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Anti-hypertensive treatment in pheochromocytoma and paraganglioma: current management and therapeutic features

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Abstract Pheochromocytoma (PH) and paraganglioma (PG) are neuroendocrine neoplasms arising from chromaffin cells of the adrenal medulla and the sympathetic ganglia, respectively. Although are unusual cause of hypertension (HT) accounting for at most 0.1–0.2 % of cases, they may lead to severe and potentially lethal hypertensive crisis due to the effects of the released catecholamines. However, both PH and PG may be asymptomatic as ~30 % of subjects are normotensive or have orthostatic hypotension and in these cases the 24 h ambulatory blood pressure (BP) monitoring is an important toll to diagnose and treat HT. HT treatment may be difficult when PH or PG occurs in pregnancy or in the elderly subjects and in these cases a multidisciplinary team is required. When surgical excision is mandatory the perioperative management requires the administration of selective α1-adrenergic blocking agents (i.e., doxazosin, prazosin or terazosin) followed by a β-adrenergic blockade (i.e., propranolol, atenolol). This latter should never be started first because blockade of vasodilatory peripheral β-adrenergic receptors with unopposed α-adrenergic receptor stimulation can lead to a further elevation of BP. Although labetalol is traditionally considered the ideal agent due to its α- and β-adrenergic antagonism, experimental studies do not support its use in this clinical setting. As second regimen, the administration of vasodilators as calcium channel blockers (i.e., nicardipine, nifedipine) may be required to control BP. Oral and sublingual short-acting nifedipine are potentially dangerous in patients with hypertensive emergencies and are not recommend. The latest evidences into the diagnosis and treatment of hypertensive crisis due to PH and PG are reviewed here.

Keywords Antihypertensive treatment · Catecholamine · Hypertensive crisis · Pheochromocytoma · Paranglioma

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Introduction

Pheochromocytoma (PH) and paraganglioma (PG) are catecholamine-producing neoplasm arising from the chromaffin cells [1]. Because the neoplasms have similar clinical presentations and are treated with similar approaches, in clinical practice the term "pheochromocytoma" refers both adrenal pheochromocytomas and catecholamine-secreting paragangliomas [2]. However, the distinction between PH and PG is fundamental because of implications for risk of malignancy, associated neoplasms and genetic testing. With the more widespread use of imaging techniques, an increasing number of PHs are diagnosed in the course of investigation of an adrenal incidentaloma [3]. However, this is likely to be an underestimate as 50 % of PHs were diagnosed at autopsy [4].

Approximately 10 % of the PHs and 20 % of PGs are malignant with poor survival but histologically and biochemically similar as benign ones. The only criterion of a malignancy is local invasion into surrounding tissues and organs or distant metastases, which may occur even a long time after the surgical resection [5]. As a consequence when PHs or PGs are considered "benign" on pathologic examination, long term follow-up is mandatory. Fortunately, the increasing availability of 18F-fluorodeoxyglucose PET (18F-FDG-PET) and the amino acid-based radiopharmaceutical L-6-[18F] fluoro-3,4-dihydroxyphenylalanine (18F-DOPA) and PET/TC has considerably improved the management of metastatic PHs as these imaging techniques have been used in detecting chromaffin cell neoplasms false-negative to I-123 MIBG scintigraphy [6].

Furthermore, ~15–20 % of subjects with catecholamine-secreting neoplasms have a germ-line mutation in genes such as SDHB, SDHC, neurofibromatosis and von Hippel–Lindau syndrome [7]. As outlined in our experiences [6, 8, 9] genetic testing is recommended in patients with PH or PG because the incidence of a hereditary syndrome reaches the 25 % of cases [7]; in these cases the early identification allows a screening for other associated neoplasms and the identification of family members who are at risk. Although the clinical presentation of PH or PG may be quite variable, the classic triad is characterized by episodic headache, sweating and tachycardia in association with HT, diagnosis and treatment of which is the topic of this paper. As will be discussed later the management of HT may be difficult when PH or PG occurs in pregnancy, in the elderly or in children and in these cases a multidisciplinary team including the endocrinologist and the internist whit expertise in the treatment of HT is required.

