Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 14 (63) No. 1 – 2021
https://doi.org/10.31926/but.ms.2021.63.14.1.3

THE ALDOSTERONE-TO-RENIN RATIO AS A SCREENING TEST IN PRIMARY HYPERALDOSTERONISM

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Abstract: *Primary hyperaldosteronism is one of the most common causes of secondary hypertension and it is associated with a higher risk of developing extracardiac complications than that of people diagnosed with primary hypertension. We present a six-month study done at the MedLife Hospital in Braşov on 62 patients who had one or more indications for primary hyperaldosteronism screening. The main conclusions drawn from this study are that there is a strong need for starting screening in primary hyperaldosteronism from an earlier age, as the target population can have a high vulnerability from a cardiovascular and a renal standpoint and that the aldosterone-to-renin ratio screening test should be recommended to a higher number of people in the target population, the positivity rate in the group studied being 47%.*

Key words: *primary aldosteronism, Conn syndrome, unilateral adrenal adenoma, secondary hypertension, aldosterone-to-renin ratio*

1. Introduction

Primary aldosteronism (PA) or primary hyperaldosteronism refers to a group of pathologies in which there is a high production of aldosterone unrelated to plasma sodium levels or renin secretion [1]. This disorder was first described by Dr Jerome Conn, an endocrinologist at the University of Michigan who, in 1955, made for the first time the connection between aldosterone secreting tumours, hypertension and hypokalaemia [2]. In the almost 65 years that followed his discovery, important milestones were reached in the understanding of PA, but the disease is still known as Conn syndrome in recognition of the man who first described its symptoms, prevalence and treatment [3-5].

PA is generally diagnosed between 30 and 60 years and it is one of the most common causes of secondary hypertension with a prevalence of 0,5% to 2% [1], [3], [6-13]. However, recent studies suggest that the prevalence rate of

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PA in secondary hypertension may be even greater, reaching 5% to 10% [1, 7-13]. This rise in case number is mainly due to implementing the renin-to-aldosterone ratio as a screening test in PA [3].

The type of hypertension observed in PA is moderately elevated to severely elevated or resistant to treatment. Also, the patients diagnosed with secondary hypertension due to PA are at a higher risk of developing extracardiac complications than those diagnosed with primary hypertension. Along with hypertension, the high production of aldosterone over a long period may result in cardiovascular impairment, sodium retention, a decrease in plasmatic renin activity and a high potassium excretion which when severe, may lead to hypokalaemia.

PA generally presents with absent or unspecific symptoms that include fatigue, muscular weakness (as a result of hypokalaemia), thirst, polyuria (as a result of low urine concentration due to hypokalemia), polydipsia and nocturia [6]. Migraines or temporal paralysis may be present in patients with severe hypokalemia, this last symptom being very rare in Caucasian patients, but more frequent in patients of Asian descent. Also, another rare symptom that has been reported is tetany, which has been observed in patients with hypocalcemic alkalosis [14].

However, it must be mentioned that spontaneous hypokalemia, with values lower than 3,5 mmol/L is rare in untreated hypertension and when it is found in a patient under diuretic treatment, it must be re-evaluated 2 weeks after stopping the treatment. Nowadays it is widely accepted that only a small fraction of patients with PA (between 9% to 37%) present hypokalaemia, the most common situation in clinical practice being that of a hypertensive patient with normal potassium blood levels, hypokalaemia being seen only in some severe cases of PA [15, 16].

2. The objective of the study

The main purpose of this study was to evaluate the most common indications of screening testing and later test confirmation in the studied patients. In order to reach this objective, the frequency of positive results for the different categories of screening test indications in PA, the frequency of positive tests for de adrenal incidentalomas, the frequency of non-secreting incidentalomas, the frequency of later case confirmation of the positive screening tests, and later case confirmation for the operable subtypes of PA were evaluated.

3. Material and methods

In this retrospective study, we evaluated 62 patients over a period of 6 months, between January to June of 2019. All of the patients included in this study had one or more indications of PA screening, which include one of the following: sustained BP above 150/100 mmHg on three consecutive measurements obtained on different days, hypertension (BP above 140/100 mmHg) resistant to three conventional anti-hypertensive drugs (including a diuretic), or controlled BP (<140/90 mmHg) on four or more antihypertensive drugs, hypertension and a family history of early-onset hypertension or stroke at a young age (< 40 years), hypertension and a first-degree family member with diagnosed PA, or adrenal incidentaloma [1]. In all patients, demographics data, BMI, medical history, including risk factors for cardiovascular diseases, were recorded.

The screening test used for PA evaluation in the selected patients was the renin-to-aldosterone ratio (chemiluminescent immunoassay). For this test, patients were asked to discontinue for at least 4 weeks before evaluation any medication or therapies that may affect the renin-angiotensin-aldosterone axis such as spironolactone, eplerenone, amiloride, triamterene, potassium-eliminating diuretics, as well as products derived from liquorice root. The only anti-hypertensive drugs allowed before testing were verapamil, hydralazine, prazosin, doxazosin and terazosin.

