.8% after surgical treatment. All subjects with PHEO were operated with adrenalectomy and the remission was observed in 37.5% of cases, while patients with CS were surgically managed in 50% of cases with 40% of HTN remission.

Conclusions. Diagnosis and management of adrenal endocrine HTN diseases are challenging for healthcare professionals and early screening is crucial for prevention of cardiovascular morbidity.

Keywords: hypertension, endocrine, primary aldosteronism, pheochromocytoma, Cushing's syndrome

Hypertension (HTN) is a chronic non-communicable disease that is considered a major cardiovascular factor and is associated with high morbidity and mortality rates. Its prevalence exceeds 30% and continues to increase worldwide, particularly in low- and middle-income countries (Romano and Minuz 2024).

One of the main pillars of cardiovascular prevention is achieving adequate blood pressure (BP) control as early as possible, which is generally the case in less than half of treated patients. Factors contributing to poor BP control include the presence of an unidentified and relatively treatable secondary etiology. Indeed, the prevalence of secondary HTN

would be higher than is known and could reach 35% in the hypertensive population and more than 50% in resistant HTN (McEvoy et al. 2024).

Endocrine etiologies are among the most common etiologies of secondary HTN, particularly of adrenal origin: primary aldosteronism (PA), pheochromocytoma (PHEO), and Cushing's syndrome (CS). PA alone is responsible for more than 12% of severe cases with HTN and its systematic screening is recommended (McEvoy et al. 2024).

Endocrine HTN remains a public health problem due to significant socioeconomic costs, target organ damage (TOD), and impact on quality of life (QOL).

Despite the fact that clinical presentation of adrenal endocrine HTN is often obvious and young individuals are mostly affected, some diagnostic and management difficulties are encountered. Etiological diagnosis is challenging due to the specific nature of hormonal tests, which must be indicated and performed in a specialized setting, as they are expensive and difficult to interpret.

Adrenal endocrine HTN is curable with early intervention through targeted etiological treatment, mainly surgical or medical, depending on the pathophysiology.

We decided to conduct this study because to our knowledge that the individualization of endocrine HTN as a cause of secondary HTN has been little studied. The aim of the present study was to describe the clinical, etiological, and therapeutic profiles of adrenal endocrine HTN in a Tunisian cohort of patients.

Materials and Methods

Study design. We conducted a retrospective observational study at the Endocrinology Department of Fattouma Bourguiba University Hospital in Monastir, Tunisia. We collected data registered from the period from January 2011 to March 2025.

Inclusion and exclusion criteria. The inclusion criteria included patients aged >18 years with HTN fulfilling the 2024 European Society of Endocrinology (ESC) criteria (McEvoy et al. 2024) with confirmed PA according to Endocrine Society criteria (Adler et al. 2025), PHEO and adrenocorticotrophic hormone (ACTH)-independent CS. Patients with incomplete data were excluded.

PHEOs are defined as neuroendocrine tumors (NETs) arising from adrenomedullary chromaffin cells that secrete one or more catecholamines (epinephrine, norepinephrine, and dopamine). Biochemical diagnosis relied on elevated

catecholamine metabolites, such as plasma-free normetanephrine (NMN), metanephrine (MN), and/or 3-metoxitiramine (3-MT) or urinary fractionated MNs and NMNs. Levels of NMNs, MNs or 3-MT greater than twice of the upper limit of the reference interval were required for biochemical confirmation of the diagnosis (Garcia-Carbonero et al. 2021).

After excluding exogenous glucocorticoid use, endogenous CS diagnosis was confirmed twice, by performing either overnight suppression test with 1 mg dexamethasone or a 24-hour urinary free cortisol test. ACTH concentrations less than 5 pg/mL were considered consistent with ACTH-independent CS.

Data collection. We collected information on demographic data, family and personal history, comorbidities, and non-antihypertensive medications. Further information on HTN has been obtained: age at diagnosis, duration in months, method of discovery, referral physician, severity grade, clinical characteristics, number and classes of antihypertensive treatments, and the presence of TOD. Biochemical and hormonal data as well as imaging study were also collected. We included therapeutic management, either surgical or medical, and the evolution.

