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HYPERTENSION CAUSED WITH URIC ACID – THERAPEUTICAL MODALITIES

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The paper presents a patient who was first diagnosed with hypertension just a few days before developing gout. Hypertension occurred along with the hyperuricemia last year after curing the patient of gout. Hyperuricemia was initially symptomatic and manifested as gout; later it was without its specific symptoms but was always associated with hypertension. Just a month after correction of the patient's previous diet, the levels of uric acid and blood pressure were normal or at pre-hypertensive values. Our case supports the concept of the predictive role of uric acid in the genesis of essential hypertension and emphasizes the application of an adequate diet in the therapy of some forms of hypertension. *Acta Medica Medianae 2011;50(3):49-53.*

Key words: *hyperuricemia, hypertension, gout, diet*

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Introduction

Though it was more than a century ago, in 1879, when Frederick Akbar Mohamed demonstrated the association between levels of uric acid and essential hypertension, there are still discussions in the literature about whether uric acid is a cause of hypertension or a secondary phenomenon (1).

Today, we know that hyperuricemia is commonly encountered in patients with essential hypertension and is considered as a risk factor for morbidity and mortality associated with hypertension and ischemic heart disease (2).

In our paper, we present a 43-year-old patient with essential hypertension and a small number of risk factors (HLP, BMI 26.3 kg/m^2) in which annual monitoring determined a directly proportional relationship between uric acid levels and the degree of hypertension.

Case report

In the early morning on the control medical examination of a 43 year-old man, just before a 10km-long march, blood pressure values of 180/110 mmHg on the left arm and 170/120 mmHg on the right were measured, which by the latest classification of the 7th JNC (Joint National Committee) report belong to the second degree of hypertension. An ECG was done, in which there were no pathological changes. The patient had no symptoms and was visibly surprised, stating that it was the first time he had ever had high blood pressure. This was confirmed by his medical documentation.

Over the next two days, his blood pressure values were monitored, and according to the latest classification of hypertension, were from 10 to 20. On the third day after the first visit, the patient came to the medical office in the morning with characteristic symptoms and signs of gout and hypertension of 150/112 mmHg on the left arm and 162/121 mmHg on the right. The gout attack had started during the night while he slept, with severe pain and tenderness in the big toe of the left foot associated with swelling and erythema. He denied previous alcohol consumption. Again, the ECG showed no pathological changes.

The patient was discharged to rheumatologists, diagnosed with gout or suspected acute gouty arthritis, and his diagnosis was confirmed by ultrasound and laboratory findings. The laboratory findings revealed increased erythrocyte sedimentation rate values (42 mm/1h), cholesterol levels (7.25 mmol/l), triglyceride levels (1.85 mmol/l), CRP (9.6 mg/l) and uric acid (546 micromoles/l). The rheumatologist gave him diprofos i.m. and prescribed him acemetacin (rantudil forte) at a dose of 60 mg daily for the next 15 days. After those 15 days he started therapy with allopurinol 100 mg (1 tablet in the morning). At the time of starting treatment with allopurinol there were no signs and symptoms of gout, the level of uric acid in the blood was 520 micromoles/l and blood pressure values on the left and right hands were elevated (TAleft-160/112 mmHg, TAright-153/106 mmHg). Less than a month after allopurinol treatment, the uric acid level was within reference values (386 micromoles/l) and blood pressure values according to the new classification were at pre-hypertensive levels (TAleft -122/83 mmHg, TAright-

133/85 mmHg). These blood pressure values were maintained in the next two months during the therapy with allopurinol. However, a week after the discontinuation of allopurinol treatment, there was another jump in blood pressure (TAleft - 152/98 mmHg, TAright -158/110 mmHg) and the control laboratory tests revealed elevated uric acid of 529 micromoles/l. In the meantime, the patient was referred to the ophthalmologists, where it was determined that there were no hypertensive changes in the retina and the microcirculation was without pathological changes, which indicates that it was probably not one of the important causes of hypertension. Further, from the laboratory analysis, we tested the levels of thyroid hormones T3, T4 (total and free), thyroid-stimulating hormone, as well as the amounts of adrenaline, noradrenaline and dopamine in 24-hour urine. All these examined parameters were within the reference values. After that the patient was put on daily control of blood pressure in the morning and afternoon for the next five months, when the values ranged from 10 to 20 hypertension and values of periodic measurements of uric acid were within the limits of 500 to 600 micromoles/l. It was observed that higher blood pressure values correspond to higher values of uric acid in the blood and vice versa. Due to the presence of asymptomatic hyperuricaemia and hypertension, the patient was advised to strictly comply by dietary recommendations, which he did not do. Since the patient refused pharmacological anti-hypertensive therapy, he was advised to change the previous diet in order to reduce levels of uric acid. A month after the beginning of the new dietary regime, control examination showed that the level of uric acid and hypertension were within the reference values.

