

Improved identification of secondary hypertension: use of a systematic protocol

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Background: The accurate identification and diagnosis of secondary hypertension is critical, especially while atherosclerotic cardiovascular heart disease continues to be the leading cause of death in the industrialized world. Nevertheless, despite the existence of diagnostic tools, there are significant variations of the estimated prevalence of secondary hypertension, due to multiple etiologies and suboptimal recognition. This study demonstrates the results of using a systematic and protocolled approach to improve recognition of the presence of secondary hypertension. In the future, this questionnaire can be a quick and effective tool to unveil secondary hypertension in a broad array of clinical settings.

Methods: A total of 28,633 consecutive patients from January 1, 2007 to January 1, 2017 were diagnosed as having primary or secondary hypertension, utilizing the International Code of Diseases. Patients were located at the Center of Hypertension, Institute of Cardiology at Austral University Hospital, Buenos Aires, Argentina and were then further classified as having TRH, or non-resistant hypertension, to which a systematic protocol was employed in search for secondary hypertension. The confirmation of secondary hypertension was subsequently confirmed by diagnostic laboratory and imaging techniques in a hospital setting.

Results: A final population of 12,284 patients with treatment resistant hypertension (TRH) and non-treatment resistant hypertension (NTRH) were included in this study, where an etiology of secondary hypertension was identified in 50.9% and 36% of patients in each treatment group, respectively. Physicians used confirmatory laboratory testing and imaging of patients who were identified as having a cause for their secondary hypertension, with no significant differences in sex, age and body mass index (BMI) among study groups.

Conclusions: These results illustrate the prevalence and distribution of the causes of secondary hypertension using a systematic, protocolled approach, which revealed a higher percentage of secondary hypertension than previously reported. This tool may be used by healthcare providers to ensure the appropriate recognition of secondary causes of hypertension in a wider range of patients with high blood pressure beyond resistant hypertension, changing the diagnostic paradigm of this condition.

Keywords: Secondary hypertension (SH); essential hypertension; treatment resistant hypertension (TRH); non-treatment resistant hypertension (NTRH); systematic protocol; hyperaldosteronism; pheochromocytoma; Liddle disease; sleep apnea; drug induced hypertension

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Introduction

Secondary hypertension (SH) is best defined as a form of hypertension with an identifiable cause and is generally considered to affect approximately 5–10% of all hypertensive patients (1,2). Nevertheless, in a comprehensive review of published work, there were significant variations of the estimated prevalence of SH, ranging from 2% to 20% depending on the underlying etiology leading to high blood pressure (HBP) and the availability of adequate diagnostic laboratory and imaging resources (1-6). The recent 2017 American College of Cardiology/American Heart Association (ACC/AHA) High Blood Pressure Guideline recommends screening for a specific form of hypertension when clinical indications and physical examination findings are present, or in adults with resistant hypertension (7). While many diagnostic tools exist to assess SH, physicians and other healthcare providers who treat hypertension may find it difficult to detect due to the multiple etiologies and suboptimal recognition of the condition.

In 2002, the Center of Hypertension was created at the Institute of Cardiology (CHIC), at Austral University Hospital in Buenos Aires, Argentina. The Center's activities are characterized by an intensive interplay between patient care, teaching and clinical-translational research. As a teaching and referral unit, the Center created a systematic and standardized approach to screen patients with hypertension in search for an identifiable cause for their HBP, based on contemporary guideline recommendations and local expertise (7-9). Utilizing the methods developed in the Center, this approach, known as the CHIC Protocol, could constitute a valuable tool for early recognition and accurate diagnosis of SH in clinical practice.

In 2017, we analyzed patient data from the preceding decade and screened for SH using this Protocol, identifying a higher level in the prevalence of SH among our patients, compared to previously published world-wide reports (1-9). Although secondary causes of hypertension are common in patients with resistant hypertension, a higher prevalence of SH persisted independent of the measured severity of BP values and SH was also identified in patients with moderate hypertension. Based on these results, we propose that our approach, originally developed for the unique diagnostic evaluation for physicians at the Institute of Cardiology, may represent a methodology that would facilitate the identification of SH in a variety of clinical sites.