Resistant HTN is defined as BP that remains above the therapeutic goal despite concomitant use of at least three antihypertensive agents of different classes, including diuretics, administered at maximum or maximally tolerated dose after exclusion of apparent treatment-resistant HTN due to non-adherence to treatment (Schiffrin and Fisher 2024).

HTN paroxysm is characterized by the sudden onset of peak BP of $>200/\geq 110$ mmHg.

Remission of HTN is defined by discontinuation of all antihypertensive medications and BP of $<130/80$ mmHg (Jha et al. 2020).

Statistical analysis. IBM® SPSS® Statistics version 22.0 was used for statistical analysis. Quantitative variables were expressed as means $\pm$ SD, and qualitative variables were expressed as frequencies and percentages. We verified the distribution of quantitative variables using the Kolmogorov-Smirnov test. In cases of normal distribution, means $\pm$ SD were used for continuous variables. Otherwise, values are presented as median [IQR, 25th–75th percentile]. Means between two independent series were compared using the Student's t-test, and between three groups by ANOVA. Medians were compared using the Mann-Whitney U-test. Percentages were compared using the Pearson chi-square test on independent series and in cases of invalidity, the two-tailed Fisher exact test was used. The significance threshold for the various statistical tests used was set at 0.05.

Results

Fifty-five patients were included in the study, of whom 60% were women. The average age of all subjects was 47.0 ± 14.9 years (mean $\pm$ SD). PA was diagnosed in 29 patients (52.8%), PHEO in 16 patients (29.1%), and ACTH-independent CS in 10 subjects (18.1%). Three patients among females with PA had a history of preeclampsia and one patient with CS

had recurrent gestational diabetes mellitus (DM). In addition, patients with PA were younger, but this difference was not statistically significant (ANOVA; $p=0.136$). In Table 1 we present selected demographic and clinical characteristics of all study participants and individually for each etiology of adrenal endocrine HTN.

In terms of baseline biochemical parameters, subjects with PA presented lower levels of kalemia

Table 1
Demographic and clinical characteristics of the participants

Parameter	Total (n=55)	PA (n=29)	PHEO (n=16)	ACTH-independent CS (n=10)	p-value
Age (years)	47.0 $\pm$ 14.9	44.4 $\pm$ 14.0	53.8 $\pm$ 13.3	47.9 $\pm$ 18.1	0.135
Gender					
Female [n (%)]	33 (60.0)	17 (58.7)	10 (62.5)	6 (60.0)	0.968
Male [n (%)]	22 (40.0)	12 (41.4)	6 (37.5)	4 (40.0)	
Residence					
Urban [n (%)]	35 (63.6)	19 (65.5)	9 (56.3)	7 (70.0)	0.742
Rural [n (%)]	20 (36.4)	10 (34.5)	7 (43.8)	3 (30.0)	
Smoking [n (%)]	9 (16.4)	3 (10.3)	4 (25.0)	2 (20.0)	0.643
First-degree family history of HTN [n (%)]	43 (78.2)	22 (75.9)	12 (75.0)	9 (90.0)	0.605
Comorbidities					
DM [n (%)]	19 (34.5)	10 (34.5)	4 (25.0)	5 (50.0)	0.427
CVD [n (%)]	11 (20.0)	9 (31.0)	2 (12.5)	0 (0.00)	–
OSA [n (%)]	2 (3.63)	0 (0.00)	1 (6.25)	1 (10.0)	–
BMI (kg/m ²)	28.3 $\pm$ 5.7	29.5 $\pm$ 5.3	27.1 $\pm$ 6.3	26.5 $\pm$ 5.7	0.245

Unless otherwise stated, data are presented as mean $\pm$ SD. Abbreviations: ACTH – adrenocorticotrophic hormone; BMI – body mass index; CS – Cushing's syndrome; CVD – cardiovascular disease; DM – diabetes mellitus; HTN – hypertension; OSA – obstructive sleep apnea; PA – primary aldosteronism; PHEO – pheochromocytoma.