Hypertension crisis definition

In clinical practice, a large number of different terms have been applied to define acute severe elevations in BP and the current terminology is somewhat confusing. Hypertensive crisis are acute, life-threatening and usually associated with marked and severe increases in BP. The 2003 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [10] defines ≪hypertensive crisis≫ as a systolic BP > 180 mmHg or a diastolic BP > 120 mmHg with or without acute target organ involvement. However, in the hypertensive crisis it is important to discriminate the emergency from urgency [11]. Hypertensive emergencies represent severe elevations in BP that are complicated by evidence of progressive target organ dysfunction and require immediate BP reduction to prevent or limit target organ damage. The hypertensive urgency is a less clearly defined condition in which severe uncontrolled HT is observed in a patient who may have evidence of previous end-organ damage related to HT, but in whom there exists no evidence of ongoing or imminent target organ dysfunction related to the sudden increase of BP. Most often this occurs in patients with previously diagnosed chronic HT [11].

Hypertension in PH and PG

According to Ye et al. [12], although are unusual cause of HT in subjects hospitalized, PH or PG may lead to severe and potentially lethal hypertensive crisis due to the effects of the released catecholamines on vital organ function. Hypertensive crisis may be precipitated by postural changes, emotion, urination, and the use of some drugs as corticosteroids, histamine, adrenocorticotropic hormone, metoclopramide, phenothiazine, tricyclic antidepressants, or anesthetic agents. Hypertensive crises may also develop as a consequence of administration of a β-adrenoceptor blocker without a preventive administration of an α-adrenoceptor blocking agents as an unopposed stimulation of α-adrenoceptors could lead to a rise in BP. Surgery and unrelated procedures in under-diagnosed patients is also associated with hypertensive crisis [13].

However, both PH and PG may be asymptomatic as ~30 % of subjects are normotensive during office BP measurement or have orthostatic hypotension [13]. In these cases, the 24-h ambulatory BP monitoring (ABPM) is an important toll to discover asymptomatic HT. There is now general agreement that 24-h ABPM is indispensable to good clinical practice [14] and there are indisputable evidences demonstrating that it is superior to office BP values in predicting cardiovascular risk [15–17]. Although 24-h ABPM was initially developed for research purposes, has

become extremely useful in differentiating essential from secondary forms of HT [18]. In details, 24-h ABPM is the only technique that permits the close examination of the circadian profile and the identification of patterns of BP behavior that may be relevant to clinical management of HT. Furthermore, 24-h ABPM may be useful in detecting a sudden increase in BP instructing the patient to activate the recording manually upon the onset of symptoms (i.e., in PH of the urinary bladder that induces transient HT by micturition). However in clinical practice, the use of ABMP in detecting hypertensive crisis in symptomatic subjects is obviously not indicated unless it is used for educational purposes.

In the secondary forms of HT due to PH or PG, 24-h ABPM very often revealed an inversion of the circadian BP rhythm and an enhanced BP variability due to high circulating levels of catecholamines [19]. One possible explanation of this BP variability is the desensitization of the catecholamine receptors due to high levels of circulating catecholamines. However, the attenuation of the night-time BP fall may be observed in normotensive subjects with PH, showing that the desensitization of the cardiovascular system to catecholamines is not complete [3].