Methods

We conducted a comprehensive search of medical records of 28,633 consecutive hypertensive patients evaluated at the Center of Hypertension, Institute of Cardiology at Austral University Hospital from January 1, 2007 to January 1, 2017. During that period, all attending physicians were instructed to classify diagnoses utilizing the International Code of Diseases (ICD9), assigning 401 to indicate essential (primary) hypertension and 405 for SH. Institutional medical records were digitized, provided by the PECTRA-BPM software and adapted for Electronic Health Record or Open EHR. For eligibility, patients were required to be 21 years old or greater at the time of the initial diagnosis, along with a complete and comprehensive medical record available for evaluation. Permission was obtained from Institutional Ethics and Review Board for the revision of clinical records, the development of our database and results analysis.

Participants were classified as having treatment resistant hypertension (TRH) or non-treatment resistant hypertension (NTRH), according to the contemporaneous definitions during the period analyzed. Accordingly, using contemporary diagnostic criteria during that period, TRH is defined as BP above goal in spite of the concurrent use of 3 antihypertensive agents of different classes prescribed at optimal dosages, with ideally a diuretic as one of the agents (10). Classifying the hypertension as resistant identifies patients who are at high risk of having SH due to persistently high BP levels and who may benefit from special diagnostic and therapeutic considerations. Moreover, patients whose BP is controlled, but requires 4 or more drugs to do so are also considered as having TRH (10). Additionally, the NTRH cohort included patients with controlled BP with up to 3 drugs (7-9).

Data analysis was made through univariate analysis and proportional rates.

The CHIC protocol: a systematic questionnaire

The CHIC Protocol consists of related blocks of questions evaluating presenting symptoms and patient history to properly identify SH (*Table 1*). These blocks of questions are related to a specific etiologies of SH, and when answered affirmatively are suggestive for specific causations of the conditions. Aptly, physicians were instructed to apply the CHIC Protocol during the consultation and complete the questionnaire based upon these observations, interviews,

Table 1 The CHIC questionnaire

No.	Description of the questions	If yes, consider:
	Questions assessing general risk of secondary hypertension	
1	Has hypertension been diagnosed either before 30 years of age or after 60 years of age?	Secondary hypertension
2	Has the patient's BP ever been recorded as 180/110 mmHg?	
3	Has the patient ever been diagnosed with resistant, refractory or malignant hypertension?	
4	Does the BP begin to increase for unclear reasons after being well-controlled?	
	Questions in the search of hyperaldosteronism (adrenal adenoma, carcinoma, and bilateral adrenal hyperplasia)—Does the patient have or ever had any of the followings signs, symptoms or conditions?	
5	Cramps?	Hyperaldosteronism
6	Muscle weakness? Asthenia?	
7	Cardiac arrhythmias or palpitations?	
8	Sleep apnea?	
9	Unprovoked hypokalemia or exaggerated hypokalemia in response to diuretic treatment?	
10	Nocturia?	
11	Family history of hyperaldosteronism?	
	Questions in the search of apparent mineralocorticoid excess—Does the patient have or ever had any of the followings signs, symptoms or conditions?	
12	Hirsutism?	Apparent mineralocorticoid excess
13	Adult acne?	
14	Alteration in menstrual cycle or amenorrhea?	
15	Polycystic ovarian syndrome?	
16	Fluid retention or edemas?	
17	Has the patient ever received prolonged corticoid administration for any medical condition?	
	Questions in the search of pheochromocytoma—Does the patient have or ever had any of the followings signs, symptoms or conditions?	
18	Moderate or severe bilateral headaches?	Pheochromocytoma
19	Sudden episodes of intense sweating in the hands and/or face?	
20	Thyroid medullary carcinoma?	
21	Palpitations? Tremors?	
22	Panic attacks?	
23	Syncope or dizziness?	
24	Facial pallor in a small body habitus?	
25	Family history of stroke or acute myocardial infarction younger than 45 years of age?	
26	Women with gestational hyperglycemia or gestational diabetes	
27	Hypertensive crisis related to urinary retention, surgical procedures, menstrual cycle related or child delivery?	
	Questions in the search of renovascular disease—Does the patient have or ever had any of the followings signs, symptoms or conditions?	
28	Sudden increase in BP after use of angiotensin converting enzyme inhibitors (ACE inhibitor)?	Renovascular disease
29	Deterioration of renal function after use of ACE inhibitors?	
30	Peripheral (carotid, femoral, aortic) atherosclerotic disease?	
31	Long standing history of smoking, dyslipidemia or type 2 diabetes?	
32	History of acute pulmonary edema?	
33	Unexplained episodes of facial flushing?	
34	Abdominal bruits?	
35	Renal asymmetry greater than 1.5 cm between both kidneys?	

