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Asymptomatic hyperuricemia is a strong risk factor for resistant hypertension in elderly subjects from general population

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Abstract

Objective—In clinical practice, patient characteristics predicting resistant hypertension (RH) include higher blood pressure levels, left ventricular hypertrophy, older age, obesity, chronic kidney disease and diabetes. On the contrary little is known about the role of serum uric acid (SUA) as a risk factor for RH in subjects from general population.

Material and methods—580 elderly subjects aged ≥65 years were enrolled in the Risk Of Vascular complications Impact of Genetics in Old people (ROVIGO) study. RH was defined as the failure to maintain blood pressure values below 140 mmHg (systolic) and 90 mmHg (diastolic) despite therapeutic interventions that include appropriate lifestyle measures plus adherence to treatment with full doses of at least three antihypertensive drugs, including a diuretic. RH was confirmed using 24-h ambulatory blood pressure measurement. Hyperuricemic was defined as the subjects having SUA ≥6.8 mg/dl or taking uricosuric drugs. Gender-specific odds ratio (OR) for RH was calculated by logistic regression analysis.

Results—The prevalence of RH was 5.7% in the cohort and was higher in women (8.3%) than in men (3.0%, $p < 0.05$). Independent of chronic kidney disease (OR 3.89, 95% confidence interval 1.49–10.1), hyperuricemia predicted resistant hypertension in women (odds ratio 3.11, 95% confidence intervals 1.06–9.1, $p = 0.03$) but not in men.

Conclusions—In elderly women from the general population, an SUA value of ≥6.8 mg/dl triples the risk of RH. SUA assessment should be recommended to better define the pattern of risk associated with RH.

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Conflict of interest statement

None.

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Keywords

Cardiovascular risk; Epidemiology; Resistant hypertension; Uric acid

1. Introduction

In the 2013 Guidelines of the European Societies of Hypertension and Cardiology, resistant hypertension (RH) is defined as blood pressure (BP) remaining above the goal (140/90 mmHg) despite a therapeutic strategy taking into consideration appropriate lifestyle measures plus the adherence to treatment with full doses of at least 3 antihypertensive drugs including a diuretic [1]. In clinical practice, patient characteristics predicting RH include higher BP (particularly systolic), older age, left ventricular hypertrophy, diabetes, obesity, chronic kidney disease and African-American race [2]. On the contrary, little is known about the role of serum uric acid (SUA) as a risk factor for RH, particularly in elderly subjects from general population.

Hyperuricemia is commonly associated with hypertension [3] and is present in 25% of untreated patients with hypertension, in 50% of patients taking diuretics and in >75% of patients with malignant hypertension [4]. In addition hypertensive patients with hyperuricemia have a 3-to-5-fold increased risk of coronary or cerebrovascular disease compared to hypertensive patients with normal SUA [5].

The aim of this study was to evaluate the role of SUA as a risk factor for RH in elderly people from general population.

2. Material and methods

2.1. Study population

The Risk Of Vascular Complications Impact of Genetics in Old people (ROVIGO) study, was conceived as a longitudinal population-based study aimed at evaluating in the long term whether cardiovascular disease depends on a particular genetic profile and/or environmental risk factors. The study cohort consisted of 580 unselected subjects (272 men and 308 women) aged 65 years or over, representative of the elderly of the general population of Rovigo in the Italian Veneto region. The results of the initial cross-sectional survey are described herein [6]. Data from the longitudinal analysis, including morbidity, mortality and incidence of new cases of hypertension, has not yet been published. A complete genetic analysis is on going. The local Ethics Committee approved the study and all the procedures were carried out in accordance with the Helsinki declaration and with institutional guidelines. Informed consent was obtained for each participant.

2.2. Data collection and disease criteria

The protocol of the study was previously published [6] and included gathering of demographic information, medical and social questionnaires, fasting blood tests, anthropometrics, electrocardiogram, clinic BP and 24-h ambulatory BP measurements.

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Procedures for taking and preparing blood specimens and laboratory analysis were standardized.

