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ORIGINAL ARTICLE

Drug Profile and Therapeutic Adherence of African-Brazilians with Apparent Resistant Hypertension

Pedro Henrique Andrade Araújo Salvatore Barletta,[1] Júlia Lasserre Moreira,[2] Vitor Fernandes de Almeida,[2] Mateus Andrade Bomfim Machado,[2] Breno Lima de Almeida,[2] Tayla Samanta Silva dos Santos,[2] Yana Mendonça Nascimento,[2] Thaise Almeida Silva,[2] Roque Aras,[2] Cristiano Macedo[2]

Faculdade de Medicina da Bahia da Universidade Federal da Bahia,[1] Salvador, BA – Brazil.
Hospital Universitário Professor Edgard Santos (HUPES),[2] Salvador, BA – Brazil.

Abstract

Background: Resistant hypertension (RH) is manifested by the presence of blood pressure values resistant to antihypertensive therapy. RH is highly prevalent among black individuals, increasing cardiovascular risk in this population and requiring effective control of this comorbidity.

Objectives: To investigate the medication profile and therapeutic adherence in black people with apparent RH.

Methods: This is a cross-sectional study, with a convenience sample of individuals with apparent RH. Data were obtained from medical records. Therapeutic adherence was assessed using the Morisky Therapeutic Adherence Scale of 8 items (MMAS-8) and statistical analysis was performed using the SPSS, version 23. Significance was set at $p < 0.05$.

Results: Of the 120 individuals, 90 (75%) were women and 72 (60%) were black. Mean SBP was 153.09 (SD 25.59) mm Hg and mean DBP, 90.82 (SD 16.91) mm Hg, with a statistical difference in relation to the target pressure for SBP. Regarding the medication profile, 79.2% of the individuals used the recommended regimen for RH (ACEI / ARB + Diuretic + CCB), with the fourth most used drug being beta-blockers. The average score in MMAS-8 was 6.62 (SD 1.38) points, with 19.2%, 50.0%, and 30.8% showing low, medium, and high adherence, respectively.

Conclusions: It was evidenced that two-thirds of the individuals did not have high therapeutic adherence and not all used the ideal regimen for the management of RH, nor full doses. Thus, most individuals were probably affected by pseudoresistance, which was initially diagnosed as apparent RH. (Int J Cardiovasc Sci. 2021; 34(3):300-306)

Keywords: Hypertension; African Continental Ancestry Group; Medication Adherence; Antihipertensive Agents; Blood Pressure; Drug Resistance.

Introduction

Systemic hypertension (SH) is an important risk factor for cardiovascular events, especially stroke, which justifies the relevance of its proper management. In a meta-analysis conducted by Sarki et al.,[1] the results showed a prevalence of 32.3% of SH, and Latin America was as one of the regions with the highest estimates (39.1%).[1] According to data from the American Heart Association, specifically in the African-American population, the prevalence of SH reaches 44.9% for black men, and 46.1% for black women.[2] A higher prevalence of SH in blacks was also identified in Brazilian studies.[3–5]

Despite this high prevalence, pressure control is achieved in most cases with the appropriate choice of antihypertensive drugs.[6] However, still 9-18% of individuals with SH have blood pressure levels resistant to pharmacological treatment, which characterizes resistant hypertension (RH).[6–8]

Mailing Address: Pedro Henrique Andrade Araújo Salvatore Barletta
Largo Terreiro de Jesus, s/n. Postal Code: 40026-010, Pelourinho, Salvador, BA – Brazil.
E-mail: pedro.barletta@hotmail.com

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RH is defined as uncontrolled in-office blood pressure (≥ 140 / 90mm Hg) despite the use of 3 or more antihypertensive drugs in adequate doses, preferably including a diuretic. [6–9] Hypertension is also considered resistant when pressure control is obtained (< 140/90 mm Hg), but only with the use of 4 or more drugs.[6,7,9] In addition to the higher prevalence of RH in the black population, African-origin patients tend to have pressure levels that are more resistant to treatment.[7,10]

However, it is worth mentioning that for the definitive diagnosis of true RH, it is necessary to thoroughly check the patient's therapeutic adherence, since pseudoresistance is often due to poor adherence and / or inadequate therapeutic regimen.[6–8,11] In situations where the patient presents only blood pressure criteria and those referring to the number of antihypertensive drugs for the diagnosis of RH, but there is no exclusion of pseudoresistance after systematic verification of therapy and adherence, the diagnosis is of apparent resistant hypertension (apparent RH).[9]

Thus, in view of the morbidity and mortality associated with SH and the importance of an effective blood pressure control, we decided to investigate the drug profile and therapeutic adherence of black people with the diagnosis of apparent RH.