Table 1 (continued)

Table 1 (continued)

No.	Description of the questions	If yes, consider:
	Questions in the search of renal parenchymal disease (diabetic nephropathy, hypertensive nephrosclerosis, polycystic kidney disease & chronic glomerulonephritis)—Does the patient have or ever had any of the followings signs, symptoms or conditions?	
36	Patient with history of low birth weight, hypertension and type 2 diabetes?	Renal parenchymal disease
37	Polycystic kidney disease or ultrasound study showing multiple cysts?	disease
38	Oversized kidneys at palpation in previous consultation?	
39	Peripheral edema or fluid retention?	
40	Urinary form?	
41	Daytime increase in weight due to fluid retention?	
42	Hyperkalemia, uremia, albuminuria? Increased creatinine, increased red blood cell count, or increased white blood cell count? Decreased glomerular filtration rate?	
43	Recurrent renal infectious diseases, cystitis or reflux?	
44	Abuse or increased use of analgesic drugs?	
	Questions focusing in the search of sleep respiratory disorders or apnea—Does the patient have or ever had any of the followings signs, symptoms or conditions?	
45	Snoring while sleeping?	Obstructive sleep apnea or central sleep apnea (OSA & CSA)
46	Witnessed apneas?	
47	Frequent daytime sleepiness?	
48	Non-restorative sleep resting?	
49	Family history of sleep apnea?	
50	Previous tonsillectomy or otorhinolaryngological structural or functional alterations? (chronic sinusitis, nasal septal deviation, nasal septal hypertrophy or polypoid disease)	
	Questions focusing in the search of Cushing disease or syndrome—Does the patient have or ever had any of the followings signs, symptoms or conditions?	
51	Facial ruddiness and moon facies?	Cushing's Disease or Cushing syndrome
52	Truncal obesity predominant with small legs?	
53	Easy bruising?	
54	Facial plethora?	
55	Red striae?	
56	Proximal myopathy?	
57	Insidious weight gain in the last year?	
58	Psychological or mood disorders, including depression?	
59	Diabetes or hyperglycemia?	
60	Polydipsia or polyuria?	
61	Hirsutism?	
62	Bone disease or fragility or osteoporosis?	
	Questions focusing in the search of thyroid dysfunction—Does the patient have or ever had any of the followings signs, symptoms or conditions?	
63	Fatigue, goiter, delayed reflexes, weight gain or difficulty losing weight, cold intolerance, dry and/or rough and/or pale skin, constipation, facial swelling or edema, hoarseness, coarse and/or dry hair or hair loss, muscle cramps and/or aches, depression, memory loss, abnormal menstrual cycles, decreased libido?	Hypothyroidism
64	Goiter, thyroid bruit, lid lag, bulging eyes, fatigue, weight loss, heat intolerance and/or sweating, fine tremor, increase bowel movements, fast heart rate, palpitations, staring gaze, nervousness, insomnia, light or absent menstrual periods, muscle weakness, warm moist skin, hair loss, hand temperature and/or humidity increase?	Hyperthyroidism

Table 1 (continued)

Table 1 (continued)

