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Causes of secondary hypertension from a single center in Northern Greece; a retrospective clinical study

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Abstract: Hypertension constitutes one of the most common diseases leading patients to the Outpatient Departments. Idiopathic hypertension is the prevailing type, but on the other hand, the possible presence of clinical entities responsible for the development of secondary hypertension should never be underestimated. We retrospectively studied 447 subjects aged between 20 and 84 years old and diagnosed with hypertension, who were thoroughly evaluated for secondary hypertension. Our analysis demonstrated that 35 out of the 447 subjects were finally diagnosed with secondary hypertension, representing a relative frequency of 7.8%. Most common causes of secondary hypertension identified in our study group were: glucocorticoid intake (n = 14), obesity hypoventilation syndrome (n = 6), obstructive sleep apnea (n = 2) and preeclamspia (n = 2). Several other causes are also reported. Our study, conducted in a single center in Northern Greece, confirms previous reports concerning the prevalence of secondary hypertension among Greek patients, shedding light on potential pathophysiologic mechanisms. In conclusion, a high proportion of hypertensive individuals still feature have an underlying cause, thus, diagnostic work-up should be thorough and exhaustive, in order the correct diagnosis to be made and the targeted treatment to be initiated.

Key words: secondary hypertension, prevalence, biomarker, diagnosis.

Introduction

Hypertension is estimated to affect approximately 20% of the worldwide population, being a major public health issue [1]. Most individuals are diagnosed with idiopathic or essential hypertension, whose prevalence reaches up to 90–95% in the general population [1]. In idiopathic hypertension there is no specific cause found and it is believed that it develops due to interactions between environmental and genetic factors. During the last decade, secondary hypertension — with the continuous improvement of diagnostic methods in daily routine — seems to have a tendency to increase. In order to achieve proper treatment, it is of exceptional significance to recognize the responsible underlying state, otherwise, if left untreated, secondary hypertension can lead to resistant hypertension, multiple organ damage and increased cardiovascular risk [2]. According to all previous data, prevalence of hypertension in Greek population ranges between 10 and 15%, but it affects increasing proportion of general population over the last decades, due to the rise of life expectancy along with the development of more accurate diagnostic modalities [3]. The prevalence of secondary hypertension in Greece is estimated to be 5–10%, with an upward tendency [3]. The primary scope of this study was to register the number of hypertensive individuals, diagnosed primarily in the Outpatient Department of Internal Medicine of General hospital of Veria. The second aim of the study was to track down those hypertensive patients that probably suffer from secondary hypertension.

Material and Methods

Our study was conducted in the Outpatient Department of Internal Medicine in General Hospital of Imathia — Veria's Unit during the period 2008–2017, after relevant approval received by the Scientific Committee and the Administrative Board of our Hospital. Firstly diagnosed hypertensive individuals were included in the present study, according to the ESC/ESH 2013 guidelines for definitions and classification of blood pressure levels. The participants were interviewed about their lifestyle, while blood pressure measurements were performed according to the suggested protocol of the ESC/ESH 2013 guidelines for the management of hypertension. Age spectrum of the participants ranged between 20 and 84 years old, with an average age of 51 years. Among the total number of 447 individuals, 257 were males and 190 females. After the initial evaluation and establishment of hypertension diagnosis, the research was focused on the probable existence of secondary hypertension, depending on their medical history, along with findings of physical examination and laboratory testing. An important factor that must be taken under consideration was the co-existing comorbidities. Forty four men and 23 women suffered from type 2 diabetes mellitus, while 8 men and 6 women were further diagnosed with congestive heart failure at

the time of diagnosis. Additional screening tests were performed, if needed, based on the ESC/ESH guidelines concerning secondary hypertension. Serum leptin levels were analyzed in all recruited participants.

Results

Our data demonstrated the presence of secondary hypertension in 35 of the 447 patients firstly diagnosed with hypertension, corresponding to a relative frequency of 7.8% (Fig. 1).

