PRIMARY ALDOSTERONISM; ONE OF THE MOST IMPORTANT CAUSES OF SECONDARY HIPERTENSION. SURVEY IN INTERNAL MEDICINE WARD.

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Abstract

Background: Hypertension is one of the most frequent diseases in the world and risk factor for major cardiovascular events like Acute Myocardial Infarction, cerebral Ischemia, arrhythmia, hospitalization and death. It is classified in primary hypertension, when there is no identified cause and secondary hypertension, which is a result of a certain organ damage like heart, kidneys, thyroid, adrenal glands, etc. In the general population, secondary HT affects 5-11% of cases. Primary aldosteronism (PA) is a rare condition characterized by overproduction of aldosterone (mineralocorticoid hormone), as a result of a disorder in the adrenal gland.

Aim: To identify the number of cases with PA in hypertensive population. To determine the methods of diagnosis and treatment. To evaluate the relation between hypokalemia and PA.

Methods: This is an observational, prospective, single-centered study, including 80 patients admitted for secondary hypertension, from June 2016-July 2018 at University Hospital Center Mother Theresa, Internal Medicine Ward.

Results: The prevalence of PA in our study was 5.9%. Mean age was 48 +/- 13 years old. Male patients were more than females. BMI was 27.97+/- 12.07 kg/m2. Most frequent diseases in addition to Hypertension were: dyslipidemia (18.7%), type 2 DM (29.9%), VCA/TIA (6.2%) and arrhythmia (5%). Hypokalemia (K+ <3.5 mmol/l) was seen in 31.2% of cases. Severe hypokalemia (K+ <2.5 mm) resulted in 6.3% of cases. The Aldosterone-to-Renin Ratio (ARR) >50 was seen in 5 % of cases. ARR <30 resulted in 20 % of cases. The gold standard for diagnosis remains Radiology. 66.3% were unilateral Adenomas, 20 % bilateral Adenomas and 7.5 % adrenal hyperplasia. Adenomas of 1-2 cm had a high prevalence (50 %) against Adenomas >2 cm (18.8%). As for the treatment, 96.2 % received conservative therapy vs 3.8 % of Surgery, followed by biopsy. Spironolactone 25 mg resulted the most used medication of his class, 53.8%. Eplerenone was used less because of its costs, but had fewer side effects.

Conclusions: The prevalence of PA in this 2-year study resulted in 5.9 % of cases with Hypertension. Hypokalemia it is present in most cases of PA, but does not always confirm its presence. The ranges of plasmatic Aldosterone and ARR were low or within normal limits, in very few cases ARR was higher than 50. Radiology remains the golden standard in diagnosing Adenomas and confirming them. it locates them and determines the dimensions and its types. Conservative therapy results superior vs surgical therapy. All classes of hypertensive medications were used in treating hypertension, but the most used remains Spironolactone, Verapamil and Doxazocine, because of lesser side effects during hormone dosage.

Key words: hypertension, primary aldosteronism, renine, aldosterone, spironolactone.

HIPERALDOSTERONIZMI PRIMAR- NJË NGA SHKAQET MË TË RËNDËSISHME TË HTA SEKONDAR. EKPERIENCA JONË NË MJEKESINË INTERNE.

Abstrakt

Hyrje: Hipertensioni arterial është një nga sëmundjet më të përhapura në botë dhe faktor risku madhor për evente si IAM, Insulte cerebrale, Aritmi, Vdekje. Klasifikohet në primar ose esencial, kur nuk ka një shkak të identifikueshëm dhe sekondar kur vjen si pasojë e prekjes së një organi të caktuar. Në popullatën e përgjithshme HTA sekondar zë rreth 5-11% të rasteve. Aldosteronizmi primar është një gjëndje që karakterizohet nga prodhimi i shtuar i aldsoteronit (mineralokortikoid) si pasojë e një crregullimi në gjëndrën surrenale, në mënyrë të pavarur dhe autonome nga sistemi reninë-angiotenzinë.