Table 2
Baseline biochemical characteristics of the participants

Parameter	Total (n=55)	PA (n=29)	PHEO (n=16)	ACTH-independent CS (n=10)	p-value
FPG (mmol/L)	6.2 $\pm$ 2.4	5.8 $\pm$ 1.6	6.7 $\pm$ 3.4	6.5 $\pm$ 2.3	0.193
eGFR (ml/min)	105.1 $\pm$ 23.4	103.8 $\pm$ 21.3	105.9 $\pm$ 24.2	107.1 $\pm$ 29.5	0.728
Kalemia (mmol/L)	3.6 $\pm$ 0.5	3.4 $\pm$ 0.5	3.9 $\pm$ 0.4	3.8 $\pm$ 0.2	0.020
Hypokalemia [n (%)]	17 (30.9)	15 (51.7)	2 (12.5)	0 (0.00)	0.002
TG (mmol/L)	1.5 $\pm$ 0.7	1.5 $\pm$ 0.4	1.3 $\pm$ 0.6	1.8 $\pm$ 0.3	0.070
TC (mmol/L)	4.2 $\pm$ 0.9	4.4 $\pm$ 1.0	4.1 $\pm$ 0.6	3.9 $\pm$ 0.9	0.100
HDLc (mmol/L)	1.01 $\pm$ 0.30	1.0 $\pm$ 0.3	1.0 $\pm$ 0.3	0.9 $\pm$ 0.1	0.217
Non-HDLc (mmol/L)	2.7 $\pm$ 0.9	2.6 $\pm$ 1.2	2.7 $\pm$ 0.6	3.1 $\pm$ 0.9	0.035
Calcemia (mmol/L)	2.26 $\pm$ 0.10	2.25 $\pm$ 0.10	2.30 $\pm$ 0.10	2.25 $\pm$ 0.10	0.302

Unless otherwise stated, data are presented as mean $\pm$ SD. Abbreviations: CS – Cushing's syndrome; eGFR – estimated glomerular filtration rate; FPG – fasting plasma glucose; HDLc – high-density lipoprotein cholesterol; PA – primary aldosteronism; PHEO – pheochromocytoma; TG – triglycerides; TC – total cholesterol.

(ANOVA; $p=0.020$) and patients with ACTH-independent CS had higher non-HDL cholesterol levels (ANOVA; $p=0.035$) (Table 2).

Hormonal assessment was mandatory for etiological diagnosis. In subjects with PA, levels of plasma aldosterone, renin, and aldosterone-to-renin ratio (ARR) were 881.2 ± 240.0 pmol/L, 3.37 ± 2.30 mIU/L, and 175.8 ± 56.5 , respectively (mean $\pm$ SD) (Table 3). In patients with PHEO, total urine MN was 10.3 ± 5.2 mg/24 h (mean $\pm$ SD) (Table 4). In addition, in subjects with ACTH-independent CS, levels of

urinary free cortisol and cortisol following 1-mg overnight dexamethasone suppression test (ONDST) were 131.8 ± 84.6 μ g/24 h and 70.1 ± 59.5 μ g/L, respectively (mean $\pm$ SD) (Tables 5).

Adrenal CT scan was performed in all cases for localization study. Fourteen patients (48.2%) with confirmed PA had no adrenal abnormalities. The remaining patients with PA had the following features: left adrenal adenoma with an average size of 1.75 cm

Table 3
Levels of plasma aldosterone, renin, and aldosterone-to-renin ratio (ARR) in subjects with primary aldosteronism

Number	Subject		Aldosterone (pmol/L)	Renin (IU/L)	ARR
	Gender	Age (years)			
1	Female	32	4650.0	3.7	930.0
2	Male	45	612.2	1.0	340.0
3	Female	32	723.0	4.2	122.2
4	Female	27	651.0	3.4	91.5
5	Male	41	752.2	3.8	157.9
6	Female	61	642.0	1.0	240.0
7	Female	60	672.0	1.7	134.0
8	Male	32	580.0	1.0	95.0
9	Female	32	640.0	1.0	145.0
10	Female	22	580.0	1.4	155.0
11	Female	52	652.0	1.3	145.0
12	Male	70	641.0	3.0	172.0
13	Male	50	1010.0	2.4	202.0
14	Female	40	570.0	1.3	101.0
15	Female	39	623.0	5.0	88.0
16	Male	57	813.0	4.4	163.0
17	Male	67	650.0	1.9	146.0
18	Female	48	606.0	4.0	114.0
19	Female	55	752.0	5.0	189.0
20	Female	66	560.0	4.0	70.0
21	Female	53	620.0	2.0	120.0
22	Male	34	750.0	5.0	94.0
23	Female	28	557.0	4.0	69.0
24	Male	43	750.0	5.0	66.0
25	Male	39	640.0	3.0	169.0
26	Female	64	740.0	4.4	133.0
27	Male	42	1290.0	0.5	250.0
28	Male	19	808.0	4.9	77.0
29	Female	44	1200.0	5.0	124.0



