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Kidney

Methylenetetrahydrofolate Reductase Gene Polymorphisms in Essential Hypertension

Relation With the Development of Hypertensive End-Stage Renal Disease

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Background: The pathogenesis of hypertensive nephropathy is multifactoral and in addition to BP, other factors contribute to the development of this renal pathology and its progression to end-stage renal disease. These include genetic predisposition and increased pleasure level of homocysteine-intermediate protein catabolism product known to induce kidney injury. The 677C → T polymorphism in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene is associated with elevated homocysteine level in the general population, and therefore it has been hypothesized to be a risk factor for the development of renal failure in the course of essential hypertension.

Methods: In this case-control, cross-sectional study the frequency of the *MTHFR* 677C → T and the 1298A → C polymorphism was compared between patients with hypertension-related chronic renal failure ($n = 90$), patients with essential hypertension without kidney injury ($n = 90$), and healthy individuals ($n = 90$) who were matched for age and gender. In addition, the influence of these polymorphisms on homocysteine concentration in individuals with essential hypertension was examined.

Results: The frequency of the *MTHFR* 677 TT genotype did not differ between groups (4.5%, 12.3%, and 11.1%, respectively). Patients with hypertension and the 677TT genotype showed significantly higher homocysteine levels as compared to individuals having CC and CT. In the multivariate correlation analysis the *MTHFR* 677TT genotype ($P < .01$; $\beta = 0.27$), age ($P < .001$; $\beta = 0.33$), and body mass index ($P < .01$; $\beta = 0.3$) were independent predictors for total homocysteine level.

Conclusions: Plasma homocysteine levels in individuals with essential hypertension is affected by the *MTHFR* 677C → T polymorphism. However, we did not prove the hypothesis that *MTHFR* 677C → T influences the risk of development of renal failure in the course of hypertension. Am J Hypertens 2005;18:1442–1448 © 2005 American Journal of Hypertension, Ltd.

Key Words: Essential hypertension, hypertensive nephropathy, homocysteine, MTHFR, polymorphism.

Essential hypertension can cause renal injury and this pathology is commonly described in the literature as hypertensive nephropathy (HN) or hypertensive kidney disease.[1] There are a number of reasons to believe that the nature of HN is heterogeneous and many other factors in addition to high blood pressure (BP) are implicated in the development of HN and progression to end-stage renal disease.[2]

Genetic factors are believed to be at least partially responsible for renal complications in patients with essential hypertension. Several animal experiments provided evidence that genetic factors could determine the susceptibility to hypertension-related kidney damage.[3–5] Clinical observations also provided arguments for the hypothesis of a genetic background of HN. As compared to whites, hypertension in African-Americans occurs earlier, is more severe, and more

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often causes chronic renal failure (crf), even after adjustment for severity of hypertension.[6,7] Furthermore, familial clustering of hypertensive crf has been demonstrated both in African-Americans[8] and in whites.[9]

Candidate kidney susceptibility genes include the genes linked to the renin-angiotensin-alodsterone system, genes encoding paracrine, and autocoid agents that influence endothelial and smooth muscle response to increased pressure and blood flow in the afferent arterioles, as well as genes for cytokines and other factors that have been implicated in the inflammatory and fibrotic processes that occur in the nephrosclerotic kidneys.[2] A few genes have been examined so far, but only the angiotensin-1 converting enzyme insertion/deletion (I/D) polymorphism is believed to be associated with increased risk of renal complications in patients with essential hypertension.[10,11]

Hyperhomocysteinemia is considered as an independent risk factor for cardiovascular diseases.[12] It is also present more frequently in patients with essential hypertension than in those without increased BP.[13] Of note, animal studies suggest that hyperhomocysteinemia may contribute to the development and progression of HN, independent of arterial pressure.[14] Given these findings and the fact that homocysteine plasma level is believed to be under genetic control, one may hypothesize that genes determining homocysteine plasma concentration may contribute to the progression of HN to crf. The natural candidate for such a hypothetical susceptibility gene is the gene encoding 5,10-methylenetetrahydrofolate reductase (MTHFR), an enzyme involved in the metabolism of homocysteine, more precisely in the process of remethylation. Two common polymorphisms exist in MTHFR. *MTHFR* 677C → T and *MTHFR* 1298A → C cause a significant reduction in enzyme activity.[15,16] In the present study we addressed the hypothesis that these polymorphisms may be associated with a greater susceptibility to the development of hypertension-related crf.

Methods

Study Design

We performed a case-control, cross-sectional explorative study to examine the association of *MTHFR* 677C → T and *MTHFR* 1298 A → C with hypertension-related crf. The primary end point was the difference in the frequency of the *MTHFR* 677C → T polymorphisms (2 alleles, 3 genotypes) among patients with hypertension-related crf, patients with long-lasting primary hypertension without kidney injury, and healthy subjects. The secondary end point was the difference in the frequencies of the *MTHFR* 1298A → C genotypes (2 alleles, 3 genotypes) between these groups. The study was also aimed to examine the association between *MTHFR* 677C → T and *MTHFR* 1298A → C polymorphisms and homocysteine plasma level in patients with primary hypertension.

Patients

The study population included the case group containing persons with hypertension-related crf, and two control groups containing either subjects with essential hypertension without kidney injury or healthy subjects. The patients of the case group were recruited between July 2002 and September 2003 from all patients at three dialysis centers in Austria (University of Vienna Medical School, Mistelbach, and Wels), and in six dialysis centers in Northern Poland (Medical University of Gdansk, Medical University of Bydgoszcz, Dialysis Units: Elblag, Zaspa, Olsztyn, Slupsk), as well as in the outpatient service of the Division of Nephrology and Dialysis, at the University of Vienna Medical School, and in the Department of Nephrology, at the Medical University of Gdansk. A detailed retrospective analysis of the medical history concerning the period before the development of chronic kidney disease was performed. The inclusion criteria were as follows: 1) long-lasting primary hypertension preceding any evidence of kidney disease (minimum of 10 years); 2) presence of another hypertension-related organ damage (ie, left ventricular hypertrophy or hypertensive retinopathy); 3) family history of primary hypertension (first degree relative); 4) presence of proteinuria below 2.0 g/24 h; 5) normal urine sediment in the medical history, 6) no signs of chronic pyelonephritis in ultrasound evaluation; 7) equal kidney size in ultrasound evaluation (the size difference no greater than 10 mm); and 8) at the time of the evaluation, crf defined as the presence of plasma creatinine level above 2 mg/dL, chronic dialysis maintenance, or status post-renal transplantation. Patients whose medical history was not enough detailed to answer these questions were excluded. Finally, 90 patients fulfilled the inclusion criteria. Nineteen patients have had a diagnosis of HN confirmed by morphological evaluation. The histological diagnosis of hypertensive nephroangiosclerosis was established on the basis of standard criteria, that is, when there was clear evidence of the involvement of medium- and small-sized renal vessels (evidence of myointimal hypertrophy, reduplication of the internal elastic lamina, media hypertrophy, and presence of hyaline eosinophilic deposits in the arterial wall).[2]

The first control group included 90 age-, sex-, and country of origin-matched patients with primary hypertension diagnosed according to WHO recommendations. The controls were recruited from patients who attended the Vienna Institute of Hypertension and General Practitioners Center (Jaskolcza) in Gdansk. The inclusion criteria were as follows: 1) primary hypertension lasting a minimum of 10 years; 2) family history of primary hypertension (first degree relatives); 3) normal renal function; 4) normal urine sediment; 5) absence of proteinuria; 6) absence of microalbuminuria (ie, urine albumin level <17 mg/g creatinine for men and <25