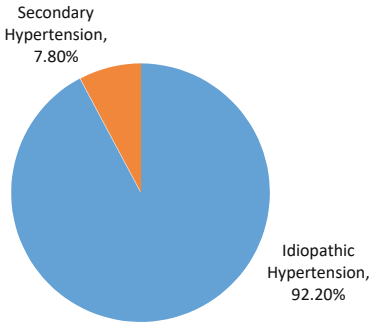

Fig. 1. Prevalence of Hypertension in 447 Greek Individuals.

Table 1 illustrates the etiological factors of secondary hypertension detected in this retrospective analysis. Glucocorticoid intake, obstructive sleep apnea and obesity hypoventilation syndrome were the predominant causes. As far as glucocorticoid dependent hypertension is concerned it would be appropriate to mention that none of the underlying diseases was causative of hypertension development. Specifically, 5 patients suffered from rheumatoid arthritis, 3 from ulcerative colitis, 2 from pemphigoid, 2 from urticaria, 1 from autoimmune hepatitis and 1 from idiopathic pulmonary fibrosis. Being detected in 40% (n = 14) of our patients, glucocorticoid treatment was the prevailing cause of secondary hypertension. On the basis that glucocorticoids are commonly prescribed in daily practice, we considered as chronic glucocorticoid treatment a period of 1-month administration.

Another significant result of this study is that 9 patients diagnosed with hypertension featured elevated serum leptin levels. Additionally, none of those patients suffered from obstructive sleep apnea, obesity hypoventilation syndrome or diabetes mellitus, diseases associated with higher circulating leptin levels. Another significant remark was that 4 of those individuals had body mass index (BMI) within normal range and they also did not exhibit features of insulin resistance phenotype. Furthermore, those 6 patients diagnosed with obesity hypoventilation syndrome as well as those patients with obstructive sleep apnea syndrome had also elevated serum

leptin levels, determining the relationship between obesity, leptin and hypertension. At this point it should also be noted that all patients with obesity hypoventilation syndrome were suffering from obstructive sleep apnea, as well, which again validates the correlation of those two clinical entities. Other remarkable causes of secondary hypertension found in this research were associated with renal vascular diseases (polyarteritis nodosa, Takayasu arteritis, Henoch Schonlein purpura), drug induced hypertension (cyclosporine, buspirone), pregnancy (preeclampsia, HELLP syndrome) or tumors (pheochromocytoma, lung carcinoid related ACTH ectopic production, gastric cancer related GHRH ectopic production).

Table 1. Causes of secondary hypertension.

	No
Glucocorticoid intake	14
Obesity hypoventilation syndrome	6
Obstructive sleep apnea	2
Preeclampsia	2
Lung carcinoid related ACTH ectopic production	1
Pheochromocytoma	1
Polyarteritis nodosa	1
Takayasu arteritis	1
Gastric cancer related GHRH ectopic excretion	1
Henoch Schonlein purpura	1
Psoriasis under cyclosporine	1
Buspirone intake	1
Fanconi syndrome	1
Arsenic toxicity	1
HELLP syndrome	1
Total individuals	**35**

Discussion

Glucocorticoid mediated hypertension

Chronic glucocorticoid treatment is not widely accepted as an individual factor of secondary hypertension. Nonetheless the discussion is vivid and ongoing. Glucocorticoids are the treatment of choice in a large variety of diseases. In a relatively high percentage, almost 20%, patients under chronic treatment with glucocorticoids,

either oral or injected, manifest hypertension and the incidence of glucocorticoid induced hypertension (GIH) is probably dose dependent [4, 5]. Several mechanisms have been proposed to explain the GIH but the exact one is yet to be found. In the recent past it was commonly thought that the adverse effect of glucocorticoid mediated hypertension was induced by excessive retention of sodium and water through activation of the mineralocorticoid receptors in the kidneys. Therefore, it was believed that patients under glucocorticoid treatment featured upregulation of mineralocorticoid receptors, which in turn led to sodium and water reabsorption. The subsequent volume expansion was the key factor for the development of hypertension [4].

