

Secondary hypertension: an overview for the practitioner

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ABSTRACT

As hypertension is a worldwide known cardiovascular risk factor, with secondary hypertension being accountable for 5-15% of the cases, this paper aims to summarize and simplify the diagnostic algorithm for the most frequent forms of secondary hypertension, with general principles regarding screening methods, clinical characteristics, pathophysiological mechanisms, and diagnostic tests. Bearing in mind that the prevalence of secondary forms of hypertension varies with age and is most frequently encountered among young adults, the diagnosis becomes of utmost importance, considering the multiple curable interventions available. Regarding elderly patients, who usually present with long-term hypertension leading to irreversible vascular remodeling, the procedures that target secondary causes of hypertension provide mainly a better control of blood pressure values with fewer anti-hypertensive drugs. Furthermore, essential and secondary hypertension can coexist, or, sometimes, several forms of secondary hypertension can be present in the same patient. Not all hypertensive patients should undergo screening evaluation, as this strategy is not cost-efficient, and many false-positive results occur. Hence, rigorous clinical judgment is essential in order to select patients who may benefit from screening procedures. As a result, early diagnosis and treatment of secondary hypertension can contribute to avoiding unnecessary complications and decreasing cardiovascular risk and mortality rates.

Keywords: secondary hypertension, screening, diagnosis.

Introduction

Hypertension (HT) represents the most common risk factor for cardiovascular death, as well as the second preventable cause of premature death after cigarette smoking. Even though it represents only 5-15% of hypertensive patients, different forms of secondary HT can affect millions of people, taking

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into account the global burden of HT [1, 2]. The prevalence of secondary HT varies with age. It occurs more frequently in younger hypertensive patients, with a prevalence of 30% for the 18–40 years age group [3].

The major difference between essential and secondary HT, with prognostic and therapeutic consequences, consists in the presence of a potentially reversible cause for the latter. The identification of a secondary cause of HT is of utmost importance, especially in young patients, as a therapeutic intervention can have a curative purpose. As for elderly patients, the procedures that target secondary causes of HT have less of a curative intention because the natural evolution of HT determines irreversible vascular and end-organ damage, which will further contribute to maintaining high blood pressure (BP) values. Even in this case, therapeutic intervention is recommended to achieve better control of BP values with fewer antihypertensive drugs. In addition, essential and secondary HT can coexist, especially in this category.

Thus, timely diagnosis and treatment of secondary HT can decrease cardiovascular risk and mortality rates. Careful selection of patients is mandatory in order to detect secondary HT. Screening for secondary forms of HT is not recommended for all

hypertensive patients, as this strategy would not be cost-efficient, and many false-positive results occur. Screening is based on several patient characteristics, as detailed in Figure 1.

Screening for secondary forms of hypertension

Several characteristics may suggest the presence of secondary HT. Particularly, screening is recommended in the following situations: young patients (<40 years) with grade 2 HT and no other risk factors or onset of HT in childhood; resistant HT (BP >140/90 mmHg despite three antihypertensive drugs, including a diuretic at an optimal dose); severe (grade 3) HT or hypertensive emergencies; a sudden increase of BP in previously documented stable patients; the presence of extensive hypertension-mediated organ damage (HMOD), disproportionate to the degree of HT. Notably, among patients with resistant HT, the prevalence of secondary forms is significantly higher than in patients with controlled BP [1, 4].

Etiologies of secondary HT vary according to age. The onset of HT during childhood or early

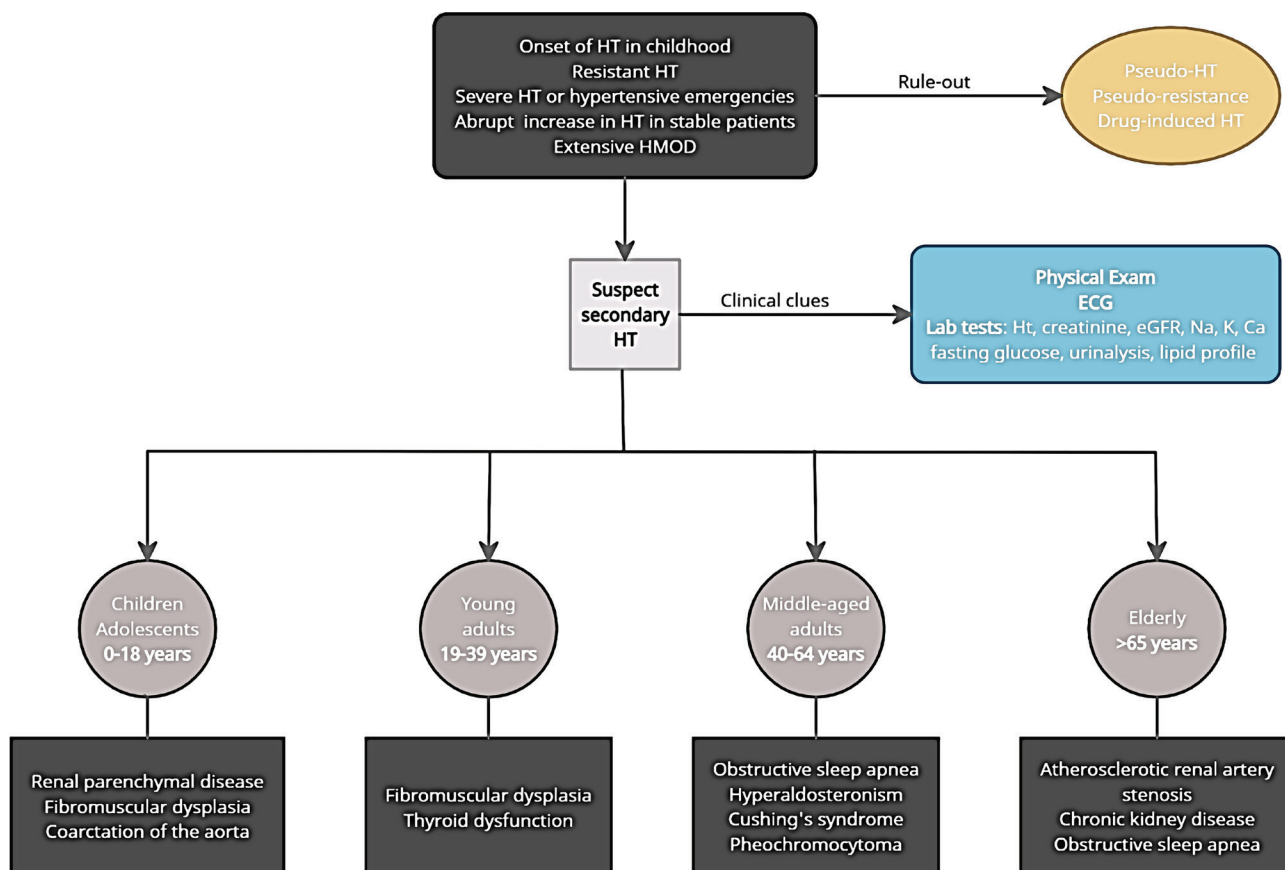


Figure 1. Algorithm approach for the initial evaluation of patients suspected of secondary HT. HT – hypertension; HMOD – hypertension-mediated organ damage; Ht – hematocrit.