No.	Description of the questions	If yes, consider:
	Questions focusing in drug-induced hypertension—Does the patient have any on the following conditions?	
65	Excessive dietary sodium intake? Increased 24 hours urinary sodium? Increased risk of salt-sensitivity, such as older patients, African ancestry and those with chronic kidney disease? Chronic use or abuse of sodium-containing antacids?	Drug-induced hypertension
66	Excessive alcohol consumption? (Over 2 drinks daily for men or 1 drink daily for women)	
67	Excessive consumption of caffeinated beverages of over 4 large cups daily (250 ml per cup)—regular intake of energy beverages containing large doses of caffeine?	
68	Chronic or acute intake of nonsteroidal anti-inflammatory drugs, aspirin, or acetaminophen?	
69	Chronic or acute intake of amphetamine, methylphenidate dexamethylphenidate, and dextroamphetamine for example indicated to the management of attention-deficit/hyperactivity disorder in children and adolescents?	
70	Chronic or acute intake of antidepressants such as monoamine oxidase inhibitors, serotonin-norepinephrine reuptake inhibitors, or tricyclic antidepressants, or atypical antipsychotics such as clozapine and olanzapine?	
71	Chronic or acute intake of sympathomimetic such as the decongestants containing phenylephrine or pseudoephedrine?	
72	Systemic corticosteroids such as dexamethasone, fludrocortisone, methylprednisolone, prednisone, and prednisolone?	
73	Chronic or acute intake of herbal supplements such as ephedra, St John's wort, and yohimbine, or laxatives?	
74	Mineralocorticoids including licorice, carbenoxolone, 9-alpha fluorocortisol, ketoconazole, and carbenoxolone?	
75	Estrogens, androgens, and oral contraceptives?	
76	Immunosuppressants, including cyclosporine treatment?	
77	Chronic use of recombinant human erythropoietin?	
78	Abrupt cessation of sympatholytic drugs, such as clonidine?	
	Questions focusing in the search of acromegaly—Does the patient have or ever had any of the followings signs, symptoms or conditions?	
79	Enlarged of the hands, feet, forehead, jaw or nose?	Acromegaly
80	Pronounced lower jaw protrusion (prognathism) with attendant macroglossia (enlargement of the tongue) and teeth spacing?	
81	Type 2 diabetes, sleep apnea and hypertension in a taller person?	
82	Thick skin? Galactorrhea?	
83	Hand temperature and/or humidity increase?	
84	Thick, deep voice and slowing of speech?	
85	Pronounced brow protrusion, often with ocular distension (frontal bossing)?	
86	Severe headaches and problems with vision typically bitemporal hemianopia?	
87	Joint pain, including arthritis and/or carpal tunnel syndrome?	
88	Hypertrichosis, hyperpigmentation and/or hyperhidrosis?	
89	Acrochordon (skin tags)?	
90	Increased palmar sweating and seborrhea (sebum production on the face)?	
	Questions focusing in the search of coarctation of the aorta—Does the patient have or ever had any of the followings signs, symptoms or conditions?	
91	For babies and infants: pale skin, irritability, heavy sweating, difficulty breathing, tachypnea, difficult feeding?	Coarctation of the aorta
92	For adults: cold legs and feet, or pain in their legs with exercise due to intermittent claudication?	
93	Dizziness or shortness of breath, faint or near-fainting episodes, chest pain, abnormal tiredness or fatigue, headaches, or nosebleeds?	
94	Pulse asymmetry between the right versus left side? BP discrepancy between upper and lower limbs?	
95	Cardiac bruit clearly heard at dorsal auscultation?	

Table 1 (continued)

Table 1 (continued)

No.	Description of the questions	If yes, consider:
	Questions focusing in the search of Liddle syndrome?—Does the patient have or ever had any of the followings signs, symptoms or conditions?	
96	Family history of severe disease or death before 45 years old, due to fatal stroke or acute myocardial infarction?	Liddle syndrome
97	Severe, resistant or refractory hypertension?	
98	Intermittent headaches or dizziness?	
99	Palpitations? Frequent ventricular premature beats?	
100	Limb asthenia or flaccid paralysis?	
101	Mild hypokalemia with metabolic alkalosis?	
	Questions focusing in carcinoid syndrome—Does the patient present with the following syndrome?	
102	Hypotension alternating with severe hypertensive crisis and tachycardia, unresponsiveness to treatment in patients from 50 to 70 years old? Flushing, diarrhea, and bronchospasm, with a history of murmurs? Pellagra with dermatitis of sun-exposed areas, rash, intestinal bleeding?	Carcinoid syndrome

The items included in the CHIC Protocol are purposed in the identification of SH and its potential etiology. Affirmative answers of each question are recorded by the health-care provider before and during the formal patient consultation. This protocolized approach transforms the patient evaluation into a format that facilitates the recognition of SH in all patients with HBP.

and physical examinations.

The administration of the Protocol begins prior to the initiation of formal consultation, which is crucial in searching for signs of SH through the observation of patient facies and body habitus. Although over one hundred questions are included in CHIC Protocol, a physician need only utilize approximately ten minutes to complete a full evaluation. If any question is responded to affirmatively, it is formerly re-evaluated to analyze for the risk of SH and to determine, following medical evaluation, which specific laboratory analyses and/or imaging tests are needed.

Results

A final population of 12,284 patients with hypertension was included in this study (mean age 59.9; SD, 19 years, 41% male, 59% female). We classified participants into two groups, based upon their anti-hypertensive treatment response: a cohort diagnosed with NTRH (7,617 patients, 62%) and the other with TRH (4,667 patients, 38%) (Figure 1). SH was documented in 41.8% (5,134 patients) of the total population.