Figure 1. Non-contrast adrenal CT-scan showing a spontaneously hypodense homogeneous 5.4 cm left adrenal nodule in a 60-years old male.

Table 4
Urinary fractionated metanephrine (MN) and normetanephrine (NMN) in subjects with pheochromocytoma

Number	Subject		MN (mg/24 h)	NMN (mg/24 h)
	Gender	Age (years)		
1	Male	41	1.65	3.81
2	Female	78	0.85	–
3	Male	58	16.95	–
4	Female	58	4.32	5.67
5	Female	67	0.24	24.80
6	Male	44	4.60	–
7	Male	30	79.90	–
8	Male	56	1.95	9.00
9	Female	53	6.71	4.00
10	Female	59	0.12	4.10
11	Female	37	20.14	19.24
12	Female	42	9.14	0.32
13	Male	62	0.51	3.56
14	Female	69	2.80	13.80
15	Female	41	4.70	21.00
16	Female	66	4.20	–

was observed in seven cases (24.1%); right adrenal adenoma with an average size of 1.7 cm was found in four cases (13.8%); bilateral non-nodular hyperplasia was observed in one case and bilateral adenomas in another one; and in two other patients, adrenal myelolipomas of 2.8 and 3 cm size were found.

CT scan revealed left PHEOS with an average size of 5.5 cm in eight subjects (50%) and right PHEOS (50%) with an average size of 4.8 cm in eight patients.

In patients with CS, imaging revealed adenomas with an average size of 2.87 cm in the right adrenal gland in five subjects, adenomas measuring 3.4 cm and 5.4 cm in the left gland in two subjects (Figure 1) and bilateral adrenal hyperplasia in three cases.

Regarding HTN characteristics, age at diagnosis of HTN was significantly lower in PA patients ($p=0.009$) and duration of the disease before etiological diagnosis was higher in cases with ACTH-independent CS, as shown in Table 6.

Specific etiological treatments were indicated in all cases, either medical (50.9%) or surgical (49.1%). For patients with PA, medical approach with aldosterone antagonists (spironolactone) was the most common option (72.4%) (Table 7). HTN improvement (remission or stabilization) was obtained in more than 82% of cases with PA with an average time of 6.3 months. All cases with PHEOS were treated surgically with open adrenalectomy and HTN improvement was reached in more than 93% of cases with significantly shorter average time of 2.2 months (ANOVA; $p=0.005$) (Table 7), whereas, 50% of patients with CS with unilateral lesions were operated and the remaining cases were managed medically either for bilateral adenomas or for major contraindications for anesthesia. Remission of HTN was achieved after unilateral adrenalectomy in 40% of cases. (Table 7).

Discussion

Diagnosis and management of adrenal endocrine HTN diseases are challenging and the understanding of their pathophysiology is crucial for clinicians.

Primary aldosteronism (PA)

PA is a spectrum of disorders characterized by inappropriately high non-suppressible aldosterone blood levels with suppressed renin activity. PA is responsible for HTN and less frequently for hypokalemia. It is considered the most common cause of endocrine HTN with a prevalence of 6 to 18%, which increases with HTN severity. PA is actually responsible for 10 to 29% of resistant HTN (De Freminville et al. 2023).

