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Major Clinical Considerations for Secondary Hypertension and Treatment Challenges: Systematic Review

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Abstract

Introduction: In this context, secondary arterial hypertension (SH) is defined as an increase in systemic arterial pressure (SAP) due to an identifiable cause. Only 5 to 10% of patients suffering from hypertension have a secondary form, while the vast majorities have essential hypertension.

Objective: This study aimed to describe, through a systematic review, the main considerations on secondary hypertension, presenting its clinical data and main causes, as well as presenting the types of treatments according to the literary results.

Methods: Following the criteria of literary search with the use of the Mesh Terms that were cited in the item below on "Search strategies", the total of 76 papers that were submitted to the eligibility analysis were collated and, after that, 23 studies were selected, following the rules of systematic review-PRISMA. In general, as an example, the search strategy in MEDLINE / Pubmed, Web of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile (Gale).

Major findings: According to epidemiological data, secondary hypertension (SH) presents an incidence of 5.0 to 10.0% of the world population. In this context, since SH cases are difficult to screen and expensive, only patients with clinical suspicion should be examined. In recent years, some new aspects have gained importance in relation to this screening. Thus, increasing evidence suggests that 24-hour ambulatory blood pressure monitoring plays a central role. The prevalence of SH is related to age and clinical characteristics. In addition, some residual hypertension remains after the pathogenic cause of secondary hypertension has been identified and removed because of the existence of essential hypertension.

Conclusion: It was concluded with the present study that secondary hypertension effects on average 7.5% of hypertensive patients. Screening in the diagnosis of secondary hypertension is expensive and laborious and should be performed only in patients with high clinical suspicion.

Keywords: Arterial hypertension; Secondary hypertension; Systemic arterial hypertension; Origin; Treatment

Introduction

Systemic arterial hypertension (SAH) is a serious public health problem in Brazil and the world [1]. It is one of the most important risk factors for the development of cardiovascular, cerebrovascular and renal diseases, accounting for at least 40.0 % of deaths due to stroke, 25.0 % of deaths from coronary artery disease and, in combination with Diabetes , 50.0 % of cases of end-stage renal failure [1,2].

In this context, secondary hypertension (SH) is defined as an increase in systemic arterial pressure (SAP) due to an identifiable cause. Thus, only 5.0 to 10.0 % of patients with hypertension have a secondary form, while the vast majority have essential hypertension (idiopathic or primary) [1,3]. Because secondary forms are rare and screening expensive and laborious, it is not cost effective to look for secondary causes of hypertension in all patients [1,4].

In addition, while most young patients (40 years) with secondary hypertension respond to specific treatment, 35.0 % of elderly patients achieve BP values are not achieved after specific treatment [5]. This suggests that, on the one hand, early detection and treatment of secondary hypertension are important to minimize irreversible changes in the systemic vasculature; on the other hand, the prevalence of primary and secondary complications concomitant with hypertension increases with increasing age [6].

SH has a prevalence of 3.0-5.0% [1]. Cause treatment can cure or improve SH control [2-4]. The situations in which secondary causes of SH should be investigated. Most cases of arterial hypertension do not present an easily identifiable apparent cause, known as essential hypertension [5-7]. A small proportion of cases of arterial hypertension are due to well-established causes, which need to be properly diagnosed, since with the removal of the etiological agent it is possible to control or cure SH [8-10].

At the primary care level, the health team should be prepared to diagnose, guide and treat cases of essential hypertension, which are the

majority [11-14]. On the other hand, suspected SH cases should be referred to specialists. Findings suggest secondary hypertension.

Therefore, the present study aimed to describe, through a systematic review, the main considerations about secondary hypertension, presenting its clinical data and main causes, as well as presenting the types of treatments according to the literary results.

Methods

Study design

Following the criteria of literary search with the use of the Mesh Terms that were cited in the item below on "Search strategies", a total of 76 papers that were submitted to the eligibility analysis were collated and, after that, 23 studies were selected, following the rules of systematic review-PRISMA (Transparent reporting of systematic reviews and meta-analyses-http://www.prisma-statement.org/).

Sources of information

The review protocol was based on the criteria of literary search with the use of mesh terms in the main databases such as Pubmed, Medline, Bireme, EBSCO, Scielo, etc. All references are registered in EndNote by the site:

http://www.myendnoteweb.com/EndNoteWeb.html?cat=myrefs&.

Search strategy

In general, as an example, the search strategy in MEDLINE/ Pubmed, Web Of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile (Gale) followed the following steps: - search for mesh terms: Arterial hypertension, Secondary hypertension, Systemic arterial hypertension, Origin, Treatment, use of the bouleanos "and" between mesh terms and "or" among historical findings.