Methods

This is a cross-sectional descriptive study, which used a non-probabilistic convenience sample of black individuals who attended a reference outpatient clinic for the treatment of RH. Data were obtained from interviews and physical examinations, as well as the collection of information from medical records, using a standardized form approved by the Research Ethics Committee. Study participants signed a free and informed consent form, and were admitted based on the demand for assistance, as they went to the clinic for follow-up visits, from February 2014 to September 2017.

The individuals completed the questionnaire about life habits, medical history, therapeutic scheme used, and adherence to the proposed therapy while seated before blood pressure measurement. The individuals were instructed to empty their bladder before the measurement. Those who had ingested caffeinated drinks, smoked, or made physical effort, had their blood pressure measured in a minimum interval of 30 minutes.

After this initial resting moment, blood pressure was measured using a digital sphygmomanometer (Omron Healthcare, BP785). The patient's bare arm was supported at the level of his precordium and the cuff was positioned 3 cm above the cubital fossa. For obese patients, the large size cuff was used (Omron Healthcare, HEM-CL24). Measurements were performed on both upper limbs, with an interval of 1 minute between them; the measurement with the highest mean arterial pressure [(2 x diastolic blood pressure + systolic blood pressure) / 3] was considered for record.

Information about the pharmacological prescription of each individual was obtained from medical records. Serum potassium (K +) and serum creatinine (Cr) levels were also obtained from medical records, for analysis of possible justification for not using drugs known to induce hyperkalemia.

The study included self-declared black or brown individuals who used 3 or more antihypertensive drugs, with pressure control not obtained, that is, systolic blood pressure (SBP) ≥ 140 mm Hg and / or diastolic blood pressure (DBP) ≥ 90 mm Hg; or who used 4 medications or more, with pressure control (SBP <140 mm Hg and DBP <90 mm Hg). Because this study assesses only the pressure criteria for the diagnosis of RH, individuals at the time of admission to the study were considered to have apparent RH.[9]

Those with uncontrolled blood pressure even when using 5 or more antihypertensive drugs were classified as having Refractory Arterial Hypertension.[9]

The Morisky Medication Adherence Scale of 8 items (MMAS-8) was used to assess adherence to the prescribed pharmacological treatment. Individuals with scores of 8, 7 - 6 and ≤ 5 were classified as having high, moderate, and low therapeutic adherence, respectively.

Statistical Analysis

Statistical analysis was performed using SPSS, version 23.0. Categorical variables were presented using absolute and relative frequencies, while continuous variables were presented using means and standard deviations. The investigation of associations was conducted using the calculation of chi-square (χ^2) and prevalence ratio (PR). The Kolmogorov-Smirnov test was used to certify the normality of the data distribution. The comparison of means was performed using Student's t test for independent samples. The mean blood pressure values obtained were compared with the target blood pressure levels of 140/90 mm Hg using the one sample t test. Similarly, the averages of the daily doses of the

antihypertensive drugs used were compared with the maximum doses of each drug, also using the one sample t rest. Significance was established at $p < 0.05$.

Results

A total of 120 individuals were included in the study, whose characterization was shown in Table 1. The mean SBP was higher than the target SBP of 140 mm Hg (t [119] = 5.603 and p <0.05), while there was no statistical difference between the mean DBP and the target DBP of 90 mm Hg (t [119] = 0.529 and p = 0.598) (Table 1).

Regarding the medication profile (Table 2), the mean amount of oral antihypertensive drugs used by each individual was 4.71 (SD, 1.08). In addition, 79.2% of the individuals used the ACEI / ARB + Diuretic + CCB therapeutic regimen. As shown in Table 2, there was a statistical difference between the average doses of the drugs used and the full doses of these drugs. Among these individuals, considering those who needed 4 drugs or more, 82.4% used some beta-blocker, and 49.5% used spironolactone (Figure 1). The mean of [K +] of those who did not use spironolactone was 4.32 (SD 0.72) mmol / L and of those who did, 4.49 (SD 0.54) mmol / L, with no statistical difference (t [91] = - 1.305, p = 0.195). The creatinine means among those who did not use spironolactone and those who did it were, respectively, 1.092 (SD 0.468) mg / dL and 1.095 (SD 0.276) mg / dL, with no statistical difference (t [93] = - 0.049, p = 0.961).

