Prevalence, Biochemical and Clinical Characteristics of Resistant Hypertension

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The objectives of the present study were to evaluate the prevalence of resistant hypertension (RH) in primary care setting and to analyse its biochemical and clinical characteristics. After 3 months of treatment and evaluation, 721 (14.01%) of 5,146 patients with hypertension did not reach target office blood pressure of < 140/90 mmHg. After exclusion of white-coat effect with ambulatory blood pressure, of secondary and pseudo- resistant hypertension, prevalence of RH was 6.74%. Lifestyle factors associated with RH were physical inactivity, obesity, high salt intake, smoking and excessive alcohol ingestion. Compared to controlled hypertension, RH patients presented higher incidence of family history of cardiovascular disease (38.90% vs 25.94%), diabetes mellitus (34.87% vs 19.01%), impaired fasting glucose (21.91% vs 19.07%), target organ damage (29.1% vs 15.95%), and cardiovascular disease (27.09% vs 17.06%). Dyslipidaemia (52.90% vs 42.03%), fasting plasma glucose (116.10±38.9 vs 107.80±37.2), HbA1c (6.41±1.42 vs 5.96±0.94), serum creatinine (1.09±0.27 vs 1.03±0.24) and microalbuminuria (21.90% vs 10.95%) were significantly higher in RH. Predictors of RH, determined by a multivariate logistic regression analysis were left ventricular hypertrophy (OD 2.14, 95% CI 1.32-3.69), renal impairment expressed as eGFR < 60 ml/min/1.73m^2 (OD 1.62, 95% CI 1.21-2.21) and the presence of cardiovascular disease (OD 1.48, 95% CI 1.02-2.16).

Keywords: Resistant hypertension, prevalence, laboratory evaluation, predictors, clinical characteristics

General practitioners are often confronted with hypertension (HT) in patients treated with multiple antihypertensive drugs, but do not reach blood pressure (BP) targets recommended by guidelines (values under 140/90 mm Hg) [1]. Resistant hypertension (RH) is diagnosed in hypertensive patients treated with three or more antihypertensive agents, in optimal doses or maximal tolerated, including a diuretic, but don't reach target BP values. RH includes also controlled hypertension treated with four or more antihypertensive drugs [2]. To differentiate uncontrolled patients, secondary to the *white-coat effect*, evaluation of BP outside the office is necessary. This is best done with ambulatory BP monitoring (ABPM). The NICE [3] and European Hypertension Guidelines [4] outline that the diagnosis of RH needs to be confirmed by an average day ABPM ≥135/85 mmHg. Prevalence of RH is reported to be 10-20% in hypertension patients managed in cardiology and nephrology clinics [5, 6] and lower, till 10%, in primary care clinics [7]. Published data show that RH is often associated with older age, obesity, diabetes mellitus and cardiovascular disease [8-13]. Target organ damages as left ventricular hypertrophy (LVH), reduced estimated glomerular filtration rate (eGFR), microalbuminuria (MAU) and macro-albuminuria have higher rates of prevalence in this condition than in controlled HT [14 - 18].

The objectives of the study were to investigate the prevalence of RH in primary care and to evaluate its biochemical and clinical characteristics.

Experimental part

Material and methods

The present observational cross-sectional study was performed during 2011 till 2017 and involved general practitioners (GPs) from 19 family medicine offices of Timiº County, Romania. A number of 5,146 hypertensive patients were evaluated at the medical visits at the GPs office. Inclusion criteria were adult patients over 18 years of age, diagnosed with hypertension, who underwent treatment and monitoring for at least three months. Exclusion criteria were secondary hypertension, acute myocardial infarction, instable angina and chronic kidney disease stage 4 and 5. In accordance to the rules of the Helsinki Declaration and with some published models and guidelines [19 -21], each participant signed a written informed consent. The Ethics Committee of the University of Medicine and Pharmacy Victor Babes Timisoara approved the study. The GPs evaluated the patients' questionnaires containing demographic data and exposure to risk factors. The examination consisted of office BP, ABPM, weight, height and waist measurements. The laboratory analyses included total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), triglycerides (TG), uric acid, creatinine, estimated glomerular filtration rate (eGFR), urine analysis, urine albumin-to-creatinine ratio (UACR), fasting plasma glucose (FPG), HbA1c and an oral glucose tolerance test (OGTT), performed in conformity to the standardized procedures.