Diagnosis and clinical picture of the hypertensive emergencies in PH or PG

Most subjects with PH or PG have sustained or paroxysmal HT (45 %) and this latter is a result of suddenly secretion of catecholamines by the neoplasm. Furthermore in the hypertensive subjects, poorly responsive to therapy or having resistant HT should be determined the 24-h urinary catecholamines excretion [2], but the pre-test probability to diagnose a PH is low and for this purpose, it is recommended to test 24-h urinary fractionated metanephrines. However, there are many institutional and international differences in the approach to the biochemical diagnosis of PH and there is still no consensus as to the ≪best test≫ [20]. Historically, many institutions relied upon measurements of 24-h urinary excretion of catecholamines and total metanephrines but plasma fractionated metanephrines has been proposed as equally effective or a superior test for the biochemical diagnosis of PH [21]. If they are normal, no further testing is needed; while, if the results are significantly elevated, imaging techniques as computed tomography or magnetic resonance imaging are indicated to diagnose PH or a PG. If this latter is confirmed, a suitable antihypertensive therapy must be started (see below). In 75 % of subjects, paroxysms with severe HT occur at least weekly and often it may be precipitated by particular triggers as postural changes, palpation of the neoplasm, abdominal compression or massage, induction of anesthesia, exertion, intake of certain foods or beverages, emotion and urination. However in clinical practice, the differential diagnosis between hypertensive crisis due to PH and other causes of hypertensive crisis (Table 1) is quite difficult, because subjects with PH may experience hypertensive crises in different ways. Some of them report severe headaches or diaphoresis, dyspnea, paresthesias, constipation or a sense of impending doom, whereas others have visual disturbances, palpitations, angina, palpitations, nausea, vomiting, and epigastric pain. This different clinical presentation is the consequence of the organ damage caused by the HT crisis; the possible organ-specific hypertensive complications due to PH or PG were shown in Table 2. Indeed physical examination, except for the presence of HT, is usually normal unless done during the hypertensive crisis. As concerning target organ damage, in PH and PG, hypertensive heart damage and retinopathy are often less severe than might be expected compared to other causes of hypertensive crisis, but a specific catecholamine cardiomyopathy can be observed.

On the contrary if the PH has been excluded but paroxysmal HT not resolved, a differential diagnosis for pseudopheochromocytoma or hyperadrenergic spells should be ruled out [22]. There are few data in the literature concerning the clinical characteristics of this disorder and its cause and management remain a mystery [23]. The clinical picture of this condition is quite similar to the true-pheochromocytoma, but this condition is not induced by a particular setting or trigger. The duration of such episodes can range from 10 mins to several hours and sometimes for days and between the paroxysms, BP remains normal or mildly elevated. Furthermore, subjects with pseudopheochromocytoma show a specific

Table 1 Causes of hypertensive crisis

Renovascular hypertension
Parenchymal renal disease (chronic)
Acute glomerular nephritis
Renin secreting or aldosterone secreting neoplasms
Pre-eclampsia or eclampsia
Pheochromocytoma or Paraganglioma
Use of recreational drugs particularly sympathomimetic agents (such as amphetamines, LSD, cocaine or ecstasy)
Withdrawal from antihypertensive agents, usually centrally acting drugs such as clonidine
Ingestion of tyramine containing foods, tricyclic antidepressants, or other sympathomimetics, combined with monoamine oxidase inhibitor therapy
Scleroderma or other collagen vascular diseases
Vasculitis
Head injury
Autonomic hyperactivity in Guillain–Barré syndrome or other spinal cord diseases

Table 2 Hypertensive emergencies due to pheochromocytoma or paraganglioma

Clinical setting	Clinical picture (symptoms/signs)
Pheochromocytoma multisystem crisis	Multiple organ failure, temperature $\geq 40°$ C, hypertension and/or hypotension
Cardiovascular system	Myocardial infarction
	Shock or severe hypotension
	Acute congestive heart failure
	Syncope
	Arrhythmia
	Dissecting aortic aneurysm Classic picture with palpitations, severe headaches or diaphoresis
Pulmonary	Adult respiratory distress syndrome
	Acute pulmonary edema
Abdominal	Paralytic ileus
	Abdominal bleeding
	Bowel ischemia
	Mesenteric vascular occlusion
	Colon perforation
	Severe enterocolitis and peritonitis
	Watery diarrhea syndrome with hypokalemia
Neurologic	Stroke
	Acute encephalopathy
	Generalized seizures
	General muscle weakness Visual disturbances
Renal	Acute renal failure
	Severe hematuria
	Acute pyelonephritis
	Renal artery stenosis by compression of neoplasm
Metabolic	Diabetic ketoacidosis
	Lactic acidosis