Table 1 – Characterization of the sample

N	120
Sex	
Female	90 (75%)
Male	30 (25%)
Age (years)	63.07 ± 11.36
Race/color	
Black	72 (60%)
Brown	48 (40%)
Blood pressure	
Mean SBP (mm Hg)	153.09 ± 25.59
Mean DBP (mm Hg)	90.82 ± 16.91

SBP: Systolic blood pressure; DBP: diastolic blood pressure

A total of 34.2% of individuals met the criteria for Refractory Hypertension.[9] Of these, 34.1% did not use spironolactone, and 53.7% did not use the combination of chlorthalidone and spironolactone.

Regarding therapeutic adherence, the mean score on the MMAS-8 scale was 6.62 (SD 1.38) points, and the percentage of individuals with low therapeutic adherence was 19.2%; moderate adherence, 50.0%; and high adherence, 30.8% (Table 3). Comparing the groups of high and low therapeutic adherence, being a man was associated with better adherence (χ^2 (1) = 4.266 [p = 0.039] and PR = 1.524 [95% CI 1.055 - 2.200]). There was no statistically significant difference between the mean age and the quantity of drugs used in these groups (t (58) = - 1.330 [p = 0.189] and t (58) = - 0.372 [p = 0.711], respectively).

Although the mean pressure levels in the group with high therapeutic adherence were lower compared to the group with low adherence, there was no statistically significant difference (t (58) = 0.809 and p = 0.422 for mean SBP and for mean DBP, t (61) = 0.810; p = 0.421).

Discussion

Regarding the diagnosis of RH, it is imperative to rule out potential causes for the difficult control of blood pressure, highlighting the inappropriate choice of antihypertensives, poor therapeutic adherence, the effect of white coat hypertension, and secondary hypertension.[6–8]

For the treatment of RH, the recommended therapeutic regimen should include oral antihypertensive drugs with complementary pharmacodynamics. With this, as an ideal therapy, treatment with 3 drugs is recommended, including a thiazide or thiazide-type diuretic (preferably chlorthalidone), a blocker of the renin-angiotensin-aldosterone system (ARB or ACEI) and a dihydropyridine calcium channel blocker (CCB), in full tolerated doses and at appropriate intervals.[8,12,13] It was observed that 79.2% of the individuals used this triple therapy. Despite this, the mean SBP verified was greater than 140 mm Hg. This may have happened due to not using the full doses of ACEI / ARB and CCB in a statistically significant way.

Tu et al.,[14] demonstrated that blood pressure levels in black people would be more sensitive to the effects of aldosterone.[14] Other studies have shown higher plasma levels of aldosterone in black people.[15,16] Given these facts, knowing that primary hyperaldosteronism is imputed in the genesis of RH,[6,8] it is reasonable to understand the importance of using aldosterone antagonists in the

Table 2 – Antihypertensive drugs and percentage of use in the sample

Drug	Percentage of individuals using the drug	Average of daily doses compared to the maximum doses of each drug (mg)[1]
Diuretic		
Hydrochlorothiazide	48.3%	25.00 ± 0.00[2]
Spironolactone	47.5%	30.26 ± 10.28 (p<0.05)
Chlorthalidone	45%	24.54 ± 2.38 (p=0.159)
Furosemide	11.7%	42.86 ± 10.69 (p<0.05)
ACEI/ARB		
Losartan	65.8%	94.94 ± 17.16 (p=0.011)
Enalapril	25%	36.00 ± 8.14 (p=0.012)
Captopril	4.2%	90.00 ± 54.77 (p=0.07)
Beta-blocker		
Carvedilol	36.7%	45.17 ± 10.52 (p=0.004)
Atenolol	21.8%	70.19 ± 29.17 (p<0.05)
Propranolol	9.2%	90.91 ± 36.18 (p<0.05)
Nebivolol	7.2%	5.56 ± 1.67 (p<0.05)
Metoprolol	5%	100.00 ± 54.77 (p=0.07)
CCB		
Amlodipine	70.8%	8.56 ± 2.33 (p<0.05)
Nifedipine	12.5%	41.67 ± 15.08 (p<0.05)
Alpha-2-agonist		
Clonidine	36.3%	0.27 ± 0.16 (p<0.05)
Vasodilator		
Hydralazine	17.5%	147.62 ± 79.41 (p=0.892)