adolescence should raise suspicion for renal parenchymal or vascular disease and coarctation of the aorta. Young adults may present with clinical signs of thyroid dysfunction or renal artery stenosis due to fibromuscular dysplasia. For middle-aged adults, endocrine causes are more frequent, including hyperaldosteronism and Cushing's syndrome, although obstructive sleep apnea is increasingly recognized as a common cause for all adult ages. In the elderly, the prevalence of atherosclerotic renal artery stenosis or renal parenchymal diseases leading to renal failure is higher than in other age groups [5].

Screening should be started after pseudo-hypertension and pseudo-resistance have been excluded (Figure 2). Pseudo-hypertension occurs in elderly patients with rigid, calcified arteries, for which excessive cuff pressure must be applied in order to compress the vessel. This leads to false-positive high BP values. Inaccurate BP measurements using an inadequate cuff size or under suboptimal conditions may also lead to false-positive results. Pseudo-resistance may occur in the setting of white coat HT. Finally, drug-induced HT must be ruled out, as many medications can increase BP. Of note, non-steroidal anti-inflammatory drugs and glucocorticoids cause fluid retention, whereas decongestants, some psychiatric drugs, dietary pills, and stimulants (amphetamine, cocaine) activate the sympathetic nervous system and increase BP. Other chemotherapeutic drugs and immunosuppressive

agents trigger elevations in BP through variable mechanisms [1].

Ambulatory 24-h blood pressure monitoring (ABPM) is a precise method to quantify BP values since it excludes the white coat effect and confirms the presence of resistant HT. Loss of the normal dipping pattern or, moreover, the presence of reverse dipping at night may point towards a secondary form of HT. The following sections will describe the most frequent causes of secondary HT, with clinical characteristics, screening, diagnosis work-up, and general treatment options.

Obstructive sleep apnea

General characteristics

Obstructive sleep apnea (OSA) is a highly prevalent sleep disorder characterized by an abrupt cessation or a significant decrease in respiratory flow through the upper airways, leading to a subsequent breathing effort against the collapsed airway. OSA is associated with multiple cardiovascular complications, including HT, heart failure, atrial fibrillation and other arrhythmias, coronary artery disease, and pulmonary hypertension [6]. Epidemiological data show high variability, as OSA remains underdiagnosed in the

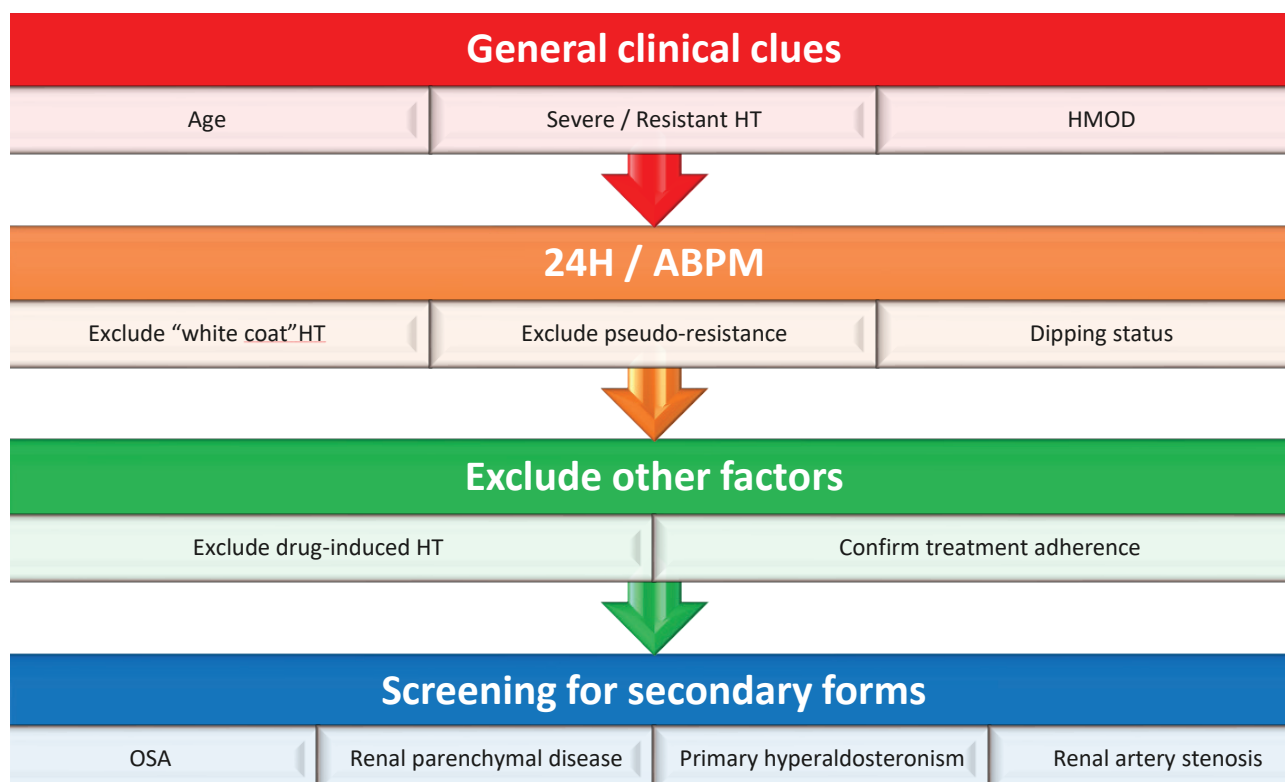


Figure 2. Essential steps to diagnose secondary hypertension. HT – hypertension; HMOD – hypertension-mediated organ damage; ABPM – ambulatory blood pressure monitoring; OSA – obstructive sleep apnea.

general population. Among hypertensive patients, approximately 40% present OSA, and the prevalence increases up to 80% in those with resistant HT [7, 8].

patients may develop anxiety disorders or depression. These symptoms should prompt the clinician to suspect OSA and proceed to further diagnostic tests [1].