The family doctors involved in the study were instructed to use the same methodology regarding BP measurement. Office BP was calculated as the average of the second and third BP measurement, made in the morning in 4220 (82%) patients and during the afternoon in 926 (18%). Validated, semiautomatic Omron HEM 7251G sphygmomanometers were used. For ABPM, BTL-08 devices were used, programmed with 4 measurements/hour during daytime and 2 measurements/hour during night-time. ABPM was accepted as good with over 70% valid

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measurements [4]. Electrocardiographic LVH was diagnosed with Sokolow-Lyon voltage greater than 38 mm. Renal impairment was diagnosed when the eGFR was < 60 mL/min/1.73 m^2, calculated with the Modification of Diet in Renal Disease equation. MAU was defined as UACR of 30 to 300 mg/g in spot urine and macro-albuminuria with UACR more than 300 mg/g [22]. Cardiovascular disease was represented by coronary heart disease, heart failure and stroke.

Statistical analysis

The statistical analyses were performed using SPSS version 12.0. Data were presented as frequencies and percentages for qualitative variables and as mean ± SD for quantitative variables. Differences between groups were assessed with the Pearson χ^2 for qualitative variables and the Student t test for quantitative data. The independent variables with $p < 0.05$ were considered as having statistical significance. Multivariate logistic regression analysis determined the independent clinical predictors of RH.

Results and discussions

From the total number of 5146 hypertensive patients evaluated and treated three months by GPs, during which BP and the compliance to treatment were monthly monitored, 4425 (85.99%) patients reached target BP, forming the controlled hypertension group. The target office BP of < 140/90 mmHg was not achieved in 721 (14.01%) cases, treated with 3 or more agents, one of which was a diuretic. They were considered as RH, based on office BP and underwent ABPM. Because of incomplete data, 27 patients were excluded, finally 694 patients being evaluated. In this population ABPM documented normal daytime mean BP values (≤ 135/85 mmHg) in 243 (35.01%) patients, these being classified as *white-coat effect*. The remaining 451 (64.99%) patients with abnormal ABPM were addressed to hypertension specialists in cardiovascular diagnosis centres. From this group, true RH was finally diagnosed in 347 cases (76.94% of patients with abnormal ABPM and 6.74% of the total evaluated hypertension population). Pseudo-resistant hypertension was diagnosed in 76 cases (16.85% of those with abnormal

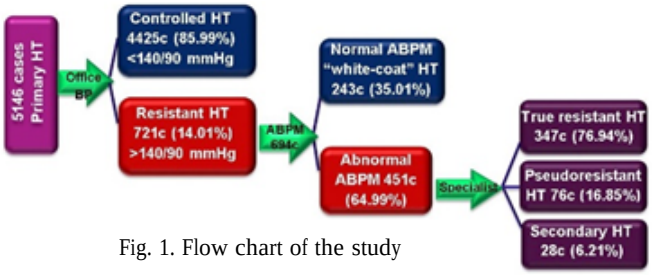

Fig. 1. Flow chart of the study

ABPM), and secondary hypertension in 28 cases (6.21% of those with abnormal ABPM) as shown in figure 1.

Patents with RH had a mean age of 63.4±11.4 years (53.02% males). Average office systolic BP was 162.1±22 mmHg and average diastolic BP was 90.2±19.3 mmHg (fig. 2).

The analysis of the circadian BP pattern showed differences between the two groups, with a higher proportion of non-dippers, 225 cases (64.48%) in RH vs. 432 (59.92%) in controlled HT, based on either systolic or diastolic BP.