Table 5

Levels of late-night plasma cortisol, 24-hour urinary free cortisol and cortisol following 1-mg overnight dexamethasone suppression test (ONDST) in subjects with adrenocorticotrophic hormone (ACTH)-independent Cushing's syndrome

Subject			Cortisol		
Number	Gender	Age (years)	Plasma late-night ($\mu\text{g/L}$)	Urinary free ($\mu\text{g/24 h}$)	ONDST ($\mu\text{g/L}$)
1	Female	23	250.0	–	35.0
2	Female	81	147.0	–	25.0
3	Male	43	250.0	222.0	260.0
4	Female	33	173.0	120.0	106.0
5	Male	66	160.0	173.0	22.0
6	Female	53	179.0	–	49.0
7	Female	33	220.0	149.0	66.0
8	Female	48	126.0	76.0	77.0
9	Male	69	160.0	–	32.1
10	Male	38	154.0	–	67.0

Despite all these alarming facts, PA screening rate remains low (3.4%) among eligible groups of patients, such as in younger age (<35 years), resistant HTN, concomitant hypokalemia, adrenal lesions, and obstructive sleep apnea (OSA) (Turcu et al. 2022).

In this study, PA was diagnosed in 52.8% of cases with adrenal endocrine HTN and considered higher compared to a similar study (33.7%) (Clemente-Gutierrez et al. 2021). The average age of patients with PA (44.4 ± 14.0 years) was significantly lower than in the other groups, but similar to most recent findings since the average age of diagnosis is around 50 years (20 to 60 years) (Chung 2024). Thus, older patients with HTN should be more targeted for active screening of PA. Indeed, longer PA duration increases the odds of HMOD and may affect ARR interpretation (Akasaka et al. 2019; Parra Ramirez et al. 2022). Recently, an increase in the incidence of PA in women has been observed, mainly related to bilateral adrenal hyperplasia rather than unilateral adenomas (Park et al. 2024). In this study, the presence of HTN in the first-degree relatives in more than 75% of patients with PA directed towards possible somatic mutations of aldosterone regulating genes present in more than 88% of Conn adenomas (*KCNJ5*, *CACNA1D*, *ATP1A1*, *ATP2B3*, and *CTNNB1*). For instance, *KCNJ5* mutations are correlated with larger adenomas and hypokalemia, especially in younger and female patients (Zelinka et al. 2020).

Table 6
Clinical characteristics and organ damage in subjects with endocrine hypertension

Parameter	Total (n=55)	PA (n=29)	PHEO (n=16)	ACTH-independent CS (n=10)	p-value
Age at diagnosis (years)	40.5±12.9	36.6±10.8	48.6±12.0	39.1±15.4	0.009
Duration of HTN (months)	85.3±103.0	93.2±115.3	50.3±84.6	118.5±111.5	0.250
Referring physician [n (%)]					
Cardiologist	20 (36.4)	11 (37.9)	4 (25.0)	3 (30.0)	0.304
GP	13 (23.6)	8 (27.6)	3 (18.7)	4 (40.0)	
Endocrinologist	8 (14.6)	1 (3.4)	6 (37.5)	1 (10.0)	
Emergency	5 (9.0)	4 (13.8)	1 (6.3)	0	
Urologist	5 (9.0)	3 (10.4)	2 (12.5)	0	
Other specialists	4 (7.4)	2 (6.9)	0.0	2 (20.0)	
Grade of HTN [n (%)]					
Grade 1	4 (7.3)	0.0	1 (6.2)	3 (30.0)	0.039
Grade 2	29 (52.7)	17 (58.6)	8 (50.0)	4 (40.0)	
Grade 3	22 (40.0)	12 (41.4)	7 (43.8)	3 (30.0)	
SBP (mmHg)	143.3±22.7	146.5±21.0	140.0±29.4	139.6±14.8	0.561
DBP (mmHg)	83.2±15.0	83.3±15.2	80.6±17.7	87.0±9.5	0.585
RPR (bpm)	75.6±12	75.5±12.7	77.0±11.2	73.7±13.0	0.794
Resistant HTN [n (%)]	18 (32.7)	10 (34.5)	5 (31.3)	3 (30.0)	0.956
HTN paroxysm [n (%)]	20 (36.4)	8 (27.6)	7 (43.8)	1 (10.0)	0.060
Number of antihypertensive drugs	2.4±1.3	2.9±1.3	1.9±0.9	1.7±1.3	0.015
HMOD [n (%)]					
CHD	8 (20.0)	7 (24.1)	1 (6.25)	0	–
Stroke	3 (5.5)	1 (3.4)	2 (12.5)	0	
Albuminuria	13 (23.6)	6 (20.7)	5 (31.25)	2 (20.0)	
CKD	7 (12.7)	4 (13.8)	3 (18.7)	0	
HR	16 (29.0)	8 (27.6)	5 (31.25)	3 (30.0)	