Of the patients identified as having SH, 53.6% [2,759] patients belonged to the NTRH group and 46.3% [2,380] were TRH patients (Figure 1). Specifically, when determining the prevalence of SH based on the category of NTRH and TRH groups, SH was identified in the NTRH and TRH groups at 36% and 50.9%, respectively. The

causes of SH and their distribution among participants are shown in Table 2. Sex, age and body mass index (BMI) were not significantly different between NTRH and TRH groups.

While the CHIC Protocol reflects a methodology to identify the risk of SH, physicians were encouraged to use confirmatory laboratory and imaging techniques for the diagnosis of the causes of SH. In consideration of the need for confirmatory diagnoses, we employed widely known procedures to detect in patients each etiology of SH, including, but not limited to, plasma renin activity, aldosterone levels, urinary metanephrine-normetanephrine concentrations, urinary vanillylmandelic acid concentrations, somatotropin levels, thyroid hormone levels and function testing, cortisol testing in saliva, blood and urine, adrenocorticotrophic hormone test, Doppler ultrasound imaging, magnetic resonance imaging, computed tomography scanning, respiratory polysomnography and genetic testing for Liddle disease.

Discussion

Our results illustrate the prevalence and distribution of the causes of SH using the CHIC Protocol, revealing a higher percentage of SH than previously reported (1-6). The original aim during the development of this questionnaire was to generate a uniform protocol for the diagnosis of SH within an expert center. However, we consider that the

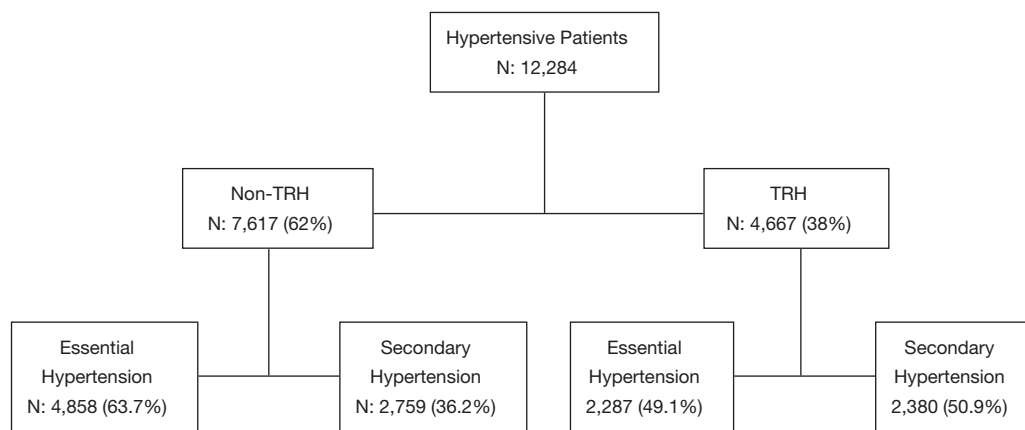


Figure 1 Demonstrates classification of participants with non-TRH and TRH in the total population, along with their respective prevalence of essential and secondary hypertension. TRH, treatment resistant hypertension.

Table 2 Distribution of specific condition of secondary hypertension

Condition	Total population (N=12,284)	NTRH (n=7,617)	TRH (n=4,667)	P
Sleep apnea (OSA, CSA), n (%)	1,639 (13.34)	939 (12.33)	700 (15.00)	0.0001
Hyperaldosteronism, n (%)	1,469 (11.96)	609 (8.00)	860 (18.43)	0.0001
Drug-induced, n (%)	804 (6.55)	546 (7.17)	258 (5.53)	0.0004
Renovascular disease, n (%)	376 (3.06)	138 (1.81)	238 (5.10)	0.0001
Renal parenchymal disease, n (%)	278 (2.26)	131 (1.72)	147 (3.15)	0.0001
Hypothyroidism, n (%)	278 (2.26)	208 (2.73)	70 (1.50)	0.0001
Hyperthyroidism, n (%)	73 (0.59)	49 (0.64)	24 (0.51)	0.3664
Apparent excess of mineralocorticoids, n (%)	67 (0.55)	52 (0.68)	17 (0.36)	0.0219
Pheochromocytoma, n (%)	58 (0.47)	22 (0.29)	36 (0.77)	0.0002
Cushing's disease and Cushing's syndrome, n (%)	48 (0.39)	41 (0.54)	7 (0.15)	0.0008
Acromegaly, n (%)	24 (0.20)	22 (0.29)	2 (0.04)	0.0027
Hyperparathyroidism, n (%)	12 (0.10)	0	10 (0.21)	0.0001
Coarctation of the aorta, n (%)	3 (0.02)	2 (0.03)	1 (0.02)	0.0869
Liddle disease, n (%)	4 (0.03)	0	4 (0.09)	0.0106
Carcinoid tumor (CARC), n (%)	1 (0.001)	0	1 (0.02)	0.2014
Guillain-Barré, Paget, n (%)	2 (0.02)	0	2 (0.04)	0.0708
Neurogenic hypertension, n (%)	2 (0.02)	0	2 (0.04)	0.0708
Total patients with secondary hypertension from the whole population; percentage from NTRH and TRH groups respectively, n (%)	5,139 (41.83)	2,759 (36.22)	2,380 (51.00)	0.0001