Pathophysiology of OSA-related HT

Although OSA and HT share similar risk factors, including male sex, older age, obesity, and dyslipidemia, a causal relationship exists between OSA and the development of secondary HT. The pathophysiological mechanisms in OSA-related HT are complex, including autonomic nervous system dysregulation, changes in the renin-angiotensin-aldosterone system (RAAS), increased oxidative stress, endothelial dysfunction, and inflammation. Episodic nocturnal hypoxemia and hypercapnia trigger chemoreceptors located in the carotid body, stimulating sympathetic outflow to the medullary cardiorespiratory centers. Cardiac response to catecholamine stimulation involves increased heart rate and BP, with loss of the normal decrease in BP during the night and the development of a non-dipper pattern, as seen during ABPM [9]. Additionally, this increase in cardiac afterload predisposes to left ventricular hypertrophy, left atrial dilation, heart failure, arrhythmias, and nocturnal cardiovascular events, such as angina episodes.

Moreover, there appears to be a connection between hyperaldosteronism and OSA, as suggested by several studies [10, 11]. Hypoxia leads to RAAS activation, increasing aldosterone levels, with subsequent intravascular fluid retention and higher BP. During the night, elevated aldosterone levels lead to fluid accumulation, especially in the peripharyngeal tissues, which in turn favors upper airway obstruction. It has been suggested that the occurrence of hyperaldosteronism is significantly associated with the severity of OSA in patients presenting with resistant HT [12]. Thus, these patients may benefit from treatment with a mineralocorticoid receptor antagonist (MRA), such as spironolactone, to substantially reduce the severity of OSA and improve BP control. Further randomized assessments are needed to prove these preliminary findings [13].

Medical history

Patients with OSA often complain of poor sleep quality, resulting in excessive daytime sleepiness, morning headaches, irritability, and impaired attention and memory during their work activities. Patients' relatives may also report frequent episodes of apnea during sleep, loud snoring, and gasping for air on awakening. It should be noted that OSA patients show a higher incidence of motor vehicle accidents due to hypersomnia and decreased vigilance. Personality and mood changes are also frequent, as these

Screening patients with OSA

Even though the high prevalence of OSA in patients with cardiovascular disease justifies the need for screening programs, OSA is still widely underdiagnosed and undertreated. Screening work-up in patients with suspected OSA includes careful consideration of the patient's symptoms and the use of several screening questionnaires, such as the Berlin questionnaire or STOP-BANG, which provide good sensibility, but lower specificity for OSA. Sleepiness can be assessed using the Epworth Sleepiness Scale, although screening utility is poor, given its low sensitivity (42%) [14].

Clinical findings

Physical examination may indicate an increased risk for OSA. The most common findings are obesity, as indicated by a body mass index above 30 kg/m², and signs of narrow upper airways, including a large neck circumference (>42 cm in males, >39 cm in females), macroglossia or other anatomical abnormalities in the oropharyngeal region (tonsillar hypertrophy, enlarged uvula, narrow palate). The latter can be evaluated using the Mallampati score. A score above 3 signifies a high risk of OSA and should prompt further diagnostic tests [15]. Other associated clinical findings include elevated BP, signs of heart failure (peripheral edema, elevated jugular venous pressure, hepatomegaly), or cor pulmonale.

Echocardiographic evaluation of patients with OSA may show left ventricular hypertrophy as a result of a chronic increase in the afterload, systolic left and/or right ventricular dysfunction, elevated estimated pulmonary artery pressure, and other findings associated with cardiac disease.

The normal nocturnal dip of BP is absent in patients with OSA as a result of the increased sympathetic tone, which characterizes the non-dipper profile on 24h ABPM. In addition, patients may exhibit either tachycardia and/or bradycardia episodes, as well as increased BP variability.

Diagnosis

Patients with a high pre-test probability of OSA should be further assessed by in-laboratory full-night polysomnography, which is the gold-standard diagnostic test. By measuring the apnea/hypopnea

index (AHI), it allows to characterize the severity of the disease and establish further treatment options. An AHI above five events per hour is diagnostic for OSA, whereas an AHI above 30 indicates severe OSA, requiring a multidisciplinary approach.

Treatment

Treatment of OSA-related HT involves lifestyle changes, such as reducing salt intake and alcohol consumption. Increased physical activity and weight loss strategies, including bariatric surgery in severely obese patients, are recommended to facilitate BP control. Upper airway surgery may be needed to correct the oropharyngeal anomalies (tonsillectomy or uvulopalatopharyngoplasty). Nighttime continuous positive airway pressure (C-PAP) treatment is the mainstay choice for moderate-to-severe and severe OSA, although its effects on HT improvement are not convincing. In general, only a mild decrease in systolic and diastolic BP has been observed in patients on C-PAP treatment [16]. Regarding the antihypertensive drug regimens, spironolactone has been shown to reduce OSA severity and BP values in patients with OSA-related resistant HT [13].

Renal parenchymal hypertension

General characteristics

The prevalence of renal parenchymal hypertension (RPHT) is 2–10%, as depicted in the guidelines for the management of arterial hypertension. An increased incidence is reported as well, making RPHT one of the most frequent causes of secondary HT [4]. The relationship between HT and renal parenchymal disease is bidirectional since HT can be both a cause and a consequence of renal disease. The spectrum of renal lesions that can determine HT is heterogeneous. Hence, acute and chronic renal diseases, both primary and secondary, with or without renal failure, are associated with the development of HT [17]. The progression of renal disease may be prevented by removing the determining and aggravating factors, such as obstructive uropathy, hypovolemia, nephrotoxic agents, and the most important one, uncontrolled HT. Therefore, early detection of renal disorders is essential [18].

Screening

All hypertensive patients should undergo a series of investigations, including the measurement of serum

creatinine concentration, estimation of glomerular filtration rate (eGFR), microscopic analysis of urine, and evaluation of proteinuria with urine dipstick test or, ideally, by determining the albumin-to-creatinine ratio in a urine spot sample [4]. Moderately increased albuminuria (30 to 300 mg/24 h) is highly associated with target organ damage; thus, it should be evaluated in any patient recently diagnosed with HT. Increased urinary albumin excretion and progressive decline in eGFR are both considered independent and cumulative risk factors. The simultaneous presence of these two indicates a higher risk of cardiovascular and renal events [19, 20].

Diagnosis

In order to confirm the diagnosis of renal parenchymal HT, a vigorously clinical evaluation is required. As a result, we should be able to assess the type of nephropathy, the grade of renal dysfunction, the severity of HT, and also the extent of target organ damage [17].