Unless otherwise stated, data are presented as mean±SD. Abbreviations: ACTH – adrenocorticotrophic hormone; BPM – beats per minute; CHD – coronary heart disease; CKD – chronic kidney disease; CS – Cushing's syndrome; DBP – diastolic blood pressure; GP – general practitioner; HMOD – hypertension-mediated organ damage; HR – hypertensive retinopathy; HTN – hypertension; PA – primary aldosteronism; PHEO – pheochromocytoma; RPR – resting pulse rate; SBP – systolic blood pressure.

In regards to comorbidities, DM was present in 34.5% of cases with PA. Park et al. (2024) have demonstrated a 15% of DM prevalence in a large cohort study and a tendency to higher incidence in older patients and incidentalomas and with this association being far from coincidental, but complex and multifactorial. In fact, in addition to hypokalemia (Sanyal et al. 2024), aldosterone may have diabetogenic effects, such as a possible direct reduction in insulin secretion and sensibility and β -cell failure via the glucocorticoid receptor. This negative association increases the risks of mortality, atrial fibrillation,

stroke, heart and kidney failure, and the underlying mechanisms would be the pro-inflammatory state and the oxidative stress induced by aldosterone (Pillai et al. 2023). OSA has become a new screening field of PA. Indeed, this latter is more prevalent in young males (<45-year-old) with HTN and OSA, and their interconnection can be mutual. As a matter of fact, OSA intermittent hypoxemia, related hypercortisolism, and obesity may activate renin-angiotensin system (RAS). Aldosterone fluid overload may cause laryngeal edema and upper airways obstruction (Heizhati et al. 2023; Sugawara et al. 2023).

Table 7
Specific treatment modalities and hypertension evolution in the participants

Parameter	Total (n=55)	PA (n=16)	PHEO (n=16)	ACTH-independent CS (n=10)	p-value
Etiological treatment [n (%)]					
Medical	28 (50.9)	21 (72.4)	0	5 (50.0)	0.001
Surgical	27 (49.1)	8 (27.6)	16 (100.0)	5 (50.0)	
HTN evolution [n (%)]					0.079
Remission	12 (21.8)	2 (6.9)	6 (37.5)	4 (40.0)	
Stabilization	36 (65.5)	22 (75.9)	9 (56.3)	5 (50.0)	
Persistence	7 (12.7)	5 (17.2)	1 (6.3)	1 (10.0)	
Time to improvement of HT (months)	3.3±2.1	6.3±2.5	2.2±1.0	3.0±0.1	0.005
Mortality [n (%)]	2 (3.6)	1 (3.4)	1 (6.3)	0	-

Unless otherwise stated, data are presented as mean±SD. Abbreviations: ACTH – adrenocorticotrophic hormone; CS – Cushing's syndrome; HTN – hypertension; PA – primary aldosteronism; PHEO – pheochromocytoma.

Duration of HTN to PA diagnosis was 93.2 months in this cohort. Diagnostic delay can exceed 35%, mainly related to non-specific symptoms and often described in women with more than three comorbidities or having more than ten symptoms or taking more than four antihypertensive medications (Ananda et al. 2024). HTN was resistant in one-third of cases. It is reported that 20% of cases with resistant HTN are associated to PA and their condition often improves after surgery. The underlying mechanisms of resistance development and maintenance are mediated by aldosterone direct organ damage (vascular and tubular inflammation, glomerular fibrosis, sodium retention, endothelial dysfunction, vascular rigidity, and insulin resistance, etc.). Hence, systematic PA screening in patients with resistant HTN is routinely recommended (Bioletto et al. 2022). HMOD was relatively frequent and could have worsened the course of HTN. For example, left ventricular hypertrophy (LVH) and albuminuria are reported to occur in 60% and 42% of patients, respectively. Together with intima-media thickness (IMT), they are considered early reversible signs of HMOD, before cardiovascular events are prevented (Li et al. 2024).