unexpected higher prevalence of SH we revealed indicates the potential benefit for wider dissemination of our protocol in other facilities for the diagnosis of SH.

A 1976 review of historical and contemporary literature by Berglund *et al.* focused mainly on higher values of HBP and severe hypertension as a means to recognize the presence of SH. They described the prevalence of primary and SH in a population sample of 7,455 Swedish men aged 47 to 54 (10). The authors identified 798 men with BP above 175/115 mmHg during preliminary screening and recalled them for further evaluation. Among these patients with unusually severe hypertension, 3–6% had renal parenchymal disease, 6% had renovascular disease and 1–6% of patients were described as having other forms of SH. This investigation led to surgical treatment in only two cases. The authors concluded that for low prevalence of SH, especially for those that are curable with surgery, does not support the need for routine screening (10). Nevertheless, as opposed to these data and subsequent recommendations, we described a significantly higher prevalence among patients with a moderate level of hypertension. If the generalized concept that associates SH mainly with severe, resistant hypertension remains unchanged, many patients as described in our population would never be diagnosed.

Rimoldi *et al.* published a detailed review revising the true prevalence of SH by classifying hypertensives as NTRH and TRH, using techniques similar to the methodology in this study (1). Compared to the prevalence of SH in TRH patients reported by Rimoldi, we detected a similar prevalence of hyperaldosteronism (17% *vs.* 6–23%), pheochromocytoma (0.77% *vs.* <1%), but a lower prevalence of patients with obstructive sleep apnea (15% *vs.* >30%) (1).

By analyzing the causes and distribution of SH, we found that hyperaldosteronism is the most frequent endocrine etiology. However, our reported prevalence, while similar to that noted by others for TRH patients, revealed a higher prevalence of hyperaldosteronism in the NTRH cohort. This suggests that hyperaldosteronism may be hidden in controlled patients (11–13). The diagnosis of hyperaldosteronism in our population was based upon increased aldosterone-to-renin ratio, in efforts to avoid over-diagnosis of incidentaloma, according to guideline recommendations (1).

Although sodium intake was not evaluated in all patients in this study, we have previously shown that there was elevated dietary sodium in a sample from the same cohort (14). There was also an increase in the prevalence of

patients with drug-induced hypertension, commonly due to the use of prescription and over-the-counter medications, including non-steroidal anti-inflammatory drugs, antacids and psychiatric drugs. In addition, associated BP elevation was seen with non-pharmacological agents such as natural laxatives, vitamins, and large doses of caffeine in energy drinks or “fat-burning” supplements.

In 2010, a review by Viera *et al.* assigned classic clues suspicious of SH to the best-achieved evidence available, including consensus, disease-oriented evidence, usual practice, expert opinion, or case series (15). The authors also classified the risk and causes of SH by age groups. From birth to 18 years old, it was suggested to investigate for renal parenchymal disease and coarctation of the aorta. In patients aged between 19 and 39, renovascular disease caused by fibrodysplasia and thyroid dysfunction was considered. For participants aged 40 to 64, aldosteronism, obstructive sleep apnea, pheochromocytoma, Cushing’s disease and Cushing’s syndrome was examined. Lastly, renal and renovascular disease and renal failure was analyzed in patients over 65 years of age (15). We did not identify the same age-related distribution of SH for patients older than 65 years old, but aldosteronism, obstructive sleep apnea, renovascular disease and thyroid dysfunction were frequently present in patients between aged between 40 and 70 years old.

Although the reported prevalence in published literature of secondary causes of hypertension has been identified to be 5% to 10% of all hypertensive patients, these rates of SH are significantly higher than the percentages identified in usual clinical practice. Under-recognition of SH in usual patient care could be due to obstacles regarding the awareness of SH and complementary methods for its diagnosis. Furthermore, factors that reduce the diagnosis of SH include the associated costs, under-recognition of clinically suggestive symptoms and the absence of systematic protocols. In addition, guidelines of scientific societies usually do not recommend its investigation in all hypertensive patients.