1 - The t test of a sample was used to compare the average dose of drugs with the full dose of each drug.
2 - All patients using hydrochlorothiazide used a daily dose of 25mg, so that the standard deviation was zero, thus making it impossible to apply the statistical test; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; CCB: calcium channel blocker

therapeutic regimen of black patients, as revealed by Saha et al.,[17] when demonstrating that treatment with amiloride or spironolactone may provide an additional reduction in blood pressure in blacks already receiving conventional antihypertensive therapy.[17] In the present study, considering those who needed 4 drugs or more, only 49.5% used spironolactone, even without plausible justification for not using it. This fact may have contributed to the high mean of SBP.

In fact, robust studies indicate that spironolactone is preferably the fourth drug to be added to the triple ARB / ACE + CCB + thiazide diuretic regimen in the treatment of RH.[12,13,18] It is noteworthy that the PATHWAY-2 study, which demonstrated the superiority of spironolactone as the fourth antihypertensive agent, compared to doxazosin and bisoprolol, based on the reduction of home SBP.[19] Based on this and the superiority of chlorthalidone over hydrochlorothiazide,[20] the most recent guidelines of the American Heart Association started to define Refractory Hypertension as the failure to control blood pressure, despite the use of at least 5 antihypertensive agents of different classes, including a long-acting thiazide-type diuretic, such as chlorthalidone, and a mineralocorticoid receptor antagonist, such as spironolactone. [12]

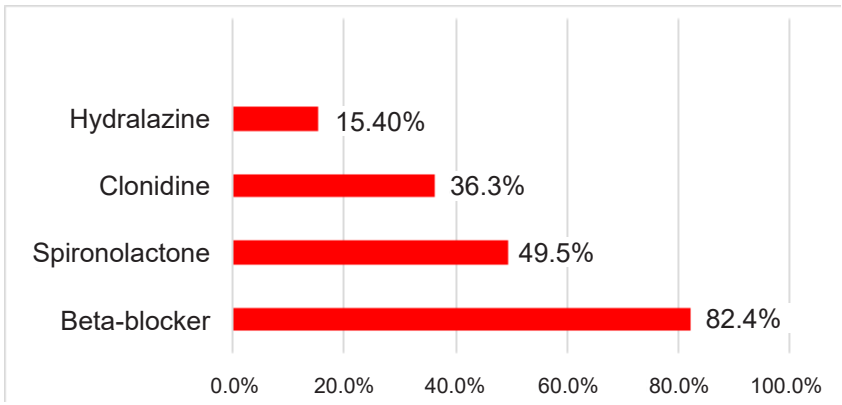

Figure 1 – Frequency of drugs added to the ACEI/ARB + CCB + DIU regimen

Table 3 – Characterization of groups according to therapeutic adherence

	Low adherence	Moderate Adherence	High adherence
Relative frequency	19.2%	50.0%	30.8%
Women	82.6%	83.3%	56.76%
Men	17.4%	16.7%	43.24%
Mean age (years)	65.74 ± 12.48	62.67 ± 12.23	62.05 ± 8.96
Mean quantity of OAH	4.78 ± 1.00	4.70 ± 1.02	4.68 ± 1.13
Mean SBP (mm Hg)	156.67 ± 28.40	152.98 ± 25.25	151.04 ± 24.80
Mean DBP (mm Hg)	91.87 ± 18.13	91.91 ± 17.73	88.39 ± 14.84

OAH: oral antihypertensive; SBP: systolic blood pressure; DBP: diastolic blood pressure

Considering this most current definition of refractory hypertension, in this study, 53.7% of the individuals who met the criteria of the 7th Brazilian Directive on Arterial Hypertension for Refractory Hypertension would not be seen as having pressure levels refractory to treatment. These data reveal, once again, the importance of ensuring that the medication regimen is the recommended regimen, before establishing the diagnosis of true RH.

On the other hand, chlorthalidone, an important medication for the control of RH, is not included in the list of Essential Medicines of the Brazilian public Unified Health System.[21] In a society where low-income individuals are mostly black and depend on the public Health System, [22,23] it is difficult to assess what is the real responsibility of the genetic background in the development of RH, given the socioeconomic issues involved.