Etiological treatment in PA aims to obtain HTN improvement at least and ideally remission as well as correction of hypokalemia and reduction of cardiovascular morbi-mortality. In this cohort, medical option with aldosterone antagonists (spironolactone) was indicated in more than two-third of cases either for bilateral hyperplasia or idiopathic PA and HTN improvement was guaranteed. Remission was achieved in only two of eight cases after adrenalectomy

for unilateral lesions. Regarding surgical treatment, the remission rate can exceed 70% and correlates with female gender, younger age, shorter disease duration, and use of two or fewer antihypertensive drugs, and BMI ≤25kg/m². While HTN persistence is correlated to male gender, older age, obesity, and larger lesions (Clemente-Gutierrez et al. 2021).

Pheochromocytoma

Pheochromocytomas/paragangliomas (PPGLs) are rare NETs that derive from chromaffin cells of the adrenal medulla (PHEO) or paravertebral sympathetic ganglia (PGL) and secrete one or more catecholamines (adrenaline, noradrenaline, and dopamine). They have an estimated annual incidence of 5 per million, and HTN is found in more than 95% of cases. Otherwise, these tumors represent only 0.2% to 0.6% of all HTN etiologies (Borozan et al. 2025).

PHEOs were diagnosed in 29.1% of cases, and the average age at diagnosis was 48.6±12.0 years (mean±SD), which is considered higher than in the other etiologies and compared to recent results (Clemente-Gutierrez et al. 2021). Nevertheless, a recent large Danish study has revealed a higher age at diagnosis of 50 to 74 years in more than half of PHEO cases, probably in relation to change in clinical presentation towards less symptomatic forms and smaller tumors (Ebbehoj et al. 2021).

HTN in patients with PPGLs results from vaso-pressive effects of excess catecholamines. Hence phenotype is variable depending on secretory nature. Permanent HTN is associated to norepinephrine secretion, while paroxysmal HTN is

mainly linked to secretion of epinephrines. Indeed, paroxysm is related to sudden and unpredictable release of catecholamines either spontaneously or triggered by physical activity, smoking, abdominal pressure, changes in posture, tyramine rich products consumption, medications (tricyclic antidepressants, histamine, phenothiazin) or surgical interventions. Normotensive forms are associated to small tumors or dopamine excess (Zuber et al. 2011).

PHEO was diagnosed after more than 50 months of HTN diagnosis, predominantly by endocrinologists and cardiologists, despite the severity and paroxysmal presentation (43.8%). Other authors described less paroxysm (20.8%) (Ebbehoj et al. 2021).

Resistant HTN was found in 31.3% of cases in this cohort. In fact, 4% of resistant HTN are related to PPGLs, therefore systematic screening is recommended, but it has been reported in only 2.4% of patients with resistant HTN (Grigoryan et al. 2023).

The etiological treatment was exclusively surgical in all cases and HTN remission rate was only 37.5% compared to other results (86%), which we can attribute to the long duration of HTN before surgery and the larger tumor size. In fact, remission rate is correlated to tumor size (<2 cm), female gender, younger age, lower BMI, number of antihypertensive medications (<2), and shorter HTN duration (<5 years) (Clemente-Gutierrez et al. 2021).

ACTH-independent Cushing's syndrome

Endogenous CS is a rare, but serious condition with an estimated incidence of 0.7 to 2.4 cases per million per year. Given its progressive development and its common aspects with metabolic syndrome, the diagnosis is often challenging. ACTH-independent CS counts for approximately 20% of cases. CS represents only 0.5% of the etiologies of HTN in general (Barbot et al. 2019), but this latter is the second common feature at diagnosis after weight gain, with a prevalence exceeding 80%, especially in ectopic and ACTH-independent CS (De Martino et al. 2025).