Treatment

RPHT is characterized by its severity and resistance; hence, combination therapy is used for achieving recommended BP targets. Usually, it consists of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) with a calcium channel blocker (CCB) and a diuretic [17]. The non-dihydropyridine CCB might be preferred for its antiproteinuric and renoprotective effects.

Acute kidney injury

General characteristics

According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, acute kidney injury (AKI) is defined as an increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 μ mol/L) within 48 hours or an increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days, or urine volume <0.5 mL/kg/hour for six hours [21].

The causes of AKI can be classified arbitrarily into pre-renal (decreased renal perfusion), renal (acute glomerulonephritis, vasculitis, interstitial nephritis, thrombotic microangiopathy), and post-renal (urinary tract obstruction) [21]. Pre-renal causes of AKI are generally associated with arterial

hypotension, the decline in kidney function being caused by volume depletion.

Both healthy kidneys and those with pre-existing chronic diseases can be affected by AKI. Rapid renal function deterioration develops in hours or days. In the presence of predisposing factors, such as advanced age, CKD, or diabetes mellitus, AKI may be precipitated by nephrotoxic drugs, aortic aneurysm intervention, sepsis, coronary artery revascularization procedures, administration of contrast agents [17].

Pathophysiology of AKI-related HT

The mechanisms involved in the pathophysiology of HT vary depending on the site of the acute pathological process, either vascular or glomerular. In the case of acute diffuse glomerulonephritis, such as acute post-streptococcal glomerulonephritis, HT develops as a consequence of sodium and water retention. This hypervolemic status is caused by a reduced GFR and increased sodium reabsorption in the collecting tubules, secondary to glomerular-tubular imbalance [22]. While in acute diffuse glomerulonephritis, the volume overload leads to HT, in vascular diseases, the primary mechanism underlying HT is ischemia via activation of the RAAS [23].

Clinical findings

The clinical presentation of these patients, usually of young age, with a recent history of streptococcal pharyngitis, includes red or dark-brown urine and edema, especially facial swelling. Regarding paraclinical findings, inflammatory markers are increased, and the urinalysis reveals nephritic syndrome, rarely nephrotic syndrome, accompanied by macroscopic hematuria. The microscopic evaluation detects dysmorphic erythrocytes, which demonstrate the glomerular origin, and granular and hematic casts. Also, as renal tubules are not affected, urinary density is normal or increased. Normal or higher but equal dimensions of the kidneys may be found with abdominal ultrasonography examination [17]. Despite the clinical and paraclinical similarities between vascular and glomerular acute disorders, the absence of edema suggests a vascular disease.[24].

Treatment

Recommended treatment for HT associated with acute glomerulonephritis consists of diuretic drugs, especially loop diuretics, if GFR is decreased. In the absence of BP improvement, ACE inhibitors can be efficient, even if plasma renin activity is low in

this form of secondary HT [25]. On the other hand, ACE inhibitors represent the first-line treatment in HT associated with acute vascular lesions. Of note, the reduction of BP after administration of antihypertensive medication frequently causes acute rises of serum creatinine by up to 20-30% of the initial value, especially in the case of RAAS inhibitors. The cause is functional and does not usually reflect an actual lesion of the kidney, although the long-term significance is uncertain [4].

Chronic kidney disease

General characteristics

Chronic kidney disease (CKD) is defined by a decrease in estimated GFR below 60 mL/min/1.73m² or persistent albuminuria above 300 mg/day [26].

Among the most common causes that lead to the development of CKD, we note diabetic nephropathy (40% of cases), hypertensive nephrosclerosis (20% of cases), primary glomerulonephritis (18% of cases), tubulointerstitial nephropathies (7% of cases) and polycystic kidney disease (5% of cases) [27].

HT is encountered in approximately 85% of patients with CKD [28]. However, the prevalence of HT differs among the various pathologies underlying CKD. For example, polycystic kidney disease is frequently associated with HT, while the prevalence of HT is lowest in chronic pyelonephritis [17].

Pathophysiology of CKD-related HT

The pathogenesis of CKD-related HT is very complex, as many pathophysiological mechanisms are intertwined: the activation of RAAS, hyperactivity of the sympathetic nervous system, renal sodium retention, and increased arterial stiffness due to a decrease in nitric oxide release [29].

Resistant HT, masked HT, and HT associated with high nocturnal BP values (non-dipper or reverse dipper profiles) are frequently present in patients with CKD. These forms of HT are also associated with lower eGFR, more pronounced albuminuria, extensive HMOD, and an unfavorable prognosis [30]. The recommendation is to screen this category of patients using 24-h ABPM, as the results carry important prognostic information.

Treatment

Regarding the therapeutic strategy, several studies have demonstrated that RAAS inhibitors are more

efficient in reducing or preventing albuminuria compared to other antihypertensive agents used in patients with diabetic or non-diabetic CKD and with associated significant albuminuria. The combination of two RAAS blockers is not recommended [4.] In order to achieve optimal BP values, lifestyle changes are required (such as a reduction in salt intake), as well as combined pharmacological therapy, including a RAAS inhibitor and a diuretic or CCB [29]. Taking into consideration that the non-dipper profile is frequently encountered amongst hypertensive patients with CKD, the administration of an antihypertensive agent before sleep could help restore the normal circadian rhythm [31, 32].

Renovascular hypertension

General characteristics

Renovascular HT (RVHT) refers to the development of HT secondary to reduced renal perfusion. It represents an important and potentially curable form of secondary HT, with a low prevalence among mild or moderate forms of HT but increasing significantly among patients with severe or resistant HT [33]. There are two major causes of RVHT:

1. *Atherosclerotic renal artery stenosis (ARAS)* – responsible for 85–90% of all cases of RVHT and recognized as the most common etiology in elderly patients. The ostium and the proximal third of renal arteries are usually affected. Approximately 20% of patients have bilateral involvement or a single functional kidney [34].
2. *Fibromuscular dysplasia (FMD)* – responsible for the development of stenoses, occlusions, aneurysms, and tortuosities of the arteries, especially those of small and medium caliber. It is a vascular, non-inflammatory, and non-atherosclerotic pathology, occurring predominantly in young individuals, especially female patients (90% cases) [35]. Lesions are found primarily in the renal arteries (75–80% of cases) and internal carotids (75% of cases), followed by vertebral arteries, visceral and external iliac arteries [36].

Other causes of RVHT include embolic occlusions of the renal arteries, aortic dissection and vascular inflammatory conditions such as Takayasu arteritis and scleroderma [37].