In addition to this, serum sodium and potassium levels were determined in all patients. In order to assess the renal function of the patients included, there were evaluated markers such as serum creatinine, serum urea and the glomerular filtration (GFR) rate was calculated. In order to assess the global cardiovascular risk of the patients included, the ESH-ESC 2013 guidelines were used, which include the combination of three components: BP levels, the coexistence of other CV risk factors (gender, age, dyslipidemia, modified basal glycemia, BMI, abdominal obesity, familial history of a cardiovascular disease started at an early age) and presence of clinical or subclinical organ damage (left ventricular hypertrophy, modified glomerular filtration rates) [17].

All data collected for this study comes from patient charts and electronic logs of the patients hospitalized at the MedLife Hospital in Brașov, and it was done in compliance with the confidentiality requirements of the personal data of studied patients. The statistical compiling of the data thus obtained was done using Microsoft Excel, which allowed the interpretation and presentation of the results under a graphic format.

4. Results

After analyzing the collected data and the general characteristics of the group of studied patients, we have observed that the female-to-male ratio is close to 3:1. From an age perspective, most of the patients were between 40 to 49 years old, with 62% of the patients included in this study having the usual age of Conn syndrome diagnosis. However, it was noticed that a significant proportion of 32% of patients was above 60 years, 13% of them being over 70 years.

Table 1

Patient distribution from the point of view of PA screen test indication

Indication	%
BP above 150 / 100 mm Hg on each of three measurements obtained on different days	26
Hypertension resistant to three conventional antihypertensive drugs (including a diuretic)	16
Controlled BP on four or more antihypertensive drugs	13
Hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age	16
Hypertension and a first-degree family member with diagnosed PA	6
Adrenal incidentaloma	23

As seen in Table 1, the main reason for screening test admission in the studied patients was a BP value higher than 150/100 mmHg on three consecutive measurements obtained on three different days, followed by the presence of adrenal incidentaloma. However, out of all the patients with adrenal incidentaloma admitted in this study, only 7% presented later confirmation of PA.

This high number of adrenal incidentaloma cases is due to the high frequency of imagistic-type evaluation in modern medicine, as the presence of adrenal incidentalomas alone and not associated with hypertension is not a clear indication for PA screening test [1, 18].

Another significant characteristic of the patients included in this study was the presence of one or several additional cardiovascular risk factors. Taking into consideration that most of the patients included have a form of hypertension, the presence of additional risk factors makes them extremely vulnerable from a cardiovascular standpoint and showcases the importance that diagnostic and treatment of PA have on their life quality and expectancy. Consequently, it was observed that 32% of the patients included in the present study present the age as an additional risk factor, 49% present modified basal glycemia or are diagnosed with diabetes, 71% have a BMI over 30 kg/m² and 85% have associated cardiovascular diseases. After calculating the stratification of total cardiovascular risk for all of the studied patients, we observed that 12% had a very high global cardiovascular risk (57% of these patients later presented a positive screening test result), 16% had a high global cardiovascular risk (20% of these patients later presented a positive screening test result) and 25% had a moderate global cardiovascular risk (60% of these patients later presented a positive screening test result)**.**

As adrenal hypertrophy and increased aldosterone secretion can contribute to an increase in urinary protein excretion and lead, in this way, to renal injury [19], the renal risk of the patients was studied along with the cardiovascular one. In light of this, we can better understand the significance of PA diagnosis and treatment not only from a cardiovascular perspective but as a way to normalize urinary protein excretion levels and reduce glomerular sclerosis [3]. From al the patients included in this study, 8% presented elevated values of serum creatinine, 11% presented modified values serum urea and 3% and presented GFR <60 ml/min/1.73m². Another key aspect that must be taken into consideration in this category of patients is that renal injury manifested through raised serum creatinine levels may lead to false-positive screening test results [1]. In our study, the positivity rate for the renin-to-aldosterone test was 57% for patients with a GFR value between 60 to 80 ml/min/1.73m² and 50% for patients with a GFR value between 45 to 69 ml/min/1.73m².

From the point of view of serum sodium levels and serum potassium levels, there were few notable modifications in this study group, with only 8% of patients presenting with hypokalemia (5% had a further positive screen test) and no one presenting with hypernatremia. There were no medication-related cases of hypokalemia in the study group. Overall, the screening test positivity rate for the patients included in this study was 47%. The confirmation rate for positive screening tests was 79% and probably is a consequence of the relatively small number of patients involved.

The next step in PA diagnosis is subtype classification, which is paramount for optimal treatment. As seen in Table 2, only unilateral subtypes of PA can benefit from surgery, with the medical treatment being the recommended route for bilateral subtypes [1].