CS-related HTN mechanisms are multiple and complex. Indeed, supraphysiological cortisol levels exceed the deactivation capacity of 11β -hydroxysteroid dehydrogenase type 2 (11β -HSD) and activate mineralocorticoid receptors leading to sodium and water retention and rise of potassium excretion causing hypokalemia (De Martino et al. 2025). Cortisol activates the renin-angiotensin-aldosterone system (RAAS) and enhances the vascular pressor response to angiotensin II. Moreover, CS

metabolic disorders and proinflammatory state, such as insulin resistance, visceral adiposity, dyslipidemia, OSA, and glucose intolerance contribute indirectly to HTN and to cardiovascular morbidity (Barbot et al. 2019).

Regarding HTN characteristics, patients were significantly younger than those with PHEO and there was a delay of 118 months to CS diagnosis, mainly because of non-specific clinical presentation. HTN was severe and drug-resistant in up to one-third of cases. In fact, these particular features indicate the systematic screening of CS, together with the non-dipping BP profile. These characteristics reflect the chronic hypercortisolism and the disrupted cortisol circadian rhythm. However, in adrenal hypercortisolism, BP nocturnal decline is more blunted than in the other entities (De Martino et al. 2025).

Endogenous hypercortisolism is associated to increased cardiovascular morbidity and mortality compared to general population, even with minimal secretion (De Freminville et al. 2023). In this small cohort of patients with ACTH-independent CS, we found no significant symptomatic cardiovascular disease (CVD), except for positive albuminuria reflecting the endothelial dysfunction. Regarding HMOD, we found a higher rate of hypertensive retinopathy (HR). The presence of severe and BP-inappropriate HMOD justifies the screening of CS (De Martino et al. 2025).

HTN remission was achieved in 40% of cases after surgery compared to the results of Clemente-Gutierrez et al. (2021), who have found remission rate of 68.8% with an odds ratio for remission probability of 0.75, yet lower than in cases with PA and PHEOs.

A 69 years-old male patient who undergone a unilateral adrenalectomy did not achieve remission. Indeed, HTN remission is negatively correlated to larger tumor size, greater number of antihypertensive drugs, male gender, older age, obesity, and preoperative HTN duration >5 years. HTN persistence reflects the vascular damage of chronic exposure to supraphysiological hypercortisolism (Clemente-Gutierrez et al. 2021).

Persistent hypertension after surgical treatment

For clinicians, it is crucial to strive for complete postoperative remission when identifying a relatively treatable disease of HTN. Therefore, a significant number of surgical patients require antihypertensive drugs to achieve BP control. The main probable reasons for the absence of remission

of HTN are as follows: long-term exposure to high hormonal levels leading to HMOD, like irreversible vascular remodeling, nephroangiosclerosis, and left ventricular hypertrophy. Some patients may have underlying “essential” hypertension that has developed or appeared independently due to genetics and older age. Additionally, misdiagnosed bilateral disease when AVS is not performed or residual functional tissue, particularly in PA, are also considered. For these reasons, predictive models of HTN postoperative persistence are required (Li *et al.* 2023).

The limitations of this study are certainly the small cohort and the retrospective design with some information gaps regarding HTN characteristics such as nocturnal sleep immersion, OSA screening, complete hormonal profile, assessment of subclinical CVD, perioperative data and prognostic factors. We should mention that the non-availability of AVS in our institution had probably led to misdiagnosing some bilateral forms of PA. Despite all these limitations, our study highlighted the importance of

individualizing adrenal causes of secondary HTN as a severe but relatively treatable disease. To the best of our knowledge, this entity has not been investigated in any previous local studies. Therefore, multicenter studies are required.

Conclusions

Adrenal endocrine HTN associated to PA, PHEO and CS is steadily recognized by learned societies and recommendations of its screening are expanded to more clinical profiles. The aims of early screening are prevention of HMOD in younger subjects and improvement of their QOL. With progression of genetic testing, more familial forms are diagnosed even before specific symptoms onset. In older subjects, identifying these underlying causes does not necessarily guarantee total remission of HTN, but may at least reduce severe HMOD.

Conflict of interest: *The authors declare no conflicts of interest.*

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