Change of diet was comprised of no more than two servings per week of red meat (beef, pork or lamb) as a main course, no more than two servings of seafood (tuna, white fish, shrimp, lobster, clams) weekly or daily intake of supplements of omega-3 fatty acids from plant sources, eicosapentaenoic or docosahexaenoic acids (EPA and DHA) instead of eating fish. An increased intake of dairy products was also advised, which includes 1 to 2 meals per day preferably with lower % of fat (0%-1.5%). Regarding alcohol, if there is already a habit, a moderate use of wine is recommended, that is 1 to 2 glasses per day. Beer and liquor were prohibited. The diet also prohibited the intake of foods with high fructose corn syrup, which is often used as a sweetener in the beverage industry, ice cream and so-called "light food", because fructose has a direct effect on uric acid metabolism and significantly increases its value after consumption. A frequent intake of fruits and vegetables rich in vitamin C (peppers, lemon, orange) was recommended because of its uricosuric effects.

Regular checks during the next three months established that there was no need for pharmacological anti-hypertensive therapy.

Discussion

Uric acid, a product of purine metabolism, is degraded in most mammals by the hepatic enzyme urate oxydase (uricase) to allantoin, which is largely freely excreted in the urine, and partly by the gastrointestinal tract. However, during the Miocene epoch (20 to 5 million years ago), two parallel but distinct mutations occurred in early hominoids that rendered the uricase gene non-functional. As a consequence, humans and the great apes have higher uric acid levels (>2mg/dl) compared with most mammals (<2 mg/dl) (2,3). It is believed that these mutations increased the likelihood of survival of hominoids, providing appropriate advantage in the Miocene period, when salt intake through diet was not sufficient. This theory is based on acute and chronic effects of uric acid in maintaining blood volume and increasing blood pressure. According to this theory, higher values of uric acid activate the renin-angiotensin system, inhibit the endothelial NO, and thus acutely increase Na+ reabsorption and blood pressure through systemic and renal vasoconstriction (3-5). This increase in blood pressure is initially resistant to salt intake. Later, due to the stimulating effect of uric acid on the proliferation of smooth muscle cells of blood vessels, endothelial dysfunction and inflammation, arteriolar kidney disease develops, with the infiltration of macrophages and T-cells into the kidney parenchyma, and leads to substantial microvascular renal disorder (artheriosclerosis), which in turn leads to renal ischemia and salt-sensitive hypertension as a chronic effect of uric acid. With this theory, we might explain the mechanism by which uric acid causes hypertension nowadays when salt intake is more than sufficient (1,3,6-8).

In humans, uric acid levels vary significantly as a result of factors that increase its creation (high intake of purines, alcohol, fructose) or reduce its excretion. Hyperuricemia is defined as a concentration of uric acid in the blood >7 mg/dl (416 micromoles/l) in men and >6 mg/dl (357 micromoles/l) in women (2). Because a large number of patients have hyperuricaemia but do not have gout (9), many authors do not consider hyperuricemia as a significant risk factor for cardiovascular or renal diseases (1). However, recent experimental studies suggest that elevated uric acid is one of the most important risk factors for cardiovascular disease, including hypertension (1,9-12). Johnson and Heinig found that rats develop high blood pressure 3 to 5 weeks after they mildly raise their uric acid level by giving them an inhibitor of uricase oxonic acid (13). If the effect continues over time, it occurs independently of hypertension and renal microvascular disease (14). Studies in humans with asymptomatic hyperuricemia have shown a significant association with hypertension, obesity, metabolic syndrome, kidney and cardiovascular diseases. Hyperuricemia

has now been found to be an independent risk factor for hypertension in several studies in humans (1). Uric acid levels higher than 5.5 mg/dl (328 micromols/l) were found in 89% of untreated adolescents with essential hypertension, but in 0% of controls (15).

A prospective study was conducted by Zhang, Sun et al. with 7.220 participants who were free from hypertension at study entry in 1999-2000. At four-year follow up, 19% of men and 11% of women developed hypertension. The authors concluded that there is a positive association between plasma uric acid concentration and the incidence of hypertension and blood pressure progression during the four-year follow-up. One limitation of this study is the lack of information on diet and drinks (such as beer), which can influence the uric acid concentrations and thus may also contribute to hyperuricemia (16). In a recent retrospective evaluation of a subset of the Framingham Heart Study - young and middle-aged adults who have never been hypertensive - it was found that the serum uric acid level was an independent predictor of incident hypertension and blood pressure progression over as few as four years. A recent analysis of the Bogalusa Heart Study has found that childhood uric acid and increase in uric acid from childhood to adulthood are both independent predictors of adult hypertension (17). It is possible that treating hyperuricemia may be effective in lowering blood pressure when hyperuricemia has not been present for a long period (such as in children with hypertension or adults with recently diagnosed hypertension) or when subjects are given a low salt diet (which would remove the renal injury-dependent mechanism) (2).