personality profile associated with psychological problems, attributable to repressed emotion related to prior emotional trauma or a repressive coping style. This condition may be due to stress or emotional distress, which is only uncovered after careful psychological evaluation. Commonly, there are absences of emotional precipitants such as fear or panic, although fear does occur as a consequence of the frightening physical symptoms. The acute management of pseudopheochromocytoma often includes an intravenous antihypertensive agent (as labetalol) combined with an oral treatment with α- and β-blockers or central α-agonists (such as clonidine) if BP remains uncontrolled. In addition, an anxiolytic agent such as alprazolam, alone or in combination with an antihypertensive agent, rapidly improves both symptoms and BP. A possible differential diagnosis between PH and pseudo-pheochromocytoma is shown in Table 3. As a consequence, three forms of intervention, alone or in combination, appear successful in the treatment of pseudo-pheochromocytoma: antihypertensive therapy with agents directed at the sympathetically mediated BP elevation, psychopharmacologic interventions including anxiolytic and/or antidepressant agents and psychological intervention, particularly reassurance and increased psychological awareness.

Antihypertensive drugs to control HT in PH and PG during hypertensive crisis

α-adrenoceptor blockers

Treatment of a hypertensive crisis due to PH require the administration of the long-lasting α-adrenoceptor blocker phenoxybenzamine, usually given intravenous 10 mg twice a day as initial dose for a total daily dose of 1 mg/kg [24]. If BP is not controlled, phenoxybenzamine can be administered by infusion (0.5 mg/kg/daily). However, phenoxybenzamine is not marketed in Italy and is used only in US [25]. As a consequence, there are regional and international differences in the management of hypertensive crisis due to the availability of various anti-hypertensive drugs.

Urapidil, a competitive selective short-acting α1 blocker with a short elimination half-life (2–4 h) can be administered intravenously as bolus of 25 or 50 mg or in continuous infusion at the doses of 10–15 mg/h [26]. It is a safe and efficient alternative to phenoxybenzamine particularly as pre-treatment standard protocol of subjects undergoing surgery for PH or PG.

In addition, as pre-operative management (see below) of these neoplasms, other α-adrenoceptor blocking agents as prazosin, terazosin, and doxazosin are recommended to use [27]. However, different from phenoxybenzamine and urapidil, these drugs are specific, competitive and short-acting α1-adrenergic antagonists and can be administered orally more time daily, respectively in doses of 2–5 mg two or three times daily for prazosin, 2–5 mg daily for terazozin and of 2–8 mg daily for doxazozin. All these short-acting agents increased the risk of severe OH immediately after the first dose and should be given at bedtime. In some centers, phentolamine [28] is administered, another short half-life α1-adrenergic blocker, usually given as an intravenous bolus of 2.5–5 mg at 1 mg/min that can be repeated every 3–5 min or given as a continuous infusion (100 mg in 500 mL of 5 % dextrose) until HT is controlled. However, phentolamine is no longer used in this clinical setting.

Table 3 Differential diagnosis between pheochromocytoma and pseudo-pheochromocytoma

Characteristics	Pheochromocytoma	Pseudo-Pheochromocytoma
Hypertensive paroxysms	Frequently associated with a particular trigger[a]	No association with particular setting or trigger
Biochemical tests (catecholamine and/or metanephrines levels)	Markedly increased	Normal or middle increased
Instrumental examinations (TC, RM, DOPA-PET TC, MIBG)	Positive	Negative
Hemodynamic pattern	Palpitations and increased heart rate	Palpitations and increased/unaffected/or decreased heart rate
Psychological background	Normal	Repressed severe trauma-related emotions, emotional distress, defensive, very even-keeled personality style
Anti-depressant or anxiolytic agents	Ineffective	Effective
Psychological intervention	Ineffective	Effective

[a] see the clinical presentation of pheochromcytoma discussed in the text

β-Adrenoceptor blockers

These agents are administered when catecholamine- or α-blocker-induced tachyarrhythmia occurs [29–31]. As above outlined, β-adrenoceptor blocker should never be used in the absence of α-adrenoceptor blocker because the former will exacerbate ephinephrine-induced vasoconstriction by blocking its vasodilator component, leading hypertensive crisis in subjects who are on a β-adrenoceptor blocker alone [29]. For this topic, cardioselective β1-adrenoceptor blockers are recommended such as metoprolol, administered 25–50 mg three to four times daily [30] and atenolol (12.5–25 mg two or three times daily). Propranol, a non-selective β-adrenoceptor blocker, may be also used to control BP and it is given in doses of 20–80 mg one to three times daily [31].