Pathophysiology of RVHT

Depending on the unilateral or bilateral vascular involvement, the mechanism underlying the oc-

currence of RVHT is different. Thus, in significant unilateral arterial stenosis, hypoperfusion of the affected kidney stimulates the RAAS. Even if the contralateral kidney responds by pressure diuresis, which reduces volume expansion, this mechanism does not prevent the increase of BP values. In this context, HT is dependent on angiotensin II. In bilateral renal artery stenosis, high levels of angiotensin II cause volume overload, which in turn causes suppression of renin secretion. As the contralateral kidney is unable to produce pressure diuresis, high BP is volume-dependent. It can be converted into angiotensin II-dependent HT in the presence of diuretic therapy, with volume depletion restoring the level of renin secretion. However, diuretic-resistant HT is common in these patients [38].

Medical history

ARAS occurs mainly in patients over the age of 50, especially men, with many cardiovascular risk factors, such as smoking, HT, diabetes, CKD, occlusive aortic disease, and coronary artery disease. The syndromes generated by renal artery stenosis range from asymptomatic (incidental renal artery stenosis, hemodynamically insignificant) to severe or resistant hypertension. ARAS is associated with accelerated cardiovascular disease (diastolic dysfunction, congestive heart failure, “flash” pulmonary edema, stroke) and ischemic nephropathy with renal tissue hypoxia, extensive microvascular disease, renal failure, and progressive renal atrophy [39].

Screening and Diagnosis

In practice, the optimal attitude starts with assessing pretest probability and choosing a screening test according to the availability and diagnostic expertise of the center. Available screening tests for RVHT are imaging (visualizing the obstruction), functional (highlighting the pathophysiological effects of the obstruction), or tests that combine the two. The gold-standard method for diagnosing ARAS remains renal arteriography, which is an invasive procedure and cannot be used for screening. The most commonly used non-invasive diagnostic methods in clinical practice are duplex renal artery ultrasonography, computed-tomography (CT) angiography, and magnetic resonance imaging (MRI) angiography (Figure 3).

Duplex ultrasonography is an accessible, functional test providing anatomical information as well. This represents the first screening choice for significant ARAS ($\geq 60\%$) as recommended by the guidelines (class I, B level of evidence), although it may overestimate the severity of stenosis [34]. Direct

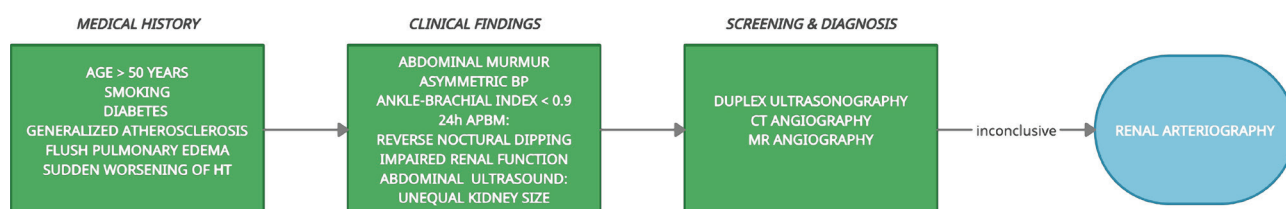


Figure 3. Diagnostic algorithm for renovascular hypertension. HT – hypertension; BP – blood pressure; ABPM – ambulatory blood pressure monitoring; CT – computed tomography; MR – magnetic resonance.

visualization of the renal arteries is combined with hemodynamic Doppler measurements. A velocity ratio between the renal artery and the aorta greater than 3.5 is suggestive of significant ARAS. A maximum systolic velocity above 200 cm/s indicates a stenosis >60%, although some studies indicate that the threshold value for severity is 300 cm/s [40]. This parameter has the best sensitivity (85%) and specificity (92%) for identifying significant angiographic stenoses [41]. Thus, Doppler ultrasonography is a reasonable method for screening patients with suspected uni- or bilateral ARAS; it helps monitor the progression of stenosis or in case of suspicion of restenosis in patients previously treated by angioplasty or surgery.

For the definitive diagnosis of ARAS, the European guidelines recommend multidetector computed tomography angiography in patients with creatinine clearance >60 ml/min/1.73m² [34]. This imaging method identifies stenosis and allows simultaneous assessment of its renal consequences. However, it is less reliable for identifying FMD affecting the distal segments.

For patients with creatinine clearance >30 ml/min/1.73m², the guideline recommendation for diagnosing ARAS is magnetic resonance angiography, with or without a contrast agent [34]. The method has very good sensitivity and specificity, with the advantage of obtaining images similar to those acquired by aortography. It is also useful in assessing renal perfusion, although this is not part of the routine examination. Accuracy is low when assessing small or distal arteries.

Clinical findings

From a clinical point of view, auscultation of an abdominal murmur, especially diastolic, may raise suspicion for ARAS. Other signs suggestive of peripheral arterial disease may be present (asymmetric BP, ankle-brachial index <0.9). Biologically, high levels of creatinine and urea may be detected. In addition, renin concentration and aldosterone-to-renin ratio are elevated due to secondary hyperaldosteronism [29]. 24-hour ABPM may reveal a reverse nocturnal dipping profile [1]. Abdominal ultrasound may

show a small unilateral kidney (<9 cm) or a difference >1.5 cm in the length of the two kidneys [39].

Diagnosis

Digital subtraction angiography remains the “gold-standard” method for defining vascular anatomy and diagnosing renal artery stenoses. An advantage would be the possibility to evaluate hemodynamic impact by measuring the translesional gradient, especially in the case of moderate stenoses. Thus, a systolic gradient >20mmHg (measured after vasodilation) or a fractional flow reserve <0.8 indicates significant stenosis in symptomatic patients and predicts a benefit in terms of BP response after stenting [42, 43]. Another functional assessment that can predict clinical response to interventional therapy is to measure the fractional flow reserve during maximal hyperemia induced by papaverine, dopamine, or acetylcholine [44]. Guidelines state that angiography may be considered in order to confirm the diagnosis of renal artery stenosis when clinical suspicion is high and the results of non-invasive examinations are inconclusive (class IIb, C level of evidence) [34].

Treatment

In patients with RVHT, the objective is to control BP and maintain renal function. There are three therapeutic options: pharmacotherapy (applicable to all patients, along with lifestyle changes); percutaneous angioplasty with or without stent placement; surgical revascularization or, in rare cases, kidney resection.