Statistical treatment of literary findings

A descriptive analysis was performed with standard parameters of mean, standard deviation and amplitude. Anderson-Darling normality test (α-level> 0.10 considering "normal") was also performed for continuous and categorical data, with consequent application of Kruskal-Wallis analysis of variance to the internal data of each study alone, accepting p -value less than 0.05 for statistical significance (Figure 1).

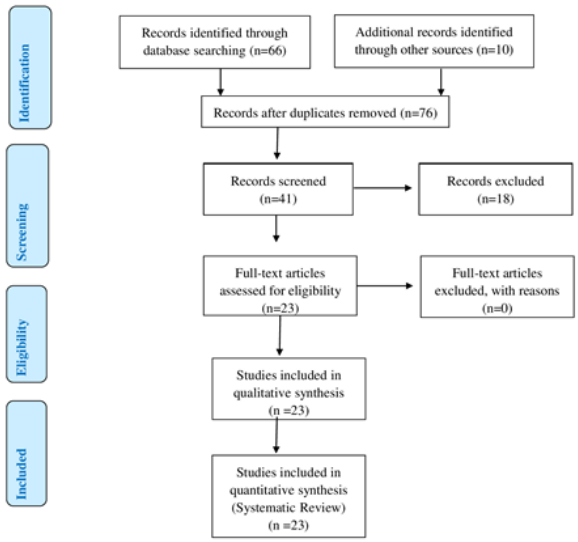

Figure 1: Flowchart of search strategy and the results obtained.

Results

The major results of the search process are listed in Tables 1, 2 and 3, as well as the Kruskal-Wallis non-parametric statistical results of the literary findings, according to Table 1.

Clinical findings	Additional studies	p-value
Snoring, daytime sleepiness, metabolic syndrome	Berlin questionnaire, polysomnography or residential polygraph with 5 or more episodes of apnea and/or hypopnea per hour of sleep	>0.05
HAR and/or with hypopotassemia (not mandatory) and/or with adrenal nodule	Determinations of aldosterone (> 15 ng/dL) and plasma renin activity/concentration; aldosterone/renin ratio >30. Confirmatory tests (furosemide and captopril). Image exams: CT with thin sections or MRI	>0.05
Elevated edema, anorexia, fatigue, creatinine and urea, changes in urinary sediment	Urinalysis, calculation of RFG-e, renal US, albuminuria/proteinuria screening	>0.05
Abdominal bleeding, sudden PAD, change in renal function by drugs that block RAAS	US with renal Doppler and/or renogram, angiography by MRI or CT, renal arteriography	>0.05
Pulses in females absent or of diminished amplitude, decreased PA in lower limbs, changes in chest x-ray	Echocardiogram and/or CT chest angiography	>0.05
Weight gain, decreased libido, fatigue, hirsutism, amenorrhea, "full moon facies", purple striae, central obesity, hypopotassemia.	Cortisol salivary, 24h free urinary cortisol and suppression test: morning cortisol (8h) and 8h after administration of dexamethasone (1mg) at 24 h. RNM	>0.05
Paroxysmal HA with headache, sweating and palpitations.	Free plasma metanephrines, serum catecholamines and urinary metanephrines. TC and RNM	>0.05

Fatigue, weight gain, hair loss, HAD, muscle weakness.	Free TSH and T4	>0.05
Heat intolerance, weight loss, palpitations, exophthalmos, hyperthermia, exhaled reflexes, tremors and tachycardia.	Free TSH and T4	>0.05
Urinary lithiasis, osteoporosis, depression, lethargy, muscle weakness or spasms, thirst, polyuria	Serum calcium and PTH	>0.05
Headache, fatigue, visual problems, increase of hands, feet and tongue	IGF-1 and basal GH and during oral glucose tolerance test	>0.05

Table 1: Major clinical findings and results of the statistical analysis between each result found in the literature. We adopted $p < 0.05$ as statistically different.

Development and discussion

According to epidemiological data, secondary hypertension (SH) presents an incidence of 5.0% to 10.0% of the world population (Table 2) [1]. In this context, since SH cases are difficult to screen and expensive, only patients with clinical suspicion should be examined. In recent years, some new aspects have gained importance in relation to this screening [2]. Thus, increasing evidence suggests that 24 h ambulatory blood pressure (BP) monitoring plays a central role [1-3].