Fasting SUA and lipids was determined by enzymatic method. For the purpose of this study, we analysed only those subjects having asymptomatic hyperuricemia, defined as SUA levels ≥6.8 mg/dl without symptoms or signs of urate crystal deposition disease or clinical history of uric acid renal disease, as well as subjects taking hypouricemic drugs. The cut-off of «abnormal» SUA is still disputed; however we used a pathophysiological approach considering the super-saturation of SUA concentration (i.e. 6.8 mg/dl) observed at 37 °C of temperature [7]. Subjects with total cholesterol ≥200 mg/dl or low-density-lipoprotein cholesterol >130 mg/dl [8] were labelled as hypercholesterolemic, those with serum triglycerides ≥150 mg/dl as hypertriglyceridemic [9]. Subjects were classified as diabetic if their fasting serum glucose was repeatedly ≥126 mg/dl, or if they had a history of diabetes and/or treatment with anti-diabetic drugs. Serum creatinine (mg/dl) was measured using by an enzymatic method (Hitachi Modular P, Roche diagnostic, USA). Albuminuria was measured using the turbidimetric method (Cobas Mira Plus, Roche, Montclair, NJ) in 24-h urine. Subjects having albuminuria ≥300 mg/day were classified as proteinuric.

Creatinine clearance (ml/min) was calculated from serum creatinine (mg/dl) using the formula of Cockroft and Gault [10]. Subjects having a creatinine clearance <60 ml/min were classified as having chronic renal disease.

Subjects currently smoking ≥1 cigarette daily were classified as smokers. Alcohol intake was recorded by means of a questionnaire and considered as ethanol consumption (ml/week), mainly from wine. Anthropometrics were measured in patients wearing light underwear without shoes. Subjects were considered obese when body mass index was ≥30 kg/m^2.

Following a 20-min rest, trained physicians measured BP using a mercury sphygmomanometer. The measurements were obtained from subjects while sitting in the supine posture position. The measurements were performed in triplicate at 10-min intervals avoiding any terminal digit preference. To minimise the “white-coat effects”, if any, the average of the last two measurements was taken into consideration as a measure of blood pressure for data analysis. Heart rate was also measured at the same time and averaged. Arterial hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic ≥90 mmHg or current treatment with antihypertensive drugs· According to the 2013 guidelines [2], hypertension was classified as resistant to treatment after a therapeutic strategy including appropriate lifestyle measures + diuretic + two other antihypertensive drugs belonging to different classes at adequate doses failed to lower systolic BP <140 and diastolic BP <90 mmHg.

An expert who did not know the aim and design of the study evaluated 12-lead standard electrocardiogram. Subjects satisfying the Sokolow-Lyon criterion [11] were classified as having left ventricular hypertrophy.

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2.3. Statistical analysis

SPSS/PASW Statistics 18.0 for Windows (SPSS, Chicago, USA) was used for statistical analysis. Continuous variables were expressed as mean and standard deviation. Analysis of variance was used to compare grouped continuous variables, and the Pearson's χ^2 test to compare the prevalence of categorical variables. Gender-specific odds ratio (OR) and 95% confidence intervals for RH were calculated for independent variables by logistic regression analysis. The null hypothesis was rejected when p was <0.05.

3. Results

The general characteristics of the population, also showing stratification in subjects with and without RH, are summarised in Table 1. Using office BP values, the prevalence of RH was 9.8% in the mixed gender cohort. No statistically significant gender differences were observed in men and women (9.2 vs. 10.6%, respectively). In contrast, using the 24-h ambulatory measurement, the prevalence of RH was 5.7% in the whole cohort and higher in women (8.3%) than in men (3.0%), $p < 0.05$. Other parameters, including SUA, clinic systolic BP, 24-h systolic and daytime systolic BP, serum triglycerides, number of antihypertensive drugs, prevalence hyperuricemia and of left ventricular hypertrophy were higher in subjects with RH. Diuretic treatment was also more prevalent in subjects with RH. In contrast, eGFR and HDLC values as well as the prevalence of uricosuric drugs were higher in the latter than in the former (Table 1).