The prevalence of lifestyle factors that contributed to the development of RH, as physical inactivity, obesity, high

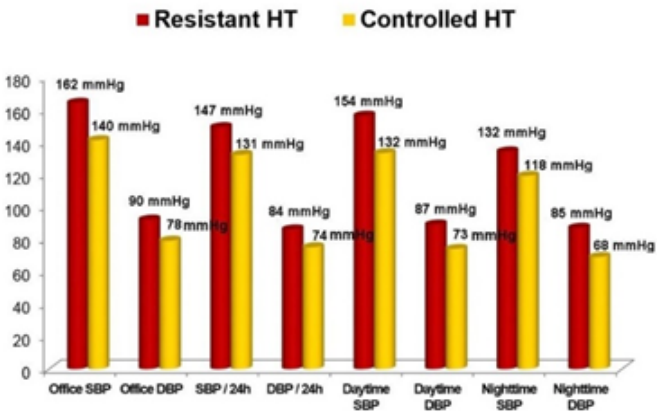

Fig. 2. Office blood pressure and ABPM data

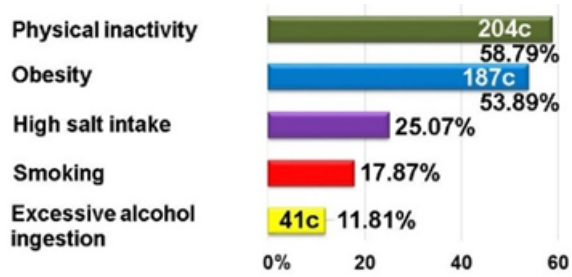

Fig. 3. Lifestyle factors associated with resistant hypertension

salt intake, smoking and excessive alcohol ingestion are presented in figure 3.

A number of 336 patients with RH were compared to 695 patients with controlled HT. The RH group vs controlled HT group, presented a trend to an older mean age (63.40±11.40 years vs 62.10±11.30, p = 0.0794), a longer duration of hypertension (13.60±10.90 years vs 13.10±9.70, p = 0.44), but these differences were not statistical significantly. No differences were noted regarding male gender (53.02% vs 52.01%), smoker status (17.87% vs 14.01%), and urban living area (57.92% vs 57.00%). Statistical significant differences were noted on: family history of cardiovascular disease (38.90% vs 25.94%), obesity with BMI > 30 kg/m^2 (53.89% vs 38.97%), LVH (8.93% vs 2.08%), and number of medication

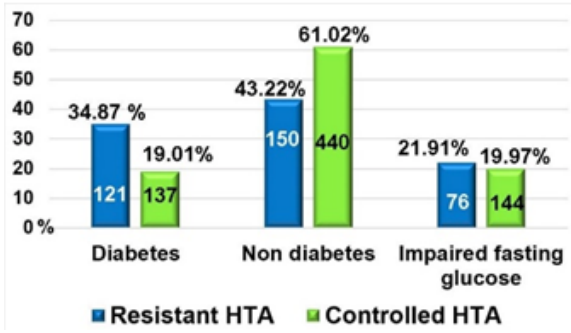

Fig. 4. Evaluation of glucose metabolism in resistant and controlled hypertension

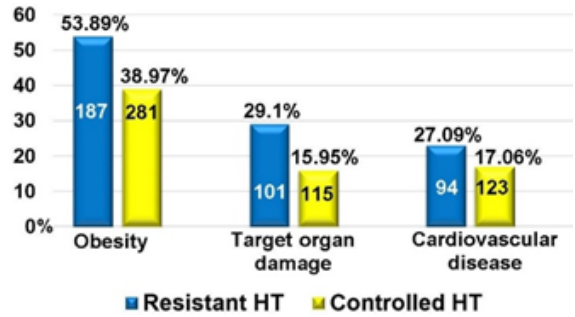

Fig. 5. Target organ damage and cardiovascular disease in resistant and controlled hypertension