All types of glucocorticoids except for dexamethasone have mineralocorticoid effect [6]. Nevertheless, even patients receiving dexamethasone for a long period eventually develop hypertension. Glucocorticoids, via their glucocorticoid and mineralocorticoid receptors, which are widely expressed in the cardiovascular system including the arterial wall, act directly for the maintenance of the vascular tone. It is possible that they enhance the biological demeanor of vasoconstrictors such as catecholamines and angiotensin II, increasing the peripheral vascular sensitivity to their actions. Hence, secondary hypertension after the long-term use of dexamethasone may be the result of an extreme response to vasoconstrictors and a rise in systemic vascular resistance [7]. Moreover, there are experimental studies trying to explain GIH by implicating to its pathophysiology certain alterations in the prostaglandin (PGD2, PGI2), nitric oxide synthesis and in the kallikrein renal excretion. These alterations possibly contribute to glucocorticoid mediated hypertension, but the exact mechanisms have not been elucidated yet [8, 9].

Furthermore, in respect to the pathophysiology of glucocorticoid induced hypertension, the potential role of the enzyme family of 11b hydroxysteroid dehydrogenase must be highlighted. These enzymes are responsible for the conversion of cortisol — which binds to mineralocorticoid receptors — to cortisone that has no affinity for these receptors [10]. Consequently, 11b hydroxysteroid dehydrogenase is of outmost importance for the prevention of the mineralocorticoid effects of cortisol and the incident hypertension. Deficiency, reduced activity or inhibition of these enzymes by substances such as licorice [11], results into hypertension due to the mineralocorticoid effect of cortisol. Thus, individuals with Cushing's syndrome were firstly suspected to present with reduced activity of the 11b hydroxysteroid dehydrogenase, although further studies have shown that not only enzyme levels but also enzyme overall activity is increased [12, 13]. It seems that the overabundance of circulating glucocorticoids potentially overwhelms the capacity of the 11b hydroxysteroid dehydrogenase, setting the glucocorticoids free to exert their mineralocorticoid activity. This is a possible explanation that applies also to the development of hypertension in cases of chronic glucocorticoid intake and ectopic ACTH production.

Mechanisms of hypertension among obese patients — the role of comorbidities

Leptin is a peptide hormone produced by the adipose cells and its excretion in the blood vessels depends on the degree of adiposity, insulin levels and macronutrient composition [14]. It is called the "satiety hormone" for its regulating effects on body weight, food intake and energy expenditure. Leptin mainly mediates its effects by binding to specific receptors in hypothalamus, especially to the long form leptin receptors (LEPRb), a member of the interleukin — 6 cytokine receptor family [15]. The activation of LEPRbs stimulates the synthesis of pro-opiomelanocortin (POMC) [16]. POMC leads to the production of a-melanocyte stimulating hormone (a-MSH). Weight reduction is finally achieved via the adherence of a — MSH to melanocortin-3 (MC3R) and melanocortin-4 receptors (MC4R). In humans, mutations of POMC and MC4R genes are associated with obesity [17, 18]. However, leptin also seems to play an important role in the stimulation of the sympathetic nervous system, having an impact on the renal function and the vascular tone. In addition, increasing evidence suggests that leptin may cause sodium retention [19].

As far as elevated BMI is concerned, obesity is strongly associated with hypertension, obstructive sleep apnea and obesity hypoventilation syndrome [12, 20]. Most obese individuals have elevated serum leptin levels and become resistant to the satiety– reducing effects of this hormone, despite the fact that leptin seems to preserve its effect on the sympathetic system [21, 22]. As previously demonstrated, hypertension is directly connected with increased serum leptin levels in both genders without the simultaneous presence of insulin resistance or increased BMI [23, 24]. Therefore, leptin resistance is primarily demonstrated with its metabolic phenomena, while — at the same time — it maintains its contributing property to the sympathetic activation seen in obesity. As a result, the selective leptin resistance model provides a new perspective into the development of hypertension even in non-obese individuals with high serum leptin levels, constituting leptin a promising biomarker in the field of hypertension.