Combined α- and β-adrenoceptor antagonists

Although labetalol is traditionally considered the ideal agent to control BP due to its α- and β-adrenergic antagonism, experimental studies do not support its routinely use in this clinical setting [32, 33]. Labetalol is a combined selective α1-adrenergic and non-selective β-adrenergic receptor blocker with a α- to β-blocking ratio of 1:7 [32] which may result in paradoxical hypertensive crisis [33]. In addition, the α- to β-antagonistic activity should be at least 4:1 to achieve adequate antihypertensive effect and this difference in part explain the poor BP control. In same manner carvedilol, another antihypertensive drug with similar effects of labetalol is not recommended, except when there are evident side effects due to the use of other α- and β-adrenoceptor blockers [30].

Calcium channel blockers and other vasodilators

Although less effective than α- and β-adrenoceptor blockers, calcium channel blockers (CCBs) are used as second line of choice to control BP [34]. The main role of CCBs may be either to supplement the combined α- and β-adrenergic blockade when blood BP is not achieved or to replace the adrenergic blockade in subjects with intolerable side effects [31]. For this purpose, CCBs block norephinephrine-mediated calcium influx into vascular smooth muscle leading a control of HT, tachyarrhythmias and catecholamine-associated coronary spasm. In this clinical setting, nicardipine is the most commonly used CCB, infused at the starting dose of 5 mg/h, increasing by 2.5 mg/h every 5 min to a maximum dose of 15 mg/h; nicardipine can be also given orally as sustained release preparation, at the starting dose of 30 mg twice daily [35]. In the pre-operative management (see below) of PH or PG, other CCBs are recommended to use orally [36]: amlodipine (10–20 mg daily), nifedipine (30–90 mg daily), and verapamil (180–540 mg daily). However, it is important to remember that both nifedipine and verapamil can be administered as extended-release action (see below).

Alternatively, control of BP may be achieved by a continuous infusion of sodium nitroprusside at 0.5–10.0 mg/kg/min, stopping the administration if no results are achieved after 10 min of infusion [37]. Another treatment option in the forms of HT resistant to conventional antihypertensive treatment is the administration of magnesium sulfate. Magnesium is predominantly an arteriolar dilator with minimal effects on pulmonary capillary wedge pressure and venous return, it reduces catecholamine release and it is a highly effective α-adrenergic antagonist and antiarrhythmic agent [38]. BP control can be achieved with a loading dose of 40–60 mg/kg followed by an infusion of 1–2 g/h. The

Table 4 Parental anti-hypertensive drugs and their contraindications/cautions in the hypertensive emergencies due to PH or PG

Condition	Drugs	Contraindications/cautions
Acute coronary syndromes	Nitroglycerin [49] + β-blocker [29–31] Nitroprusside [37, 54] + β-blocker	Hydralazine [60]
Acute pulmonary edema	Nitroglycerin [1] + loop diuretic [1] Nitroprusside [2] + loop diuretic	β-blocker, verapamil [36]
Ischemic stroke	Nitroglycerin, Nitroprusside Labetalol [30]	Nifedipine [55]
Hypertensive encephalopathy	Nitroprusside, Labetalol [32, 33] Nicardipine [35],	Centrally acting sympatholytic agents
Intracranial hemorrhage	Labetalol, Nicardipine [61]	Nitroprusside with caution [54], nifedipine
Subarachnoid hemorrhage	Nimodipine [36]	Nitroprusside with caution [1]
Dissecting aortic aneurysm	Nitroprusside + β-blocker	Vasodilators [2]
Acute renal impairment	Fenoldopam, nicardipine	Diuretics with caution [1]
Adrenergic crisis	Phentolamine [28] + β-blocker, Labetalol	β-blocker in monotherapy
Eclampsia	Methyldopa, hydralazine, MgSO [8, 42]	Nitroprusside [1]

parental anti-hypertensive drugs recommended for the treatment of hypertensive crisis due to PH or PG is summarized in Table 4.