Secondary hypertension cause	Prevalence (%)	Clinical findings
Obstructive sleep apnoea	10.0	Neck circumference; obesity; peripheral oedema.
Renal parenchymal disease	5.0	Peripheral oedema; pallor; loss of muscle mass.
Renal artery stenosis	4.5	Abdominal bruits and peripheral vascular disease.
Primary aldosteronism	7.0	Muscle weakness
Thyroid disease	1.5	Hyperthyreodism: tachycardia; accentuated heart sounds; exophthalmus; Hypothyreodism; Bradycardia; muscle weakness; myxedema.
Cushing's syndrome	0.5	Obesity; hirsutism; skin atrophy; Striae rubrae; muscle weakness; osteopenia.
Phaeochromocytoma	0.3	The paroxysmal hypertension; pounding headache; perspiration; palpitations; pallor.
Coarctation of the aorta	0.8	Different Blood Pressure (≥ 20/10 mmHg) between upper–lower extremities and/or between right–left arm; and delayed femoral pulsations; interscapular ejection murmur; rib notching on chest Rx

Table 2: Major causes of secondary hypertension, prevalence and clinical findings of each pathology.

In addition, obstructive sleep apnea was identified as one of the most frequent causes [4,5]. Furthermore, the introduction of catheter-based renal denervation for the treatment of patients with resistant hypertension (AHR) increased the interest and the number of patients evaluated for renal artery stenosis indicating SH [5].

Despite adequate therapy or even removal of the secondary cause, blood pressure rarely returns to normal [6-8]. This means that some SH patients also have concomitant essential hypertension or irreversible vascular remodeling [9-13]. Thus, in patients with potentially reversible causes of hypertension, early detection and treatment are important in reducing irreversible changes in the vasculature (Table 3) [14-18].

The prevalence of SH is related to age and clinical characteristics [19,20]. In addition, some residual hypertension remains after the pathogenic cause of secondary hypertension has been identified and removed due to the existence of essential hypertension [21,22]. The phenotype of essential hypertension can manifest itself from 3 years of age and is the predominant form of hypertension in children after 6 years of age. Among children with hypertension, those with essential hypertension are older, have a family history of stronger hypertension and a lower prevalence of prematurity [23].

In patients with resistant hypertension, despite the use of three antihypertensive drugs, including an ideal dose diuretic, the prevalence of secondary forms is significantly higher than in patients with controlled BP [9-12]. There are also other less frequent causes of SH [23]. These causes have multifactorial origin and some literary studies are presented in the next paragraphs [13-16, 22].

According to other causes, SH may be linked to major bleeding events and death beyond the treatment strategy of vitamin K antagonist or oral anticoagulants [1]. In this study with 2,792 patients (mean age, 65.6 ± 19.9 years) during the 2-year study, hypertension is responsible for 1,077 (39.0%) patients; bleeding greater than 474 (17.0%); death by 29 (1.0%) and 72 (3.0%) in 1 month and 1 year, respectively. As a result, four out of ten patients with major bleeding had hypertension; of these 8 in 10 will die within 1 month [1].

In addition, tumors of juxtaglomerular cells are rare, usually benign, and are one of the treatable causes of SH [4]. There are approximately 100 cases reported in the literature, and the diagnosis is usually made based on a high index of clinical suspicion, especially in patients with hypokalemia and hypertension. There was a report on a case of a 22 years old woman with resistant hypertension and renal and cardiovascular lesions in target organs [4]. She had elevated plasma renin and nodular renal mass. A lumpectomy was performed and histological examination confirmed a reninome. After surgery, blood pressure and serum renin levels returned to normal without medication. This paper focuses on the need to exclude rare secondary

causes of hypertension in young patients with resistant forms of the disease [4].

Another study determined that high uric acid is associated with postpartum hypertension in women without chronic hypertension [5]. Those with high uric acid were compared with normal. Logistic regression was performed to determine the association of elevated uric acid with postpartum SH. Five hundred and fifty-six women met criteria. A level of AU ≥ 5.2 mg/dL was associated with SH (adjusted odds ratio 2.44, 95% CI, 1.63-3.64). The association was stronger among overweight and obese women [5].

A study of 877 patients showed that increased SH variability is associated with acute ischemic stroke and may also have a negative impact after intracerebral hemorrhage [6]. It was determined whether the increase in SH was detrimental in the ATACH-2 (Anti-Hypertensive Treatment of Cerebral Bleeding II) study. In this secondary analysis of ATACH-2, it has been shown that increased SH is associated with worse long-term neurological outcome [6].