Obstructive sleep apnea — Obesity hypoventilation syndrome

Obstructive Sleep Apnea and Obesity Hypoventilation Syndrome, are two clinical entities that usually co-exist. The interrelation of obstructive sleep apnea and obesity hypoventilation syndrome with hypertension has been previously established [25, 26], while they are also closely related to increased overall cardiovascular risk [27]. The significance of these two conditions, is such that they are recognized as independent causes of hypertension and even as major ones,

especially in cases of resistant hypertension [28, 29]. Many factors are implicated as contributors into elevated blood pressure present in individuals with obstructive sleep apnea. Conceivably, its manifestation is a compound of persistent activation of the sympathetic nervous system, aldosterone excess and endothelial dysfunction provoked by the presence of constant hypoxia.

As far as obesity hypoventilation syndrome patients are concerned, there is evidence that the intermittent hypoxemia and/or hypercapnia are key factors for the perpetual activation of the sympathetic nervous system [30, 31]. This higher vascular sympathetic nerve activity and the subsequently higher circulating catecholamines levels lead to increased peripheral vascular resistance and critical nocturnal surges of blood pressure [32]. High sympathetic tone is also present during daytime even in the absence of hypoxemia, incidentally leading to hypertension. Moreover, the repetitive tissue hypoxia elicits the release of endothelin from the vascular endothelium causing additional vasoconstriction and increased oxidative stress, leading to a "vicious" circle with the deposit of advanced lipid oxidation end products (ALES) and oxidation derivative carboxylation end products on the arterial wall [33].

Another considerable pathophysiological mechanism is the development of secondary hyperaldosteronism in obstructive sleep apnea. It has been proposed that obese individuals have higher serum aldosterone levels, predisposing to hypertension manifestation. Aldosterone regulates circulating blood volume by enhancing renal sodium and water reabsorption along with potassium excretion. Its production is predominantly stimulated by the circulating potassium levels but also via the renin angiotensin aldosterone (SRAA) system and specifically by angiotensin serum concentration. Chronic sympathetic activation constantly activates SRAA which leads to aldosterone overproduction and subsequently to the expansion of the intravascular volume [34, 35].

Paraneoplastic endocrine disorders

Specific allusion must be made to a 52 years old patient with gastric cancer. From his medical history, he was diagnosed with gastric cancer at the age of 50. Six months before the initial diagnosis of hypertension, he suffered an acute myocardial infarction. His impressive cardiac remodeling (6 months after the cardiac incident, depicted on cardiac ECHO and MRI) led us to consider a possible correlation of his stomach tumor's properties with the unexpectedly quick recovery of his myocardium [36]. Another significant observation was the patient's acromegaly, which strongly correlates with hypertension [37]. As a result, the idea of possible paraneoplastic ectopic production of GHRH due to gastric cancer was finally confirmed with laboratory and screening tests [38, 39].

Overview

A previous study of 1,020 individuals held in Japan estimated a prevalence of 9.1% for secondary hypertension with major causes the primary aldosteronism and Cushing's syndrome [40]. In the largest available retrospective study in Greece conducted by Douma et al, the authors documented primary hyperaldosteronism as the major cause of secondary hypertension in Greece, whose prevalence reached up to 11.3% of all cases in a study group consisting of 1616 patients [41]. At the same time another recent prospective study, conducted in a hypertension center of Northwest China estimated a much higher proportion of 39.5% among its 3,003 individuals for secondary hypertension [42].

Conclusion

The results of this study indicate a prevalence of 7.8% for secondary hypertension in a study group consisting of 447 individuals, newly diagnosed with hypertension. Our study highlights the proportion of secondary hypertension among hypertensive patients and gives prominence to common and frequent etiologies. We have emphasized on the significant correlation between glucocorticoids and hypertension. An additional major finding is the link between leptin and hypertension. It seems that leptin constitutes an attractive and promising biomarker, even in non-obese patients, in hypertension. Obstructive sleep apnea syndrome along with obesity hypoventilation syndrome are continually gaining ground as important clinical entities predisposing to resistant hypertension, along with the increasing incidence rates of obesity. Several other causes, including autoimmune diseases, paraneoplastic syndromes, toxic agents and pregnancy related complications were also identified. Larger, multicenter clinical studies are required in order to provide a more accurate assessment of the prevalence of secondary hypertension in Greece.

Conflict of interest

None declared.

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