Management of BP in the pre-operative period

Different forms of preoperative pharmacologic preparation were proposed for PH or PG but no randomized controlled trials have compared the different approaches and there is no universally accepted method of preparation for surgery in patients with catecholamine-secreting neoplasm [25]. Combined α-adrenergic and β-adrenergic blockade and calcium channel blockers have been used successfully for BP control. An α-adrenergic blocker is given 10–14 days preoperatively to normalize BP and expand the contracted blood volume particularly in subjects with recent myocardial infarction, catecholamine cardiomyopathy, refractory HT, and catecholamine-induced vasculitis. As above outlined, phenoxybenzamine is the preferred drug for preoperative preparation to control BP and arrhythmia in most centers in the United States [28]. When an adequate α-adrenergic blockade has been achieved, β-adrenergic blockade is initiated, which typically occurs 2–5 days preoperatively. As above mentioned, the β-adrenergic blocker should never be started firstly and should be avoided subjects with history of asthma or congestive heart failure [30]. Therefore, when the β-adrenergic blocker is administered, it should be used cautiously and at a low dose, for example 10 mg of propranolol orally every 5 h in the first day of β-adrenergic blockade followed (if tolerated) by a single long-acting dose with a goal heart rate control ranged between 60 and 80 beats per minute.

Although perioperative α- and β-adrenergic blockade is widely recommended, a second regimen that has been utilized involves the administration of CCBs. The main role for this class of drugs may be either to supplement the combined α- and β-adrenergic blockaded when BP control is inadequate or to replace the adrenergic blockade in patients with intolerable side effects. For this topic, nicardipine is used in most center of the US while in our country the verapamil is available and that is recommended in subjects with supraventricular tachycardia or when β-blockers are contraindicated.

Management of the hypertensive crisis in malignant PH or PG

Effective treatment of HT in malignant PH or PG has not been established. Therefore, controlling chronic overproduction of catecholamine is one of the most important therapeutic targets to maintain homodynamic stable, to improve performance status of subject, to reduce the symptoms due to chronic catecholamine increase and even more fatal arrhythmia and heart failure.

Until now, treatment options for malignant PG are limited to chemotherapy and radionuclide therapy [39]. Although molecular target therapies such as tyrosine kinase inhibitors and the mammalian target of rapamycin inhibitor are promising and under clinical trial in the Europe and North America, chemotherapy is the only therapy available to start only in selected cases. Finally, radionuclide treatment may be considered in patients with metastatic disease and no resectable lesions and can be performed using β-emitting isotopes coupled with MIBG or somatostatine analog [40]. Treatment of the hypertensive crisis is not different from malignant than non-malignant PH or PG.

Hypotension in PH or PG

Rather than HT, a typical hemodynamic disturbance that may occur in subjects with catecholamine-producing neoplasms is orthostatic hypotension [41–43]. The mechanisms

leading orthostatic hypotension OH are not well known but the common opinion is that hypovolemia, impairment of the peripheral response to catecholamines, the ratio of epinephrine and norepinephrine secreted by the neoplasm (epinephrine induces vasodilatation), myocardial contractile dysfunction, and baroreflex failure may all contribute to OH [42, 43].

During 24-h ABPM, OH may be observed and as found in our experience [8], OH is the most important factor contributing to the altered or inverted circadian BP variation as OH leads to BP falls and heart rate elevations during day-time [44] and on the contrary, to relatively decreased BP (reflecting a higher sympathetic tone) and heart rate values during the night-time (Fig. 1). In rare cases where the neoplasms secrete only epinephrine, OH dominate the clinical picture [45] with a rapid cyclic fluctuations of HT and OH (i.e., every 7–15 min). The pathophysiology of this hemodynamic fluctuation is not well known [46] but a rapid fluid repletion and treatment with an α-adrenergic antagonist is effective.