While it is reasonable that conventional practice and current guidelines attempt to avoid unnecessary costs in the pursuit of the diagnosis of SH, including testing for neurohormonal studies, suppression-stimulation tests or imaging, we suggest that using a systematic, standardized protocol as described herein, justifies an approach that does not abandon the search for SH in all patients. On the contrary, the CHIC Protocol may represent an opportunity to increase recognition of SH through anamnesis (or a detailed account of a patient’s medical history) and physical

examination in all hypertensive patients. We consider our approach an inexpensive tool that primary care physicians and other healthcare providers can use prior to the initiation of formal consultation for an accurate reflection of the patient's risk for SH. It is important to note that steps for the early recognition of SH using the CHIC Protocol require a straightforward evaluation prior to assessment by a hypertension specialist. Acquiring information using the CHIC Protocol represents a systematic approach to diagnose SH, facilitated by the application of this structured anamnesis, even if done by a non-specialist.

Overall, we have not revealed any novel diagnostic laboratory tests for the detection of SH, but have described the usefulness of applying what has been already shown to be beneficial: a systematic protocol that can be utilized in a broad range of hypertensive patients. Therefore, this approach can be a significant change of our diagnosis paradigm and could contribute to the appropriate recognition and diagnosis of SH in a wider range of patients with moderate and severe hypertension.

The main limitations of our study include its retrospective character and the associative relationship of certain etiologies for SH that have not been shown to have a causative role in all cases. Therefore, to positively assume that a condition is the direct cause of the development of hypertension, its treatment must be accompanied with a cure for the diagnosed SH. Further studies, including follow up evaluations are imperative to elucidate this dilemma.

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Footnote

Conflict of Interest: Dr. Ferdinand is a consultant for Amgen, Sanofi, Quantum Genomics, Novartis and Boehringer Ingelheim. Dr. Carol Kotliar often gives lectures for Novartis, Boehringer Ingelheim, Baliarda, Elea, Abbott,

Gador and Menarini. The other authors have no conflicts of interest to declare.

Ethical Statement: Ethical approval to the use of an authorized data base and the protocol of the study was obtained from the Institutional Review Board at the Austral University and the Department of Academic Development from the Austral University Hospital. CIE (Committee of Institutional Evaluation) number 14-055.

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Provider approaches for the application of the questionnaire

Application of the CHIC Protocol can be completed through physical observation of the patient during the consultation, as well as systematic questioning that can uncover critical components of their medical history. During the initial greeting you can perceive the patient's hand temperature, and if it is sweaty, fragile, or has tremors, consider possible disorders such as Cushing's syndrome, pheochromocytoma, thyroid dysfunction, scleroderma, or cerebrovascular disorders. While the consultation begins, dedicate a few seconds to carefully look at the facies for relevant data, such as the presence of prominent ciliary and jaw arches, with flattened nose and separated teeth in a large patient of either sex, in whom an acromegaly could be suspected. These suspicions may prompt for the investigation of other signs of acromegaly later in the consultation, such as galactorrhea, early visual disturbances, and polyuria. Suspect Cushing's disease or Cushing's syndrome if the patient has a rounded face, with ruddy cheeks and prominent abdomen, but with very thin and fragile legs. Exophthalmia may be present in patients with thyroid disorders or hypercortisolism. Pallor in a thin person, with a history of panic attacks may indicate pheochromocytoma. Hirsutism in women can identify patients with hyperandrogenism or mineralocorticoid receptor stimulation.

Revealing the family history to identify hereditary conditions that could lead to SH, such as Liddle's disease, polycystic kidney disease or pheochromocytoma is critical. Liddle's disease, as well as pheochromocytoma, although rare in clinical practice, should always be considered in the anamnesis due to the high mortality associated with both conditions. These conditions often lead to events such as fatal myocardial infarction and stroke, where etiological diagnosis is made after autopsy. Liddle's disease usually manifests in childhood or adolescence, however, if BP is not measured, uncontrolled hypertension can go unnoticed and the patient may only note occasional myalgia or asthenia that could be underestimated during the first years of treatment.

If the patient is first diagnosed with hypertension in adulthood with hypokalemia, consider hyperaldosteronism. Similarly, if hypokalemia is present in a patient on diuretic therapy, clinicians should not be confused with diuretic effects that may mask or mitigate the presence of this condition. If hyperaldosteronism is suspected, the

laboratory data may be misinterpreted in view of reduced renin and aldosterone associated with metabolic alkalosis.