Parameters	Resistant HT n = 347	Controlled HT n = 721	P-value
	Nr, %	Nr, %	
Dyslipidaemia	183 (52.90%)	303 (42.03%)	0.0008
Hyperuricemia	51 (14.7%)	101 (14.0%)	0.7592
	Mean±SD	Mean±SD	
FPG, mg/dL	116.10±38.9	107.80±37.2	< 0.0001
Hb A_{1c} %	6.41±1.42	5.94±0.94	< 0.0001
Creatinine, mg/dL	1.09±0.27	1.03±0.24	0.0003
Uric acid, mg/dL	5.40±1.8	5.30±1.7	0.3774
Potassium, mg/dL	4.71±0.44	4.47±0.42	< 0.0001
eGFR,ml/min/173 m^2	65.20±17.5	79.30±19.2	< 0.0001
LDL-c, mg/dL	139.20±49.5	127.80±43.1	< 0.0001
HDL-c, mg/dL	45.80±10.8	45.90±12.1	0.0061
TG, mg/dL	179.00±88.97	137.0±72.32	< 0.0001

Table 1
BIOCHEMICAL CHARACTERISTICS OF RESISTANT AND CONTROLLED HYPERTENSION

administrated (3.64±0.56 vs 1.92±0.73), p < 0.0001 for all these comparisons.

Patients with RH, compared to controlled hypertension, presented statistically significant increased levels of serum creatinine, potassium, fasting plasma glucose, HbA1c, LDL-c, TG and lower HDL-c; glucose metabolism has also a different evolution in resistant/controlled hypertension (Fig. 4). Renal impairment, expressed by a reduced eGFR and a higher prevalence of MAU, was significantly more prevalent in RH. Target organs for both types of HT are represented in figure 5. UACR of RH group, compared with the controlled HT group, showed statistical significant differences concerning norm-albuminuria (UACR < 30 mg/g) present in70.2% vs 83.9%, p < 0.001 and MAU (21.90% vs 10.95%, p < 0.001) (fig. 6). Although the prevalence of macro-albuminuria (UACR > 300 mg/g) was not statistically significant greater in the RH group, this condition was more often met in RH (8.08 vs 5.12%, p = 0.061). Cardiac involvement, expressed as LVH on ECG, was present in

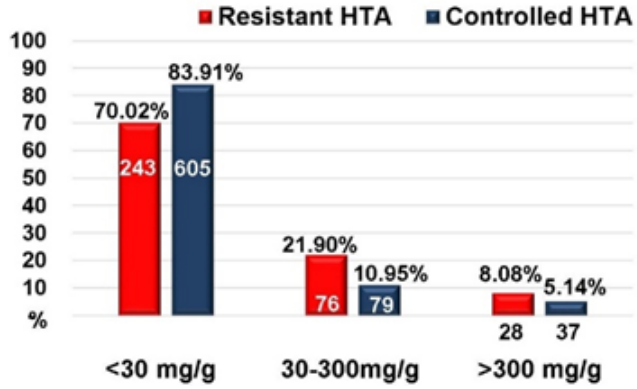

Fig. 6. Albumin/creatinine ratio in resistant and controlled hypertension

8.93% of patients with RH; biochemical characteristics seem to evolve different in resistant/controlled hypertension (table 1).

Predictors of RH, determined by a multivariate logistic regression analysis were: LVH (odds ratio, OD 2.14, 95% confidence interval, CI 1.32-3.69), renal impairment, expressed as eGFR < 60 mL/min/1.73m^2 (OD 1.62, 95% CI 1.21-2.21) and the presence of cardiovascular disease (OD 1.48, 95% CI 1.02-2.16).

The present observational cross sectional study evaluated the prevalence, the demographic, clinical and laboratory characteristics of RH in Timi' Country, Romania. Many studies have demonstrated that RH is an increasingly problem and may affect as many as 15-20% of the hypertensive population [23]. The prevalence depends on the definition used for RH, characteristics of the study population, and methodology of study, being around 5-10 % (in trials in primary care) till 20-25% in hypertension clinics [24, 25]. Based on office BP measurements, the prevalence of RH was 14.01% in our study, but after exclusion of *white-coat effec*t, of pseudo-resistant and secondary hypertension, true RH was present in only 6.74%, which is relatively low, compared to trials conducted in other countries [6].