PH or PG in pregnancy

PH is a rare cause of HT during pregnancy, with clinical features similar to those in the general population [47]. However, these neoplasms warrants special consideration, because if undiagnosed, they are associated with high mortality (i.e., 40.3 % maternal and 56 % fetal mortality) and morbidity. The primary goals for the management of PH in pregnancy are early diagnosis, avoidance of a hypertensive crisis during delivery, and definitive surgical treatment. Hypertensive crisis due to PH in pregnancy is due to the catecholamine release that can occur during clinical examination with abdominal palpation, postural changes, anesthesia and pressure from the uterus, fetal movements and neoplasm hemorrhage and the use of anti-emetic medications (i.e., metoclopramide) during pregnancy. There are no retrospective or prospective studies that have specially addressed the diagnostic values of biochemical tests for PH or PG in pregnancy. However, plasma-free metanephrine and urinary fractionated metanephrines assessment are the first recommended tests to perform in the diagnostic work-up of PH. MRI without gadolinium as well as ultrasonography are the imaging tests of choice in the pregnant woman. Stimulation tests and 123-I-MIBG scintigraphy are not considered safe for pregnant women. Other tests, such as plasma catecholamines, urinary vanylmandelic acid, or plasma chromogranin A, have less accuracy than plasma or urinary fractionated metanephrines and should not be preferably used for this purpose. Surgical removal of the neoplasm by laparoscopy is the new gold-standard in treating adrenal PH. Pre-operatively, the patients are to be pretreated with α-blockade (10–14 days) followed by β-blockade [48].

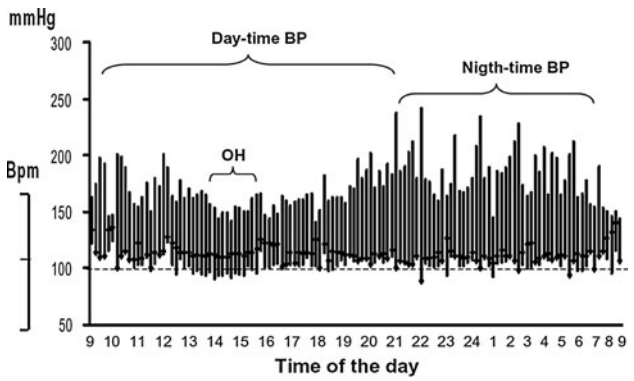

Fig. 1 24-h ambulatory blood pressure (BP) monitoring revealing a non-dipper profile with higher night-time than day-time BP values and many BP peaks with a high BP variability. Then, mean heart rate (small black squares) values were steadily greater than 100 bpm, and it also shown an episode of asymptomatic orthostatic hypotension (OH)

In spite of pregnancy-related HT (gestational HT and pre-eclampsia) where HT develops after 20 weeks and it is unlikely paroxysmal, HT in the context of PG or PG can develop during any gestational phase. As consequence if HT develops in a pregnant woman in the first 20 weeks, it should not be labeled erroneously as gestational HT or pre-eclampsia. Other signs of pregnancy-related HT, such as ankle edema, proteinuria and an elevated plasma uric acid are not compatible with PG. On the contrary, the presence of unexplained orthostatic hypotension in a pregnant hypertensive patient should arouse immediate suspicion of a hidden PG.

The antihypertensive treatment of PH in pregnancy is not clearly defined since the published literature largely consists of case reports [9]. Medical therapy should be initiated with α-adrenergic blockade followed by β-adrenergic blockade (i.e., propranolol or esmolol) to control tachycardia and tachyarrhythmias [48] and vasodilators as intravenous nitroglycerin [49]. Labetalol does not have adequate α-adrenergic blocking properties to justify its use when a catecholamine-secreting neoplasm is suspected [50] but it used in the setting of pregnancy-induced hypertensive crisis because they have a little placental transfer mainly due to their negligible lipid solubility [51].