As shown in Table 2, only chronic kidney disease and hyperuricemia predicted RH (OR 4.4, 95% confidence intervals 1.24–15.7, $p = 0.02$) in women but not in men (OR 1.46, 95% confidence intervals 0.51–4.21, $p = 0.5$).

4. Discussion

Five to 15% of hypertensive patients do not achieve an adequate BP control despite three or more antihypertensive agents [1]. Subjects with RH represent one of the most important clinical challenges in the management of hypertension. Resistant hypertensives are characterized by several factors: longer history of hypertension, obesity and other accompanying factors, such as diabetes, left ventricular hypertrophy, albuminuria and renal dysfunction [12]. In addition to other diagnostic and therapeutic manoeuvres (excluding secondary hypertension, ensuring treatment adherence and optimizing therapeutic schemes), 24-h ambulatory BP monitoring (24h-ABPM) is crucial in the clinical evaluation of these patients. 24h-ABPM discriminates between those with out-of-office BP elevation (true resistant hypertensives) and those with white-coat RH. The latter represent about one-third of subjects with RH [13]. In agreement with published studies [12,13], these studies confirm that 24h-ABPM leads to a better characterization of true RH, that is commonly overestimated when diagnosed using office BP values [1]. In addition, although patients with RH may have elevations in both systolic and diastolic BP, in our study isolated systolic hypertension was the more common form of RH diagnosed in the elderly.

A large number of observational and epidemiological studies have revealed an increase risk of hypertension with increasing levels of SUA, an association that remains independent of

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the traditional cardiovascular risk factors [14–16]. From a pathophysiological point of view, oxidative stress due to xanthine oxidase activity appears to be involved in the association between hyperuricemia and hypertension [15]. In detail, this mechanism has been clearly investigated in animal models [17,18], where SUA increase leads a rise in BP that can be prevented or reversed with uricosuric drugs or xanthine oxidase inhibitors [19]. However, studies performed in humans and specifically in the elderly led controversial results regarding the relationship between SUA and BP [20,21].

The association between SUA and BP is not as strongly supported in the elderly population, and SUA-lowering agents have different effects on controlling BP in the elderly and in the young adults with hyper-uricemia [22,23]. However, large controlled studies are needed to formally establish the effect of SUA lowering on BP control and on hard cardiovascular and renal endpoints. The ongoing Febuxostat for Cerebral and caRdiorenovascular Events prEvEntion stuDy (FREED; ClinicalTrials.gov Identifier: NCT01984749) is currently investigating the effect of xanthine oxidase inhibition on cardiovascular and renal endpoints in elderly hyperuricemic patients. The results are expected in late 2017.

In our study, performed in elderly subjects from the general population, the risk of RH independently tripled in women but not in men when SUA was ≥6.8 mg/dl. Age was an independent predictor for the elevation of SUA, and it is well known that the relationship between age and the occurrence of hyperuricemia differs between men and women [23]. Hyperuricemia correlates negatively with age in men but positively in women [24,25], possibly due to sex hormonal interactions [26]. Elevated SUA levels and the incidence of hypertension is exceedingly rare in women during the fertility phase, but rises with menopause, potentially explained by an effect of oestrogen on SUA renal handling [27].

In our study, chronic kidney disease (CKD) was the highest risk factor for RH. CKD is very frequently associated with RH as a risk factor or comorbidity, and suggests an impaired prognosis in hypertensive subjects with RH [28]. In patients with CKD, RH is a common condition due to a combination of factors including sodium retention and volume expansion, increased activity of the renin-angiotensin system, and enhanced activity of the sympathetic nervous system [29]. On the other hand chronic hyperuricemia seems to be associated with a greater risk of arterial stiffness in women but not in men [30]. We postulate that when it coexists with CKD is likely to promote a vascular remodelling leading RH (Fig. 1).