Personal history and the search for pheochromocytoma

In hypertensive women who have had deliveries, it is important to obtain a history of hyperglycemia or gestational diabetes, which may be a manifestation of pheochromocytoma. Other antecedents of suspicion are syncope, hypertensive crisis during defecation or urination, or the presence of nocturnal headaches that awaken the patient and subside after urination. Headaches of the hypercatecholamine state are usually bilateral and pulsatile and hypercatecholamine crises of pheochromocytoma are sufficiently characteristic to not be confused with panic attacks. In suspected cases, evaluating a urine sample during a panic attack for urinary catecholamines is helpful, and it is of value to investigate the presence of triggers such as alcohol intake, menstrual periods, or the use of anesthetics.

In addition, arrhythmias can be key, although it is infrequently associated with SH with electrolyte disorders such as hypokalemia (hyperaldosteronism or hyperproduction of ACTH, Liddle's syndrome or pheochromocytoma).

Systematized questioning

Asking targeted question is a great strategy when assessing SH using the CHIC Protocol, as it may identify risk factors that will not be elucidated through patient observation alone. For example, birth weight has been associated with an increased risk of nephropathy and premature aging. Additionally, the patient's weight history may lead to a pheochromocytoma if associated with progressive weight loss. The search for obstructive sleep apnea is important in obese subjects through questioning about their patterns of rest, snoring and morning sleepiness. However, its diagnosis usually goes unnoticed in non-obese hypertensive patients who have had otorhinolaryngological disorders associated with predisposing anatomical conditions, trauma in athletes, rhinoplasty, and some alterations in central regulation linked to cerebrovascular diseases. Not only is the patient's nocturnal rest pattern important to determine in obese or thin patients alike, but it is also useful to interrogate about the characteristics of diuresis, such as polyuria, foam in the

urine, pollakiuria, dysuria or recurrent infections.

The diagnosis of neurogenic hypertension is rarely suspected, but it may explain hypertension associated with stress, especially accompanied by hyperventilation. A simple maneuver is to measure the respiratory rate in acute or chronic stressful conditions. The history of syncope in a hypertensive patient also increases the suspicion of autonomous imbalances that must be accompanied with the evaluation of changes in heart rate, with standing to differentiate from orthostatic hypotension, dysautonomia and pheochromocytomas. Lastly, situations where there is an increase in intracranial pressure can also cause hypertension such as with cerebral infarction, brain tumors, diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DIDMOAD syndrome).

The initial questioning is also a reliable source of the data necessary to establish the diagnosis of hypertension secondary to pressor effects of drugs or interventions. For instance, a patient with COPD or immunological diseases may receive corticosteroids chronically. Nevertheless, it is unlikely for low-dose corticosteroids to cause HBP and although chronic use could be linked to some degree of a pressor, it may not be necessary to suspend these drugs for the control of BP when they are clearly indicated and necessary. The list of prescribed or over-the-counter drugs associated with hypertension are too numerous to list and beyond the scope of this comment, but it is recommended to remain alert for the consumption of any substance that may be promoting the increase in BP. The sodium content of food is essential to determine risk for HBP and

adherence to sodium restriction, with education regarding the hidden sodium in foods is essential.

Some relevant signs in the physical examination

Lastly, there are important points to note regarding relevant signs during the physical examination, which may suggest SH. It is important to advance the examination from the feet to the head, since palpation of the pulses and detection of asymmetry may lead you to suspect the presence of aortic coarctation. The temperature and humidity of the extremities during the handshake at the beginning of the consultation, as well as any observed edema may be associated with disorders in the regulation of sodium in nephrogenic causes and hyperaldosteronisms. At this point, the patient may refer to additional history about joint problems that will add to the suspicion of acromegaly and Cushing's. If stretch marks are observed on the abdomen, careful auscultation is important for renal murmurs that may be attributed to fibrodysplasia in young women or to atherosclerotic renovascular disease in older persons with proatherogenic factors. Finally, café-au-lait spots may trigger the suspicion of multiple endocrine tumors, as well as hirsutism and an increase of hair on arms or abdomen may signal states of hyperandrogenism.

In the general assessment, other secondary causes should be considered, including conditions associated with endocrine disorders such as vitamin D deficiency, obesity, male hypogonadism, and hyperparathyroidism.