学 位 論 文 の 要 旨

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学　位　論　文　名　Evaluation of Asymmetric Dimethylarginine and Homocysteine in Microangiopathy-Related Cerebral Damage.

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論 文 内 容 の 要 旨

INTRODUCTION

Lacunar infarction and white matter hyperintensity (WMH) are cerebrovascular disorders often found in the elderly. They frequently occur concomitantly and are known to share common risk factors, i.e., aging and hypertension. As the two entities might well share a common etiology, the combined entity of small-vessel disease or microangiopathy-related cerebral damage (MARCD) has been proposed to integrate them. The nitric oxide (NO) has attracted much attention because it was thought not only to regulate cerebral blood flow but also to prevent arteriosclerosis by inhibiting fibrosis and the proliferation of smooth muscle cells in the arterial wall. Recently, much attention has been paid to asymmetric dimethylarginine (ADMA), a unique endogenous inhibitor of the NO synthases (NOS). A higher level of ADMA was reported to be associated with coronary artery diseases, hypertension, atherosclerosis, and cerebrovascular diseases. Considering the functional significance of NO *in vivo*, we hypothesized that ADMA was a good candidate for

a risk factor for MARCD. Hyperhomocysteinemia has been recognized as a risk factor for atherosclerosis. In the study of cerebrovascular diseases, a high total homocysteine (tHcy) level has been reported to be a risk factor not only for atherothrombotic infarction but also for MARCD. Concerning the pathophysiology of hyperhomocysteinemia in MARCD, recent studies pointed out the possibility that the deleterious effects of homocysteine on the cardiovascular system were mediated through ADMA. All the observations above lead us to perform a cross-sectional study to examine a hypothesis that ADMA and tHcy levels were associated with MARCD.

MATERIALS AND METHODS

Seven hundred and twelve consecutive participants (401 males and 311 females) who voluntarily visited the Shimane Institute of Health Science for a health screening examination between 2000 and 2003 were recruited into the study. Histories of smoking, hypertension, diabetes mellitus and hypercholesterolemia were obtained through an interview. Participants were considered to have these diseases when they had been already diagnosed by medical doctors. Venous blood was collected after overnight fasting. Plasma was separated within 30 min of the blood being drawn and kept frozen at -80°C until the measurement of fasting blood glucose (FBG), L-arginine (Arg), symmetric dimethylarginine (SDMA), ADMA, and tHcy. Total cholesterol (T-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were measured in the serum. The plasma Arg, SDMA and ADMA concentrations were measured with high performance liquid chromatography. The total homocysteine (tHcy) concentration was measured using a commercial kit. Diagnosis of MARCD : WMH and lacunar infarction were diagnosed and rated on T2-weighted MR images (0.2T, Siemens). As the participants with lacunar infarction showed no apparent signs or symptoms due to the lesions, they were all categorized into the 'silent' lacunar infarction (SLI). WMH was graded according to Fazekas et al. Subjects with MARCD were defined as those with SLI and/or WMH grade≥2 . A hundred and forty-six participants were categorized as MARCD (+). The statistical analysis was performed with JMP v.6 (SAS Institute, Cary, NC, USA).

Because of a skewed distribution, TG, FBG, tHcy, and Arg/ADMA were analyzed after log-transformation.

RESULTS AND DISCUSSION

The ADMA ($P < 0.001$) and SDMA level ($P < 0.05$), and the Arg/ADMA ratio ($P < 0.01$) differed significantly between MARCD (+) and (-) according to nonparametric Wilcoxon test, while the tHcy level did not ($P = 0.37$). Classical risk factors such as age, blood pressure, and the presence of hypertension differed significantly between the two groups as well. There was no significant correlation between tHcy and ADMA, Arg, or Arg/ADMA in the present study. By contrast, SDMA showed a modest but significant correlation with tHcy (r=0.15, P <0.001). Estimated GFR (eGFR) showed significant inverse correlations with tHcy (r =−0.20, P <0.001) and with SDMA (r= −0.50, P <0.001). In the logistic analysis, the association of Arg/ADMA with MARCD remained significant [odds ratio and 95% confidence interval, 0.19 (0.05, 0.73), $P < 0.05$] even after adjusting for the effects of age and hypertension. This observation supported the pathological role of ADMA in this disease entity. In contrast to ADMA, tHcy did not have a significant association with MARCD in the population we studied. The tHcy level showed a significant correlation both with SDMA and with eGFR. This suggested that tHcy was substantially influenced by the renal function. Careful evaluation of renal function and other confounding factors may be essential when examining the effects of tHcy in clinical and epidemiological studies.

CONCLUSIONS

In the present study, we reported that Arg/ADMA, but not tHcy, is associated with MARCD in a Japanese population. Studies on the pathological role of ADMA in MARCD as well as large-scale prospective studies would be warranted.