Qëllimi: Të identifikohet numri i rasteve me hiperaldosteronizëm primar në popullatën hipertensive. Të përcaktohen mënyrat e diagnostikimit dhe trajtimit të tij. Të vlerësohet lidhja e AP me hipokaleminë.

Metoda: Në këtë studim u përfshinë 80 pacientë të hospitalizuar në pavionin e MI, në periudhën qershor 2016 - korrik 2018, me diagnozë: suspekt HTA me natyrë sekondare. Studimi është prospektiv, rast kohort.

Rezultatet: Prevalenca e AP në studimin tone rezultoi 5.9 %. Mosha mesatare e pacientëve ishte 48+/- 13 vjec, meshkuj më tepër se femra. BMI rezultoi 27.97 +/- 12.07 kg/m2. Sëmundjet shoqëruese me frekuencë më të lartë përmenden: Dislipidemia (18.7%), DM tip 2 (29.9%), AVC/TIA (6.2) dhe Aritmia (5%). Hypokalemia (K+ <3.5 mmol/l) u pa në 31.2% të rasteve, hipokalemi severe (K+<2.5 mmol/l) në 6.3% të rasteve. Raporti RAA >50 u pa në 5 % të rasteve. RAA<30 u pa në 20% të rasteve. Imazheria ishte me rëndësi të madhe në vendosjen e diagnozës. 66.3% të rasteve rezultuan adenoma unilaterale, 20 % bilaterale dhe 7.5% hiperplazi e surrenales. U pa prevalencë e lartë e adenomave 1-2 cm (50%) dhe >2 cm (18.8%). Përsa i përket trajtimit, 96.2% morën terapi medikamentoze dhe 3.8% kirurgji të shoqëruar me biopsi. Spironolactoni 25 mg rezultoi medikamenti më i përdorur i klasës së tij, në 53.8%. Eplerenoni u përdor më pak për shkak të kostos së tij, por pati më pak efekte anësore.

Konkluzione: Prevalenca e AP në këtë studim dy-vjecar rezultoi 5.9% e rasteve me HTA. Hipokalemia është bashkëshoqëruese e AP, por nuk e vërteton gjithmonë atë. Vlerat e aldosteronit plazmatik dhe RAA kanë qënë normale ose të ulta, dhe në shumë pak raste RAA>50. Imazheria mbetet gold standart në vendosjen dhe konfirmimin e diagnozës së AP. Ajo lokalizon adenomat, hiperplazinë, përcakton përmasat dhe llojin e tyre. Terapia medikamentoze rezultoi superiore ndaj asaj kirurgjikale. U përdorën të gjitha klasat e antihipertensivëve në trajtimin e HTA, por kryesorët mbeten Spironolactoni, Verapamili dhe Doxazocina.

Fjalë kyçe: HTA, hiperaldosteronizmi, Reninë, Aldosteroni, spironolakton.

Introduction

Arterial hypertension (HTN) is one of the most frequent cardiovascular diseases in the world, defined as increased SBP >140 mmHg and DBP >90 mmHg (1). The latest global prevalence is almost 1 billion people, and about 150 millions are registered in Central and East Europe (2). The prevalence of hypertension in the adult population rates among 20-45% (2). It is evaluated as the most important risk factor of global mortality and morbidity and the most related with cardiovascular diseases because of the high risk of acute myocardial infarct, VCA, heart failure and renal disease. In 95% of cases the causes remain unknown and it is known as essential or primary hypertension (3). 5 % of cases are identified as secondary hypertension (4). This is important because knowing the cause helps curing the HTN. The most frequent causes of

secondary HTN are renovascular diseases and endocrine disorders like primary aldosteronism (PA), pheochromocytoma, Cushing disease, etc (5). Despite the improvement in controlling HTN during the last 3 decades and the wide range of available antihypertensive medications, 5-30 % of patients are not in the recommended values of blood pressure, according to the latest guidelines. As such, blood pressure (BP) monitoring is important to avoid the possible complications (6).