Finally, among a small proportion of subjects the prevalence of uricosuric treatment was higher in those without than with hyperuricemia, which explains in part the higher level of SUA detected in the latter. We speculate that uricosuric treatment improves BP and, as a consequence, reduces the prevalence of RH. In support of our hypothesis, the literature shows a trend toward improvement associated with administration of urate-lowering drugs, in particular for the xanthine oxidase inhibitors [31,32]. The demonstrated efficacy of urate-lowering therapy on outcomes other than gout flares leads to the consideration that treatment may be beneficial even in the absence of overt gout when hyperuricemia accompanies other clinical conditions, such as CKD or cardiovascular risk factors like RH. However to confirm this hypothesis, randomized clinical trials aimed at evaluating the effect of treatment of hyper-uricemia in reducing RH prevalence are mandatory.

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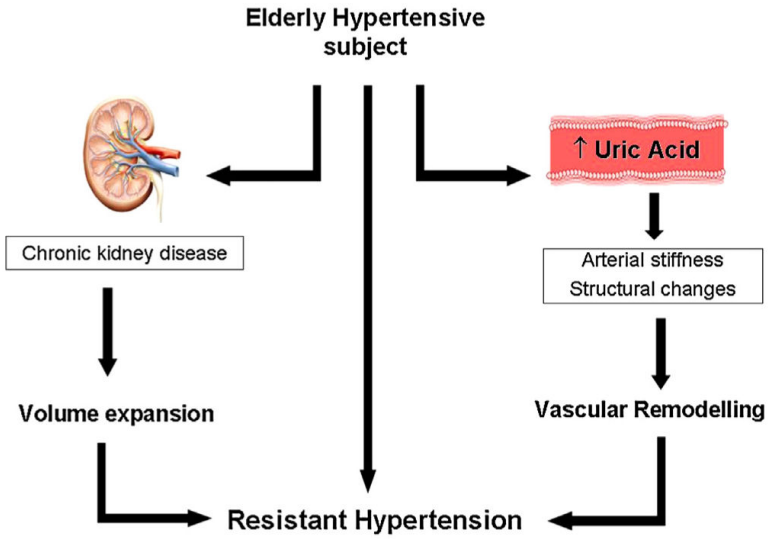

Fig. 1.

The proposed mechanisms supporting resistant hypertension development in the hypertensive elderly subjects are shown. Chronic kidney disease and hyperuricemia (i.e. serum uric acid ≥6.8 mg/dl) independently increase the risk of resistant hypertension by volume expansion (left side) and vascular remodelling respectively (right side).

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Table 1

General characteristics of the 580 unselected men and women stratified according to the presence of resistant hypertension (RH). BMI: body mass index. SUA: serum uric acid; SBP, DBP: systolic and diastolic blood pressure; HR: heart rate; TC, HDLC, LDL: total, high-density- and low-density-lipoprotein serum cholesterol; TG: serum triglycerides; ATH: anti-hypertensive; ABPM: ambulatory blood pressure monitoring. NS: non-significant difference.