Among the adrenergic blockers, phenoxybenzamine is the preferred long-acting α-blocker that may be administered as a bolus of 1–5 mg or as a continuous infusion of 1 mg/min. It is generally safe for fetus, but it crosses the placenta and leads of perinatal depression and transient hypotension [52]. As consequence, the surgical intervention (cesarean section) remains the therapy of first choice and it is recommend if the fetus is previable (<24 weeks

gestation). Prazosin, although less potent of phenoxybenzamine causes less reflex tachycardia and make the use of β-blockers unnecessary [53]. If BP remains uncontrolled, sodium nitroprusside may be used, but this has to be infused at a rate of <1 mg/kg/min to avoid fetal cyanide toxicity [54].

Nifedipine has been widely used via oral or sublingual administration in the management of hypertensive emergencies and in pregnancy-induced HT. However, oral and sublingual nifedipine administrations are potentially dangerous and are not recommend. In fact, sudden uncontrolled and severe reductions in BP accompanying the administration of nifedipine may precipitate cerebral, renal, and myocardial ischemic events that have been associated with fatal outcomes particularly in the elderly [55]. The Cardiorenal Advisory Committee of the FDA has concluded that the practice of administering sublingual/oral nifedipine should be abandoned because this agent is not safe and inefficacious [56].

Hypertensives crisis in Children

Sustained HT in observed in about 60–90 % of cases, paroxysmal HT is less common compared to adults [57], while acute hypertensive emergencies and urgencies (systolic and/or diastolic BP $\geq$ 99th percentile plus 5 mmHg) occurs infrequently in children with PH or PG. The classic symptoms of headache, palpitations, and sweating are usually accompanied by abdominal pain and back pain, vomiting, weight loss, polyuria, visual disturbances, anxiety, and attention deficit-hyperactivity.

There have been no randomized clinical trials evaluating management of pediatric hypertensive emergencies and despite the lack of evidences the use of the antihypertensive agents derived from small observational studies or has been extrapolated from randomized controlled trials in adults [58]. The children with acute severe HT and life-threatening symptoms and/or target-organ involvement should receive intravenous medication that lowers BP by no more than 25 % below the initial values over the first 8 h of treatment [59]. For this goal, intravenous bolus doses of labetalol (0.2 mg/kg per dose) or hydralazine (0.2 mg/kg per dose) but with caution [60] followed by labetalol or nicardipine infusion should be started [61, 62]. Like in adult subjects, oral α-adrenergic blockade with doxazosin or prazosin is employed with the addition of β-blockade only after α-blockade has been reached [63]. Alternatively, CCBs or metyrosine may be used [64]. However, surgery is the treatment of choice but a good preoperative medical management of HT for at least 10–14 days is recommended (see pre-operative treatment above).

Hypertensive crisis in the elderly

PH and PG are uncommon in the elderly but the prevalence is likely to be higher than reported, as PH is frequently undiagnosed due to lack of classical symptoms of sympathetic overactivity and confounding effects of aging and comorbidities. In particular, PH is often masked by arteriosclerosis and for this reason PH is more likely to result in elderly a fatal outcome than in younger subjects. In the elderly, PH was characterized by cardiomegaly and left ventricular hypertrophy rather than the classical symptoms [65] as above mentioned, as with aging there is a decreased in cardiovascular responsiveness (baroreceptor function) to catecholamines [66]. In the other hand, in the elderly the clinical picture of severe weight loss and severe HT is suggestive of PH. Furthermore, we emphasize the importance of an early diagnosis of PH in elderly subjects as they often have less signs and symptoms and more severe cardiovascular complications due to refractory HT than younger subjects. The pharmacological treatment of the hypertensive crisis in the elderly with PH is not different from younger subjects.

In conclusion, PH and PG may lead to severe and potentially lethal hypertensive crisis due to the effects of the released catecholamines. Appropriate antihypertensive drugs are used to manage HT, to control associated cardiovascular symptoms, and to prepare patients for surgical intervention.

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