Aim

To identify the prevalence of PA in hypertensive population. To determine the methods of diagnosis and treatment. To evaluate the relationship between hypokalemia and PA, and Aldosterone-to-Renin Ratio (ARR) with PA.

Materials and Methods

This is an observational, prospective, single-centered study including 80 patients admitted for secondary hypertension, from June 2016 - July 2018, at University Hospital Center "Mother Theresa", Internal Medicine Ward. In this study were included all patient suspected for PA, and all the other causes of hypertension were excluded.

A special database was created for gathering general information from the patients, including risk factors, other diseases, familiar cases, lifestyle, medication taken by the patient, surgeries. A consent paper from the patient was signed before each procedure.

Results

80 patients hospitalized in Internal Medicine Ward, "Mother Teresa" hospital, were included in the study with suspected diagnosis of PA. The prevalence of PA, according to our study and the statistics, resulted 5.9%. Mean age was 48 +/- 13 years old. BMI ranges were between 18-40 kg/m^2, mean BMI was 27.96 +/-12.07 kg/m^2. BMI > 30 was observed in 8.7% of cases. The most frequent comorbidities were dyslipidemia in 18.7 % of cases, type 2 diabetes mellitus in 29.9% of cases and cerebrovascular accident (CVA) and transient ischemic attack (TIA) before hospitalization were present in 6.2 % of cases. Cardiac arrhythmias consisted in only 5 % of cases.

According to the lab analysis, the most important indicator for diagnosing PA were the levels of blood potassium. In our study, 93.8% of cases had K^+ >3.0 mmol/L and in 6.3 % of cases we had severe hypokalemia. Hormone levels measurements showed ARR >50 in 5 % of patients, ARR >15 in 12.5 % and 20 % of cases had normal values. 62.5 % of patients couldn't measure the hormone levels for different reasons. During hospitalization echocardiography and 24 hours automatic blood pressure monitoring (ABPM) were performed. Mild left ventricle (LV) hypertrophy was seen in 40 % of cases and 35% of them had severe LV hypertrophy. 24 h ABPM showed 36.2% grade I hypertension, 18.8 % grade II, 7.5 % grade III and 13.7 % isolated high systolic blood pressure. Imaging related with types of PA and their dimensions showed that: 66.3 % were unilateral adenomas, 20 % bilateral and 7.5 % were classified as adrenal gland hyperplasia. In this study we evaluated that the majority of patients get medical conservative treatment, 96.2 % of cases, and only 3.8 % of patient are treated in surgery department, with adrenalectomy and respective biopsy.

Discussion.

Considering the global impact it has on health, the control of HTN is of extreme importance. Great efforts are made and continue to control and treat secondary forms of HTN, including PA (7,8). According to different studies, PA is evaluated as 5-11 % of worldwide hypertensive population (9). In our 2-year period study, 80 patients with PA, were included and based on the statistical data of Statistic Service, in 'Mother Teresa' University Hospital, the prevalence was 5.9 % among all