Subtypes of primary aldosteronism Table 2

Subtype		%	%	Possibility of surgery
Normal imaging				
Adrenal nodules	Right	16		+
	Left	68	61	+
	Bilateral	16		–
Diffuse adrenal hyperplasia	Right unilateral	12		+
	Left unilateral	38	13	+
	Bilateral	50		–

5. Discussion

From a demographic perspective, it was observed that the patients included in this study, which had indications for PA screening test, were mostly female (75%) and were mainly included in the 40 to 49 age group (32%). The sex ratio was thus similar to the 3:1 (female: male) sex ratio present in the medical literature. However, it was observed that a significant segment of the patients included in this study was in the 60 to 69 age group (21%), with the average age of diagnosis present in the medical literature being 30 to 60 years old. While this data could be a direct consequence of the small number of patients included in this study, it is recommended that screening for aldosteronism should start at an earlier age, as a late diagnosis of this disease is associated with a more unfavourable prognosis in patients [1], [3].

Among the key objectives of this study was observing the general state of health of patients who presented with PA screening test indications. An average of 50% of the patients included in this study have a medium to very high cardiovascular risk, with risk factors varying from age (32%) to diabetes (15%) and obesity (71%). In addition to this, an average of 40% of the patients included in this study have a decreased GFR, and 2% had a previous diagnosis of chronic kidney disease at the start of the study. Also worthy of mentioning is that the majority of patients with PA have some form of renal injury which can only be diagnosed after initiating treatment for PA, the reason for this being the high GFR caused by the raised aldosterone plasma levels [3], [5]. Overall, the screening test positivity rate was above average for both patients with cardiovascular risk, as well as for those with renal risk. This data portrays the vulnerability of these patients and adds further reason to a comprehensive screening of PA in patients who have indications for this test. Furthermore, conducting a surgical treatment where possible, or otherwise initiating a medical treatment, could greatly improve the quality of life for these patients and increase their life expectancy [3].

Another key aspect of this study was examining the positivity rate of patients with adrenal incidentaloma, irrespective of whether or not they were previously diagnosed with hypertension. As this situation is not a clear indication for PA, the positivity rate in these cases was 3%. This percentage suggests the high prevalence of non-secreting adrenal incidentalomas, the current indication in the medical literature being that screening tests are not necessary upon discovery of an adrenal incidentaloma if the patient was not previously diagnosed with some type of hypertension [3].

Taking into consideration that in the

past hypokalaemia had been considered an essential element for PA diagnosis, during this study the frequency of renin-aldosterone ratio test positivity in association with low plasma levels of potassium was also observed and showed that only 10% of the patients with a positive screen test had hypokalaemia. These results were consistent with the data present in the medical literature, which specifies that hypokalemia has low sensitivity for PA diagnosis and hypernatremia when present, is transitory [1,6]. The most extensive study to date on this theme showed that only half of the patients with an adrenal secreting adenoma and 17% of the idiopathic cases had hypokalaemia [15].

Overall, the screening test positivity rate for the patients included in this study was 47%, with a further confirmation rate of diagnosis of 79%. In the medical literature, a confirmation rate for positive screening test of 50% is specified, the high confirmation rate present in this study being, most probably, a consequence of the small number of patients included. As previously stated, in this study, there were included only patients which had one or several indications for PA, the leading reason for admission being a hypertension value of over 150/100 mmHg on three consecutive measurements. This decision comes from the awareness of the high costs associated with testing all the patients previously diagnosed with hypertension. However, it must be stated that this selective method of screening test recommendation may lead in some cases to a late PA diagnosis, which in return can lead to a more severe type of hypertension or a treatment-resistant type of hypertension, as a result of prolonged exposure to high plasma levels of aldosterone. In addition to this, a late PA diagnosis has been associated with a decreased response to treatment once the treatment can be initiated [3].

The last main objective of this study was evaluating the frequency of positive screening tests in association with an operable subtype of aldosteronism. This inquiry was made as surgical treatment for PA, where possible, is curative in nature. From the patients included in this study, 50% of the ones with diffuse adrenal hyperplasia and 84% of the ones with adrenal nodules could benefit from surgery. These high rates of surgery-compatible types of PA enhance once again the need for screen testing in the susceptible population.

Adrenal incidentalomas are not linked to a high positive rate of screen test for PA screening test positivity and do not need further investigation if they are not associated with hypertension or other indications for PA screening test. Also, hypokalaemia and hypernatremia are not a sine-qua-non condition for the diagnosis of PA, the most common clinical case in the day-to-day practice being that of the patient with normal plasma levels for both potassium and sodium.

There is a need for recommending the renin-to-aldosterone ratio screening test at a larger scale in the target population, the 47% positive rate being at the lower end of the 50% to 70% positive rate met in other clinical studies. In addition to this, the later confirmed cases present in this study had been associated with a high rate of operability and thus a high rate of curative treatment.

6. Conclusions

This study concluded that there is a high need for starting PA screening in the target population from an earlier age. The

benefits of this decision are depicted by the general vulnerability of these patients from a cardiovascular and a renal standpoint and the more subdued prognosis for those that start treatment later in life.

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