Regarding therapeutic adherence, Rajpura et al.,[24] used the 4-item Morisky scale to assess how the perception of SAH and drug therapy influences therapeutic adherence, finding a 18.8% prevalence of high adherence, 47%, moderate adherence, and 34.2% low adherence.[24]

Morisky et al.,[25] In the MMAS-8 validation study, observed that 15.9% of the study sample had high adherence, 52.0% moderate adherence, and 32.1% low adherence.[25] In comparison with the studies cited, the present study revealed a lower prevalence of low therapeutic adherence (19.2%) and a higher prevalence of high adherence (30.8%). This may be due to the fact that the sample consisted of patients with apparent RH followed in a reference clinic, so that a stronger belief in the severity of the disease and need for medications may have contributed to better adherence.[24] Nevertheless, a considerable portion of the individuals did not have full

adherence to pharmacological treatment, which may also have influenced the high mean SBP.

In the present study, men showed higher adherence to drug treatment. This finding corroborates the systematic review conducted by Hope et al. with individuals using statins, in which being a man was a predictor of better therapeutic adherence.[26] However, the literature shows different results regarding the association between sex and adherence to pharmacological treatment: women showed greater adherence to the antihypertensive treatment regimen in a study conducted in Jordan,[27] while there was no statistical difference between the sexes in individuals from rural Vietnam.[28] These findings may be indicative that cultural and social factors have an important contribution to therapeutic adherence found in different countries.

De La Sierra et al.,[29] analyzed a large Spanish cohort of individuals treated for RH, finding a prevalence of 12.2% of RH; after investigating the data regarding ambulatory blood pressure measurement (ABPM) of these patients, it was found that in 37.5% of the cases, the ineffectiveness of the treatment was due to the white coat effect.[29] Considering the relevance of the white coat effect, the authors and the current guidelines for the management of SH point to ABPM as a valuable tool in the diagnosis of true RH, being the next propaedeutic step to be adopted in patients with apparent RH, as in the case of the present study.[8,12,13,30]

Because it is a cross-sectional study, there are inherent limitations to this type of research design. The number of individuals may not have been sufficient to demonstrate a statistically significant difference between the pressure levels of the groups of high and low therapeutic adherence and the performance of a multivariate analysis could reveal factors that better influence adherence. Adherence to non-drug therapy was not assessed. Furthermore, the use of indirect methods to assess medication adherence, such as MMAS-8, is vulnerable to memory bias, so that the answers given may not be reliable to the individual's real behavior.

Since no ABPM data were obtained, the study was not able to accurately distinguish between pseudoresistant patients and patients with actual RH. A comparison of the results of black patients with those of individuals who did not declare themselves as African-Brazilians could also have been considered.

It is evident that resistance to treatment with antihypertensive drugs is multifactorial. As evidenced in the literature, the appropriate choice of antihypertensive drugs, as well as the strengthening of the doctor-patient bond for better adherence to treatment, is essential for the management of RH. The importance of spironolactone in the treatment of RH, especially in black people, should be disseminated among physicians and reported in national guidelines. The white coat effect should not be underestimated either, so that the relevance of ABPM in the diagnosis of true RH should also be emphasized in future Brazilian guidelines.

Future studies that aim to assess the understanding of the mechanisms by which socio-environmental issues influence blood pressure levels in the black population are essential for the creation of public health policies and for the guarantee of equity.

Conclusion

The present study showed that two-thirds of the individuals did not have high therapeutic adherence and some of them did not use the ideal triple regimen for the management of RH, nor did they use full doses. These data culminated in the conclusion that most individuals included in the study were probably affected by pseudoresistance, which was initially diagnosed as apparent RH.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the *Hospital Ana Nery* under the protocol number 08501212800000045. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Author Contributions

Conception and design of the research: Macedo CRB, Aras-Jr R. Acquisition of data: Barletta PHAAS, Machado MAB, Almeida BL, Moreira JL, Almeida VF, Santos TSS, Silva TA, Nascimento YM. Analysis and interpretation of the data: Barletta PHAAS, Machado MAB, Almeida BL, Moreira JL. Statistical analysis: Barletta PHAAS, Machado MAB. Writing of the manuscript: Barletta PHAAS, Moreira JL, Almeida VF, Machado MAB, Almeida BL. Critical revision of the manuscript for intellectual content: Santos TSS, Silva TA, Nascimento YM, Macedo CRB, Aras-Jr R.

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