hypertensive population (10.11). This figure is within the range mentioned by international studies. First of all, the predominance of male patients versus female was observed, respectively 57.5 % vs 42.5%. Mean age was 48+/- 13 years old, almost the same limits as in international studies (12). Mean BMI was 27.96 +/- 12.07 kg/m^2. In relation with comorbidities, the most significant are dyslipidemia (18.7 %), type 2 Diabetes Mellitus (29.9 %), CVA and TIA (6.2 %). 5% of cases had cardiac arrhythmias, such as atrial fibrillation and sinusal tachycardia, these events happened during hospitalization (13.14). One of the purposes of our study was to evaluate the correlation between hypokalemia and PA. According to the lab database, 31.2 % of cases had $K^+ < 3.5$ mmol/l and 6.3 % severe hypokalemia ($K^+ \leq 2.5$ mmol/l). Considering the number of patients included in the study, we must emphasize that these values are statistically significant ($p < 0.05$) (15). We can determine that hypokalemia accompanies PA, but does not prove it, which means that its presence it is not related with the presence of adenomas. There are patients with normal ranges of potassium, but had adrenal adenomas (16). These results are almost equivalent to those mentioned by European studies and published in various journals. Hormonal level measurements like plasma aldosterone, rennin activity and their ratio have a more important role (17). What is worth emphasizing in this study, there are very few cases where ARR was above the normal limits, respectively 5 % of cases. 20 % were within normal ranges or lower, if we take the latest guidelines as a base, these values would definitely exclude primary aldosteronism (18). So, just as with potassium, we confirmed the presence of adrenal adenoma through imaging or biopsy, but with lower ARR. We must remember that hormonal levels are highly influenced by plasmatic potassium, as well as the right correction of mild/severe hypokalemia (19). Certain antihypertensive medications, levels of plasmatic sodium, and the procedure of blood collection play a significant role (20).

Radiology results proved once again its importance in diagnosing early cases of primary aldosteronism. 66.3 % were unilateral adrenal adenomas, 20 % bilateral adenomas and 7.5% adrenal hyperplasia (21). Through imagery we can determine their size and localization, and whether or not it will be subjected to surgery (22). 1-2 cm adenomas had the highest prevalence, 50 % of cases, statistically important (p – 0.031). 18.8 % are adenomas > 2 cm and 17.5 % less than 1cm (23).

Lastly, conservative management of primary aldosteronism predominates in 96.2 % of our patients (24). Only 3.8% were subject to surgery for adrenalectomy and follow-up biopsy (25). Regarding drug treatment, Spironolactone is the most used of the class of mineralocorticoid receptor inhibitors, at almost 53.8 % of cases (26). Its dosage depending on BP values, plasmatic levels of K^+ and other antihypertensive drugs. Eplerenone, another one from the mineral corticoid inhibitors, has fewer side effects than spironolactone. It is rarely used because of higher financial cost, compared to spironolactone. Doxazocine 2 mg (22.5 %) and Verapamil 80 mg (21.3 %) are two antihypertensive medications used, especially in the period before hormonal dosing, for keeping BP under control and because they don't influence hormonal levels (27). Their dosage is dependent on the severity of blood pressure; they can be given alone or combined with other antihypertensive drugs. Every patient has its individual dosage related to the BP and other comorbidities (28.29).

Limitations

A major limitation of this study was the high financial cost, related with hormonal level measurements. This laboratory tests are done privately by patients and not all of them had the financial possibilities.

Second, the limited number of patients included in the study. This comes as a result of not being able to dose the hormonal levels privately and the lack of an accurate database for hypertension from all causes.

In the third place, unlike the guidelines, that recommended in the first place hormonal level

measurements and then radiology, we do the opposite. We perform Angio-CT or MRI, confirm the presence of adenomas or hyperplasia and after that the hormonal dosing (30).

Conclusions

PA prevalence studied in the two- year period June 2016 – July 2018, at Internal Medicine Ward, resulted 5.9 %. Hypokalemia accompanies PA but does not always prove it. Having mild or severe hypokalemia does not mean we have PA, but it doesn't exclude it either. According to our results the same can be said for the hormonal level measurements. In most of our cases, the ARR was within normal limits, or lower and we had PA proven by radiology. Radiology remains the gold standard for the diagnosis of primary aldosteronism, for localizing unilateral or bilateral adenomas, or adrenal hyperplasia and defining their size. Unilateral aldosterone-secreting adenomas have higher prevalence than other types. Follow-up every six months with lab tests and radiology is done for every patient diagnosed with PA that is not subjected to surgery.

Conflict of interest: No conflict of interest

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