Items	All subjects (n = 580)	Without RH (n = 547)	With RH (n = 33)	*p*-value
Age (yrs)	73.2 ± 4.8	73.1 ± 4.8	73.7 ± 5.2	NS
Female gender (%)	53.1	51. 6	78.8	<0.05
BMI (kg/m^2)	26.7 ± 3.7	26.7 ± 3.8	27.0 ± 3.0	NS
Obesity (%)	49.5	46.2	3.3	NS
SUA (mg/dl)	5.29 ± 1.4	5.26 ± 1.4	5.80 ± 1.6	<0.05
SUA >6.8 mg/dl (%)	20.3	17. 7	63.6	<0.05
Clinic BP values				
SBP (mmHg)	143.3 ± 18.4	141.3 ± 16.6	158.2 ± 4.7	<0.05
DBP (mmHg	79.6 ± 11.6	79.8 ± 11.6	77.1 ± 0.3	NS
HR (bpm)	71.8 ± 9.6	71.9 ± 9.5	71.2 ± 11.7	NS
24-h ABPM values				
SBP (mmHg)	137.9 ± 13.6	137.4 ± 13.7	146.6 ± 9.2	<0.05
DBP (mmHg)	76.8 ± 6.7	76.9 ± 6.7	75.7 ± 6.5	NS
HR (bpm)	71.2 ± 8.0	71.6 ± 8.2	68.1 ± 6.8	NS
Day-time SBP (mmHg)	141.1 ± 13.8	140.4 ± 13.8	151.6 ± 8.7	<0.05
Day-time DBP (mmHg)	78.8 ± 7.0	78.9 ± 7.2	90.2 ± 4.6	NS
Day-time HR (bpm)	73.2 ± 8.2	73.4 ± 8.1	70.0 ± 7.7	NS
Night-time SBP (mmHg)	126.5 ± 16.4	126.5 ± 16.6	128.7 ± 11.1	NS
Night-time DBP (mmHg)	70.0 ± 8.4	70.1 ± 8.5	67.9 ± 7.5	NS
Night-time HR (bpm)	64.5 ± 8.6	64.4 ± 8.6	64.0 ± 8.1	NS
Diuretic treatment (%)	23.8%	19.2%	10 0	<0.05
Number of ATH-drugs	1.0 ± 1.24	0.8 ± 0.9	4.2 ± 0.5	<0.05
Serum glucose (mg/dl)	102.1 ± 25.1	102.6 ± 25.4	104.4 ± 18.6	NS
Diabetes (%)	18.8	18.5	24.2	NS
Serum creatinine (mg/dl)	0.92 ± 0.32	0.92 ± 0.34	0.99 ± 0.31	NS
eGFR (ml/min)	68.3 ± 16.8	62.2 ± 16.7	60.1 ± 16.9	<0.05
Uricosuric drugs (%)	9.4	13.4	4.2	<0.05
Proteinruia (%)	14.3	11. 6	17. 8	NS
LVH (%)	45	38.7	52.6	<0.05
TC (mg/dl)	206.4 ± 70.6	200.6 ± 72.1	210.8 ± 41.2	NS
HDLC (mg/dl)	61.2 ± 16.0	61.3 ± 16.2	60.1 ± 14.3	NS
TG (mg/dl)	114.4 ± 63.6	113.3 ± 64.4	133.2 ± 45.4	<0.05
LDCL (mg/dl)	120.1 ± 33.7	120.5 ± 33.6	121.5 ± 34.5	NS
Smoking (%)	6.7	6.9	3.0	NS
Ethanol (g/week)	28.4 ± 21.9	27.44 ± 20.0	29.2 ± 23.5	NS

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Table 2

Multivariate logistic regression analysis for resistant hypertension by gender. CKD: chronic kidney disease. Other abbreviations as in Table 1.

Items	Wald	Coefficient (SE)	p value	Odds ratio	95% confidence intervals
Women (n = 308)					
CKD (yes/no)	7. 71	1.35 (0.48)	0.005	3.89	1.49–10.1
SUA >6.8 mg/dl (yes, no)	4.32	1.13 (0.54)	0.038	3.11	1.06–9.10
Diabetes (yes/no)	0.76	0.44 (0.54)	0.383	1.61	0.55–4.72
LVH (yes, no)	0.65	0.35 (0.43)	0.423	1.41	0.61–3.2
Age (years)	0.43	0.09 (0.34)	0.509	1.13	0.89–1.36
Obesity (yes, no)	0.14	−0.20 (0.55)	0.707	0.81	0.27–2.42
Diuretics (yes, no)	0.12	1.01 (0.32)	0.246	1.24	0.83–2.89
Men (n = 272)					
CKD (yes/no)	2.71	1.27 ±0.772	0.099	3.59	0.78–16.2
SUA >6.8 mg/dl (yes, no)	0.49	0.51 ±0.722	0.481	1.66	1.06–9.1
Diabetes (yes/no)	0.41	0.36 ±0.761	0.629	1.44	0.32–6.4
LVH (yes, no)	0.36	−0.42 ± 0.69	0.574	0.65	0.16–2.52
Diuretics (yes, no)	0.23	0.93 ± 0.46	0.416	1.02	0.76–3.10
Age (years)	0.03	0.09 ± 0.34	0.509	1.00	0.69–1.16
Obesity (yes, no)	0.04	−0.01 ± 0.74	0.954	1.19	0.27–6.6