Besides the established effects of uric acid in rat models, uric acid also stimulates the proliferation of human vascular smooth muscle cells in tissue culture experiments (with higher doses leading to higher degrees of proliferation) (4,18) and induces the expression of CRP even in physiological values (in our case, CRP is 9.6 mg/l) (19). Uric acid enters human aortic vascular smooth muscle cells via the organic anion transporter (OAT) URAT-1, which is expressed in the non-stimulated and uric acid stimulated (6h) human aortic VSMC, as assessed by RT-PCR. Hence, except in the kidney, the organic anion transporter (OAT)URAT-1 has a more generalized expression in human VSMC (20). There is also evidence that elevated uric acid may potentiate the effects of angiotensin II to induce renal vasoconstriction, which could possibly be mediated by its effect to up-regulate angiotensine type 1 receptors on VSMC (vascular smooth muscle cell) (21). These findings provide strong support to the theory mentioned earlier about the effect of uric acid on the human organism.

A group of American scientists (Mazzali, Monilda et al) developed an animal model of mild hyperuricemia by giving oxonic acid to rats. This model showed that systolic blood pressure (SBP) directly correlated with serum uric acid levels and a 1mg/dl (59,485 micromols/l) change in uric acid was associated with a 30 mmHg to 40 mmHg increase in blood pressure. They concluded that this effect was primarily a result of hyper-uricemia-induced arteriolopathy and not secondary to hypertension (14). Another animal model developed by Feig, Mazzali et al. confirmed that an increase in blood pressure is linearly related to the rise in uric acid (r_0.77) (22).

Results from a very small, unblinded pilot study in children suggested that uric acid may contribute directly to the onset of hypertension in some humans. Five children aged 14 to 17 years, with newly diagnosed and as yet untreated essential hypertension, were treated for one month with allopurinol as a solitary pharmacologic agent. All five children had a decrease in BP by both casual and ambulatory monitoring, and four of the five were normotensive at the end of the 1st month. All five also had a rebound in their BP after discontinuation of the therapy (22). Sundstrom, Sullivan et al. examined the relationship of serum UA (uric acid) to longitudinal BP tracking in a large community-based sample of non-hypertensive individuals. They found that serum UA was positively associated with longi-tudinal BP tracking at short-term follow-up (four years). In the subgroup of individuals with optimal BP and normal kidney function at baseline, they observed an association of UA with BP progression (23). To date, fourteen prospective studies in adults and adolescents have examined this association; of these, twelve studies have documented a direct association with either incident hypertension or increase in BP (24). Nakanishi et al. found that the association between UA and hypertension was stronger among leaner men (<30 kg/m^2) (25). In a prospective cohort study by Forman, Choi and Curhan concluded that plasma uric acid level was not associated with incident hypertension in older men (>60yr); however, this phenomenon is possible in younger population (26). Krishnan, Kent et al. concluded that hyperuricemia increases the risk of developing hypertension by 80%, independent of baseline blood pressure measurements, renal function, serum lipid levels, body mass index, proteinuria, alcohol use and age (27). If hyperuricemia precedes the development of hypertension, then it cannot simply be a secondary phenomenon (28).

That modern diet has a significant impact on serum uric acid has been confirmed in a recent study, which prospectively examined over a 12-year period the relationship between dietary risk factors and incident gout in 47.150 male participants (the Health Professionals Follow-up Study [HPFS], 730 incident gout cases) with no history of gout at baseline. The study confirmed some of the long-standing suspicions about increased levels of serum uric acid (red meat, seafood, beer, liquor), exonerated others (wine and purine-rich vegetables), and also identified potentially new protective factors (dairy products) (29). Our patient was recommended a change in diet accordingly to new healthy eating guideline pyramid corrected with the findings of this 12-year prospective study.

Conclusion

Our case supports the concept of the important role of uric acid in the genesis of hypertension and imposes the need, when it comes to hypertensive patients, for a careful selection of laboratory tests, which would include determining the concentration of uric acid in the blood.

Our case also suggests that in the treatment of essential hypertension, non-pharmacologic measures should be given an appropriate chance.

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HIPERTENZIJA UZROKOVANA HIPERURIKEMIJOM – MODALITETI LEČENJA

Bojan Stošić i Ivana Tufegdžić

Prikazan je bolesnik kod koga je prvi put dijagnostikovan povišen krvni pritisak nekoliko dana pre razvoja gihta. Hipertenzija se zajedno sa hiperurikemijom održava godinu dana posle izlečenja gihta. Hiperurikemija je u početku bila simptomatska i manifestovala se pojavom gihta a kasnije se održava bez pratećih simptoma karakterističnih za ovo oboljenje ali sve vreme praćena hipertenzijom. Mesec dana nakon korekcije dotadašnjeg režima ishrane, nivoi mokraćne kiseline u krvi i krvni pritisak vraćaju se na normalne ili prehipertenzivne vrednosti. Naš slučaj podržava koncept o prediktornoj ulozi mokraćne kiseline u genezi esencijalne hipertenzije i ističe primenu adekvatnog režima ishrane u terapiji određenih oblika hipertenzije. *Acta Medica Medianae 2011;50(3):49-53.*

***Ključne reči**: hiperurikemija, hipertenzija, giht, ishrana*