The SEPHAR II trial, based on office BP, confirmed that 27.68% of the Romanian treated patients performed the criteria of RH. As ABPM was not done, patients with pseudo-resistant hypertension and 3 white-coat3 HT were included, contributing to the overestimation of RH [26, 27]. Data from the Spanish Society of Hypertension on 68,045 patients with ABPM, indicate a 12.2% prevalence of RH [28]. The prevalence of RH has a growing tendency, concomitant with the growing prevalence of obesity, diabetes, sleep apnoea and aging of the population [29, 30]. In the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) trial the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the prevalence of RH was 18% and, respectively, 15 % [31, 32]. An explanation of the lower incidence of RH is a better selection of patients at enrolment, by exclusion of pseudo-resistant HT. One of the main causes of pseudo-resistant HT is the poor adherence to treatment that can be caused by side effects, high costs of medication, great number of tablets administrated, and an inefficient education of the patients [33, 34]. The RESIST-POL Study, using drug titration, demonstrated the general low adherence to antihypertensive treatment, as only 13.9% of patients had drugs concentrations over the limit of quantification, 86.1% had at least one drug under this limit and 13.9% had no detectable drug in their blood [35]. To determine the prevalence of true RH, titration of the drug concentrations is also needed [36].

Factors involved in RH must be detected and removed [37, 38]. Obesity determines excessive sodium retention, sympathetic stimulation, renin-angiotensin system activation, insulin resistance and sleep apnoea [39-42]. Excessive alcohol consumption contributes to increased BP, risk of stroke and a worse evolution [39]. Excessive salt intake (more than 6 g/day) is known to contribute to RH, the effect being greater in individuals who are sensible to salt as elderly, with obesity and kidney disease [43–48]. A small number of patients take drugs that can increase BP as non-steroidal anti-inflammatory agents, aspirin, oral contraceptives, amphetamines, gluco- and mineralo-corticoids, nasal drops, liquorice, etc. [46-51]. The main characteristics of patients with RH are presented in figure 8. In this study predictors of RH were: LVH, renal impairment and the presence of cardiovascular disease; other studies

revealed abdominal obesity and current smoker status as RH predictors [24].

MAU, an early marker of intra-renal vascular dysfunction, had a prevalence of 21.90% in our study. Cuspidi reported a prevalence of 17% for microalbuminuria and demonstrated that it is less sensitive for detecting TOD than echocardiography or carotid ultrasonography [30]. Nogueira et al., [52] confirmed a higher prevalence, of 29.4%, for MAU. LDL-cholesterol, serum creatinine and diabetes mellitus were independently associated with albuminuria [53, 54]. MAU is a powerful risk predictor of cardio-vascular morbidity and mortality and of all-cause mortality in patients with RH, independent of traditional CV risk factors, renal function and ABPM levels. Trials showed that the cardiovascular risk is 2-4 times greater in RH. These patients develop 50% more cardiovascular events in the follow up, compared to controlled HT [55-58].

The present study has some limitations as it reflects especially the experience in primary care settings, presenting limited possibilities to evaluate complete target organ damage and cardiovascular disease.

Conclusions

The prevalence of true resistant hypertension was 6.74%. Before confirming true RH, *white-coat effect*, pseudo-resistance or secondary hypertension must be excluded. RH was associated with high BP values, obesity, diabetes mellitus, metabolic syndrome, hypertriglyceridemia, high LDL-c and creatinine, low HDL-c, target organ damage as LVH, microalbuminuria, reduced eGFR and cardiovascular disease. Considering the unfavorable prognosis of RH, an increased effort for detecting its clinical and biochemical characteristics and for improving its management is fully justified.

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