Most classes of antihypertensive drugs are effective in treating RVHT and can slow the progression of kidney disease. ACE inhibitors and sartans are well tolerated by most patients with significant renal artery stenosis, reducing morbidity and mortality [45]. They are very effective in the presence of unilateral renal artery stenosis (class I indication, B level of evidence) [34]. Previously, administration of ACE or sartans was absolutely contraindicated in

bilateral renal artery stenosis or ARAS in the unilateral functional kidney. However, the latest guidelines state they may be considered even for this category of patients if they are well tolerated and only under close monitoring (class IIb indication, B level of evidence) [34]. Reduction of BP is obtained in 86–92% of patients with RVHT by using these drugs in combination with a CCB, a beta-blocker, and a diuretic [18, 46]. Pharmacological antihypertensive therapy should be supplemented with antiplatelet drugs and a statin. The latter showed benefits in survival, slowing disease progression, and reducing the risk of restenosis after stenting [47]. A progressive decline in renal function and resistant HT are strong indications for surgical revascularization. Percutaneous transluminal renal angioplasty should be considered for the treatment of FMD [34].

Primary hyperaldosteronism

General characteristics

Primary hyperaldosteronism (PA), also known as Conn's syndrome, represents one of the leading causes of secondary HT, with a prevalence of 6% in unselected hypertensive patients, rising to 23% in patients with resistant HT [48]. Identifying PA as a cause for secondary HT is extremely important, as these patients are at higher risk for cardiovascular (particularly atrial fibrillation) and cerebrovascular complications than patients with essential HT and matched BP values [49].

PA is defined by an increased secretion of aldosterone, independently of its normal regulators (RAAS and sodium status). Considering the systematic use of adrenal vein sampling (AVS), most PA cases are caused by unilateral hyperaldosteronism, mainly an aldosterone-producing adenoma or, more rarely, unilateral adrenal hyperplasia. Bilateral adrenal hyperplasia (idiopathic hyperaldosteronism) accounts for one-third of cases. Aldosterone-producing carcinomas or familial forms occur very rarely [49].

Pathophysiology of PA-related HT

Aldosterone is a salt-retaining hormone secreted by the glomerular layer of the adrenal cortex. Circulating levels of aldosterone are controlled by several regulatory mechanisms, mainly the RAAS and, less importantly, the adrenocorticotrophic hormone and plasma potassium levels. Its main role is to facilitate sodium reabsorption, together with potassium and hydrogen secretion at the site of the distal tubule and collecting duct. By retaining sodium, aldoster-

one is responsible for maintaining BP values. In addition, independently of angiotensin II or BP, aldosterone plays a role in the pathophysiology of cardiovascular disease, particularly heart failure, through various mechanisms: it promotes oxidative stress, vascular remodeling, myocardial fibrosis, and left ventricular hypertrophy.

Autonomous aldosterone secretion causes increased sodium reabsorption through upregulation of epithelial sodium channels (EnaC) in the collecting tubules, leading to volume expansion and HT.

Clinical findings

Clinical findings are not very specific, and many patients can remain asymptomatic. Patients may present with symptoms associated with moderate to severe hypokalemia, such as neuromuscular symptoms, including fatigue, muscle weakness, or cramps. Other clinical findings include resistant HT, constipation, polyuria, and polydipsia.

PA might be suspected in the case of spontaneous or diuretic-induced hypokalemia, although this occurs only in a minority of patients [49]. Frequently, OSA and PA coexist, so a confirmed diagnosis or clinical characteristics of OSA should prompt investigations for PA. A family history of PA, an early-onset HT, or cerebrovascular events at a young age should raise suspicion. Atrial fibrillation not explained by other causes may also be suggestive. HMOD, such as left ventricular hypertrophy, diastolic dysfunction, microalbuminuria, and CKD greater than what one would expect based on BP values, should also prompt further investigations for PA [50].

Screening

Hypertensive patients with hypokalemia, either spontaneous or diuretic-induced, and those with resistant HT should be considered for PA screening. The first step is to perform the plasma aldosterone-to-renin ratio (ARR) and a simultaneous plasma aldosterone concentration (PAC) and plasma renin activity (PRA). It is important to know that several conditions should be fulfilled in order to avoid false-positive or false-negative results. Blood sampling is performed in the morning after the patient has been awake for 2 hours and in the sitting position for about 15 minutes. Potassium levels should be normalized before screening tests, and withdrawal of interfering medications should be taken into consideration. Of note, aldosterone antagonists should be withheld for at least four weeks prior to testing. Regarding other drugs (such as beta-blockers, central alpha₂-agonists, ACE inhibitors, ARB,

non-steroidal anti-inflammatory drugs, potassium wasting diuretics), all agents should be interrupted for two weeks in the case of unequivocal results. In patients with severe HT, preferred antihypertensive regimens include long-acting verapamil, hydralazine, and doxazosin, which have minimal effects

on ARR. An ARR above 20, associated with decreased or undetectable PRA and inappropriately high PAC, usually above 15 ng/dL, is highly suggestive of PA [29]. Further confirmatory tests should be performed as part of the diagnostic algorithm (Figure 4).