As a possibility of treatment to SH, a recent study proposed a scheme of treatment of hypertension. Sodium intake should be restricted to 100 mEq, i.e. around 2.3 grams per day [9]. Strict diets, however, are often uncomfortable and rarely combined with stringent compliance. A total of 291 patients on antihypertensive treatment were studied, 240 of whom were instructed to avoid salty foods, such as cheese and cured meats, and switch from standard bread to unsalted bread. The remaining 51 paired patients constituted a control group and received only generic dietary guidance. At [U]/24 h, K [U]/24 h, and PA at the office were recorded before the start of the diet and after 9 ± 1 weeks of diet [9]. Thus, the intervention group had a significant decrease in body weight (71.75 ± 14.0-70.54 ± 13.33 kg, $p<0.0001$), sodium excretion (153.1 ± 44.61 a, $p <0.05$), systolic and diastolic BP (134.16 ± 16.0 to 126.5 ± 10.53 mmHg, $p=0.014$ and 80.59 ± 11, 47 to 75.9 ± 8.72 mmHg, $p=0.026$ respectively) and drug use (1.71 ± 0.91 to 1.49 ± 0.84 DDD, $p<0.05$). The response rate to antihypertensive therapy increased (51.4% to 79.5%). In the control group, no significant or substantial changes were observed. The results suggested that even a minimal reduction in apparent sodium intake (± 0.5 grams per day) may improve BP values and response rates in treated hypertensive patients while reducing the use of antihypertensive drugs [9].

In this context, another study also analyzed the SH reduction [11]. We then evaluated whether a multifaceted community-based intervention package, provided primarily by non-medical health professionals, can improve long-term cardiovascular risk in people with hypertension by addressing the barriers identified in the patient, healthcare provider, and levels of the health system. HOPE-4 is a community-based randomized, parallel group controlled trial involving 30 communities (1,376 participants) in Colombia and Malaysia. Participants aged ≥ 50 years and with newly diagnosed or poorly controlled hypertension were included [11].

In this work, communities were randomized to routine care or to a multifaceted intervention package that involves (1) detecting, treating and controlling cardiovascular risk factors by non-medical community health professionals using simplified management algorithms based on tablets, decision support and counseling programs; (2) free dispensing of combined antihypertensive and cholesterol lowering drugs, supervised by local physicians; and (3) support from a participant indicated to the participant (a friend or family member) [11]. The primary endpoint was the change in the Framingham risk score after 12 months between the intervention and control communities. Secondary outcomes including changes in blood pressure, lipid levels and inter heart risk score were assessed. Therefore, the study served as a model to develop low-cost, effective and scalable strategies to reduce cardiovascular risk in people with SH [11].

Added to this, according to epidemiological data, half of hypertensive patients did not reach target blood pressure with pharmacotherapy, partly due to poor adherence [10]. Thus, music therapy is an adjunct therapy that has been shown to be effective in reducing blood pressure. The objective was to investigate the effect of Thai instrumental folk music on blood pressure in Thai hypertensive patients. A randomized control trial of stage 2 hypertensive patients was under observation at Srinagarind Hospital, Khon Kaen, Thailand. One hundred and twenty participants were randomized to music listening group and control group (1:1) [10]. The musical audition group was assigned to listen to Thai instrumental folk music once a day for a month [10].

In this study, the primary and secondary endpoints were home blood pressure (day 0 and 30) and office blood pressure (day 0 and 120), respectively [10]. Systolic blood pressure (BP) and diastolic blood pressure (DBP) in the music listening group were significantly reduced compared to baseline (-9.5 ± 7.1 mmHg and -6.1 ± 5.7 mmHg, respectively). Both the initial BP and DBP on the 30th day of the music listening group were significantly lower than in the control group (-6.0 mmHg and -3.15 mmHg, respectively), while differences in BP and DBP between two groups were not significant [10]. This study demonstrated that Thai instrumental folk music audition was effective for the reduction of BP and DBP in SH patients. This therapy can be used as an alternate approach simultaneously with pharmacological treatment [10].

Early onset of hypertension (i.e., 30 years) in patients without other risk factors (i.e. family history, obesity, etc.).
Increased blood pressure in prepubertal children.
Resistant hypertension (140/90 mmHg despite three antihypertensive drugs including a diuretic).
Severe hypertension (180/110 mmHg) or hypertensive emergencies.
Sudden increase of BP in a previously stable patient.
Non-dipping or reverse dipping during 24 h ambulatory BP monitoring.
Presence of target organ damage.

Table 3: General clinical characteristics suggestive of secondary hypertension.

Conclusion

It was concluded with the present study that secondary hypertension effects on average 7.5% of hypertensive patients. Screening in the diagnosis of secondary hypertension is expensive and laborious and should be performed only in patients with high clinical suspicion. Despite having found and treated adequately a secondary cause of hypertension, BP rarely returns to normal, since some of these patients also have concomitant essential hypertension. Thus, early detection and treatment is imperative in such patients in order to avoid irreversible changes in the systemic vasculature.

Declaration of Potential Conflict of Interest

The authors declare no conflict of interest.

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