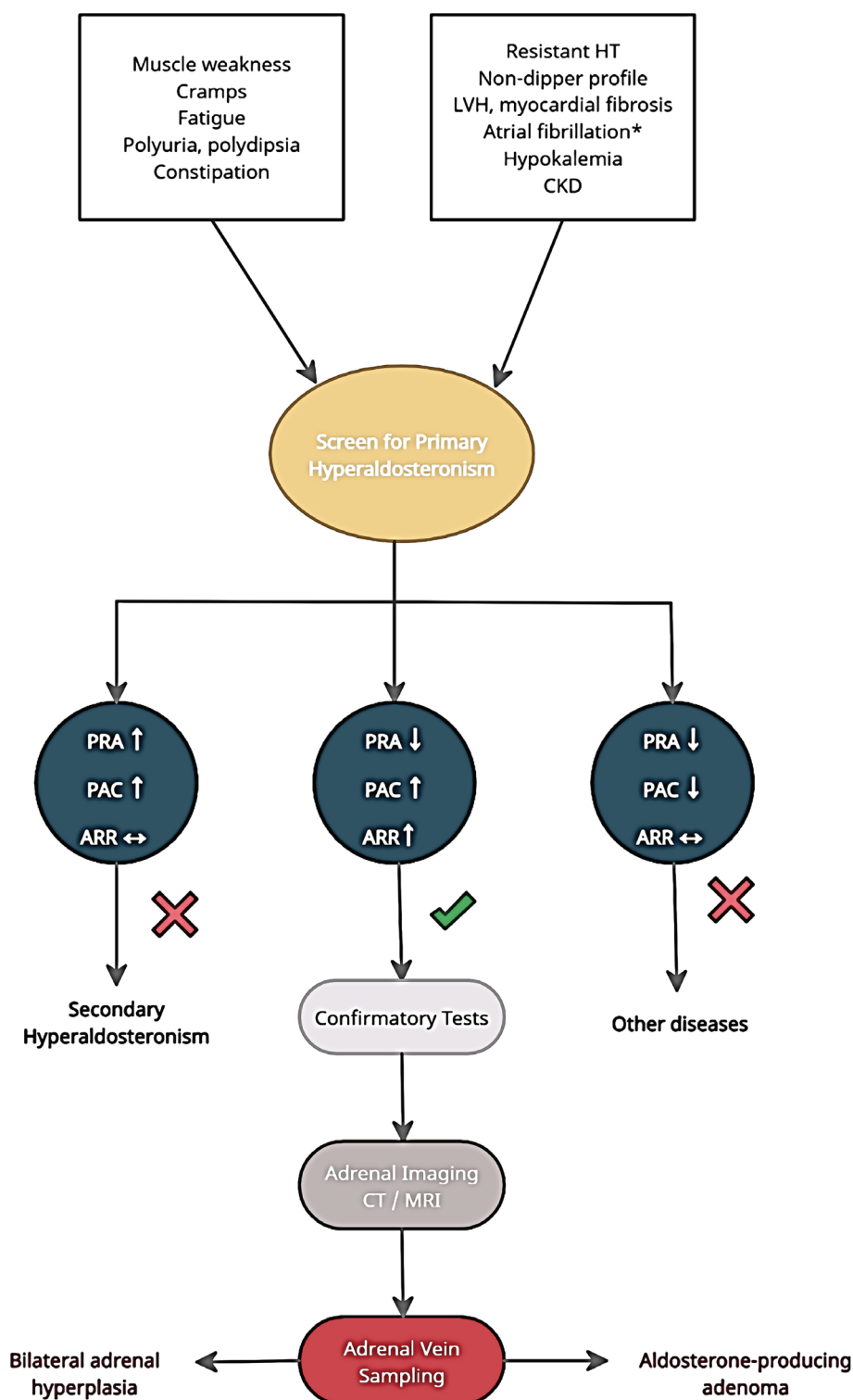


Figure 4. Diagnostic algorithm for Primary hyperaldosteronism. HT – hypertension; LVH – left ventricular hypertrophy; CKD – chronic kidney disease; PRA – plasma renin activity; PAC – plasma aldosterone concentration; ARR – aldosterone to renin ratio). * – Atrial fibrillation non explained by other causes may be suggestive.

Diagnosis

Confirmatory tests include oral sodium loading, saline infusion, captopril challenge test, and fludrocortisone suppression. None of these tests is currently approved as a gold standard, and some physicians no longer recommend them. The choice between these four tests must take into account the patient's compliance, the experience of the center, and other physiologic parameters. For instance, oral sodium loading and saline infusion tests are not recommended in patients with severe HT, heart failure, or CKD [51].

If a confirmatory test is positive, adrenal imaging (usually the CT scan) should be performed in order to direct operative management and exclude an aldosterone-producing carcinoma. However, imaging tests alone are insufficient to dictate patients toward adrenalectomy, as discordant data exist between CT scans and AVS [49].

AVS is the key test to subtype PA, thus identifying patients with aldosterone-producing adenoma, suitable for surgery. As this procedure carries significant risks, it should only be performed in patients with unequivocal biochemical evidence of PA who accept the surgical option and are reasonable candidates for general anesthesia [29, 52].

Treatment

The standard treatment for patients with bilateral adrenal hyperplasia is an MRA, either spironolactone or eplerenone. In patients intolerant to therapeutic doses of MRA, amiloride can be used in order to inhibit aldosterone-induced renal sodium reabsorption by blocking ENaC channels [29]. For patients with unilateral disease, the guidelines recommend adrenalectomy [53]. Following this procedure, BP control improves significantly in the majority of patients, and approximately one-third are cured and require no further antihypertensive treatment [54].

Cushing's syndrome

General Characteristics

Cushing's syndrome (CS) comprises a heterogeneous group of diseases characterized by chronic exposure to increased glucocorticoid levels that can be either endogenous or exogenous. It accounts for less than 1% of endocrine causes of resistant HT [1]. Exogenous or iatrogenic CS is the most frequent form associated with steroid use in any form (enteral, par-

enteral, inhaled, topical). Endogenous CS can be adrenocorticotropic (ACTH) dependent, resulting from excess production by the pituitary gland (70% of cases) or from ectopic ACTH production (10–15% of cases), a paraneoplastic syndrome associated with small-cell lung cancer. The remaining 15–20% of endogenous CS is attributed to ACTH-independent forms associated with cortisol-secreting adrenal tumors [55]. CS is associated with many complications, including metabolic syndrome, hypertension, and type II diabetes mellitus, which increase the risk of cardiovascular and cerebrovascular events and mortality. However, the prevalence of HT is 20% in iatrogenic CS, whereas, in adult patients with endogenous CS, it rises to 80% and even 95% in patients with ectopic ACTH secretion [56].

Pathophysiology of CS-related HT

Hypertension in Cushing's syndrome results from a complex interplay between multiple pathophysiological mechanisms. Among these, the intrinsic mineralocorticoid activity of cortisol, activation of RAAS, increased cardiac response to circulating catecholamines, enhancement of vasoconstriction, and suppression of vasodilation are all mechanisms that will lead to an increase in both cardiac output and peripheral vascular resistance and, ultimately, HT [56].

Clinical characteristics

Adults presenting with CS have typical characteristics. Central obesity, facial rounding known as "moon faces", thin skin, and HT are most frequent. Other clinical findings include hirsutism, striae rubre, buffalo hump, proximal muscle weakness, osteopenia or osteoporosis, ecchymoses, and psychiatric disturbances. Impaired glucose tolerance or diabetes are frequently associated conditions [50].

Screening and diagnosis

Exogenous use of steroids should be excluded before proceeding to specific screening tests. Patients with suggestive clinical features and those with adrenal incidentalomas should be considered for testing. Three first-line tests are available: 24-hour urinary free cortisol, late-night salivary cortisol test, and overnight dexamethasone suppression test. Two positive measurements are required for a likely diagnosis of CS. The next step is to measure the morning ACTH levels in order to distinguish between ACTH-dependent and independent CS [29].

Patients will be further referred to specialized endocrinology centers to establish optimal treatment strategies, either surgical removal of the tumor or pharmacotherapy with ACTH suppressors (somatostatin analogs, dopamine agonists), inhibitors of steroidogenesis, or glucocorticoid-receptor antagonists.

Treatment

The severity of HT in CS is strongly correlated with the duration of the disease. HT usually improves with specific treatment of hypercortisolism, so identifying and removing the cause is essential. This is often accomplished by surgical means [56]. Antihypertensive treatment in CS involves RAAS blockade with either an ACE inhibitor or sartan as a first-line therapy, followed by an MRA in hypokalemic patients. Beta-blockers are not considered a first-line class in patients with CS, partly because of their possible contraindications (metabolic syndrome, glucose intolerance), frequently encountered in these patients. CCB are safe to use in association with other drugs. Thiazide diuretics should be used with caution, as they may aggravate hypokalemia, hyperuricemia, and diabetes [57].

Pheochromocytoma

General characteristics

Pheochromocytoma and paragangliomas (PPGL) are rare tumors originating from the neural crest-derived chromaffin cells, located either in the adrenal medulla or in extra-adrenal paraganglia, characterized by excessive production of catecholamines (adrenaline, noradrenaline and/or dopamine). PPGL represent an uncommon cause of secondary HT, comprising 0.2% of unselected hypertensive patients. HT is invariably noted in 90% of patients, either paroxysmal or stable [58].

Clinical characteristics

The classic presentation of PPGL is referred to as “the 5 Ps”: paroxysmal HT, pounding headache, perspiration, palpitations, and pallor. However, the actual presentation of the disease is highly variable, which is why it is called “the great simulator”. Other clinical findings include anxiety and panic attacks, tremors, nausea, dyspnea, or abdominal pain. Hypertensive paroxysms can be precipitated by physical activities or tumor manipulation.

Screening and diagnosis

Screening for PPGL should be performed in highly selected patients who present with resistant HT and associated catecholaminergic spells, paradoxical response to beta-blockers, suspicion of syndromic PPGL (multiple endocrine neoplasia type 2, von Hippel Lindau, neurofibromatosis type 1), family history of PPGL, incidentaloma suggestive of PPGL [1]. Of note, only 5% of adrenal incidentalomas prove to be PPGL [59]. Screening involves the evaluation of catecholamine metabolites by using two tests: 24-hour urinary fractionated metanephrines and plasma-free metanephrines. The latter should be performed after a standardized protocol, as many conditions, including drugs, have effects on metanephrine levels. Examples include acetaminophen, sulfasalazine, tricyclic antidepressants, monoamine oxidase inhibitors, and sympathomimetics.

If screening is positive, patients should be further evaluated with CT imaging of the abdomen and pelvis using the adrenal protocol. MRI represents an alternative, especially for paragangliomas located in the cervical region.

Treatment

Surgery is the gold-standard treatment for solitary PPGL, typically adrenalectomy for most intra-adrenal tumors. Pre-operative management of HT involves alpha1-blockade, while beta-blockers can be associated in order to manage tachycardia. They must never be used alone, but only in combination with alpha1-blockers. Surgical treatment usually improves BP control, although persistent HT may indicate incomplete resection or metastases [58].

Thyroid disease

Thyroid hormones manifest direct and indirect effects on the cardiovascular system. Both hyper- and hypothyroidism can lead to HT, which is usually mild. In hyperthyroidism, the excess of circulating thyroid hormones leads to increased heart rate and increased cardiac output. Triiodothyronine has a direct positive inotropic effect and also acts on resistance arterioles, causing a decrease in peripheral vascular resistance. These lead to the development of hypertension, mainly based on the elevation of systolic BP, causing a widened pulse pressure. In contrast, hypothyroidism has opposite effects. Bradycardia is usually the most common cardiovascular sign. Decreased contractility and decreased heart rate lead to low cardiac output and increased peripher-

al vascular resistance, which explains why hypothyroidism is accompanied by diastolic hypertension, leading to narrowed pulse pressure [60]. Screening involves measuring the plasma concentration of the thyroid-stimulating hormone.

Hyperparathyroidism

Hyperparathyroidism is associated with HT and increased cardiovascular risk, although the mechanisms are still poorly understood. Parathyroidectomy seems to improve BP control, while other studies show no effect, with many patients remaining hypertensive after surgery [61, 62].

Coarctation of the aorta

Coarctation of the aorta, characterized by constriction of the aortic lumen, usually near the ligamentum arteriosum, is a rare cause of secondary HT. It is usually diagnosed in childhood, although it may be detected in adults, as symptoms may not be present. The classic presentation includes HT in the upper extremities with delayed or absent femoral pulses, accompanied by a systolic murmur at the upper left sternal border or in the left interscapular area. Additional signs include notching of the posterior ribs on chest radiography. Transthoracic echocardiography is used as a screening tool, while confirmation can be obtained with CT or MRI. The choice between surgical repair and percutaneous balloon angioplasty is based on the patient's characteristics. Patients require long-term follow-up, as many develop chronic HT, despite anatomically successful repair. [63]

Acromegaly

Acromegaly results from hypersecretion of growth hormone (GH) from a pituitary tumor, and it is associated with many complications, including diabetes, cardiovascular diseases, and respiratory disorders. The prevalence of HT in acromegalic patients is around 30%. Possible mechanisms for the development of HT include direct cardiovascular effects of growth hormone (GH) and insulin-like growth factor-1, GH-mediated sodium reabsorption and expansion of plasma volume, increased sympathetic activity, and hyperinsulinemia [64]. Treatment includes surgical removal of the tumor, radiation therapy, or GH-blocking drugs.

Conclusions

Screening for secondary HT is recommended, but not for all hypertensive patients, as it was outlined in the present paper. Clinical judgment is essential when choosing to perform screening tests. However, we must consider that primary and secondary HT can coexist or, sometimes, even more than one cause of secondary HT can be present in the same patient. Some general characteristics of patients can raise suspicion and point toward a diagnosis.

Secondary HT affects a small proportion of hypertensive patients, but it is frequently undiagnosed, leading to irreversible vascular remodeling and target organ damage. Timely identification of patients who may benefit from screening is essential, as treating the secondary cause will lead to improved BP control or, occasionally, even allow BP values to return to normal. Understanding the underlying disease with the pathophysiological mechanisms that lead to HT enables us to choose optimal treatments. This algorithm will limit the development of cardiovascular complications and improve the quality of life for our patients.

Conflict of Interests

The authors confirm that there are no conflicts of interest.

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