Tissue Plasminogen Activator –7351C/T Polymorphism and Lacunar Stroke

To the Editor:

Jannes et al reported that a polymorphism in the tissue plasminogen activator (tPA) gene (−7351C/T) was associated with ischemic stroke in an Australian population. Stratification for stroke subtype demonstrated an association with lacunar infarction (OR: 2.7; 95% CI, 1.1 to 6.7), but not with other stroke subtypes. The authors interpreted this result as providing evidence that fibrinolytic factors play an important role in maintaining small vessel patency. The polymorphism is located within the binding site for the transcription factor Sp1, in the enhancer region of the tPA gene, and the TT genotype has been associated with significantly reduced vascular tPA release rates.

This association could give clues to the pathogenesis of lacunar stroke, but first replication in independent populations is important, particularly because the original association was found in a small sample size, with only 43 patients in the lacunar subgroup. Therefore, we attempted to replicate it in a prospectively collected group of patients with well-phenotyped lacunar stroke. In addition, we determined whether the polymorphism predisposed to 1 particular type of lacunar stroke. It has been suggested that patients with larger lacunar infarcts (isolated lacunar infarction [ILI]) without leukoaraiosis may have microatheroma at the origins and proximal portions of the perforating arteries. In contrast, patients with lacunar infarction and confluent leukoaraiosis (ischemic leukoaraiosis [ILA]) may have a diffuse arteriopathy affecting the smaller perforating vessels. Previous studies have suggested different genetic associations in the 2 groups.

Three hundred and twelve consecutive white patients presenting with lacunar stroke attending participating stroke services were recruited. Lacunar stroke was defined as clinical lacunar syndrome with accompanying lesion on MRI or CT. All patients had brain imaging and imaging of the carotid arteries with duplex or MR angiography. Patients with subcortical lesion ≥1.5 cm in diameter, cortical infarction of any size, a potential cardioembolic source and large-vessel disease defined as carotid, vertebral, or basilar intracranial artery stenosis ≥50% were excluded. Two hundred and twenty-six (72%) had MRI and 86 (28%) had CT.

The principal center consecutive patients with lacunar stroke were recruited regardless of the presence of leukoaraiosis. To increase the number of cases with ischemic leukoaraiosis, in 4 additional centers, consecutive patients with ischemic leukoaraiosis were recruited. Patients were divided into 2 groups: ILI (absent/mild leukoaraiosis) or ILA (moderate/severe leukoaraiosis) according to a previously validated method. Six hundred and twenty-six age- and sex-matched controls free of symptomatic cerebrovascular disease were recruited by sampling family doctor lists from the same geographic locations as the patients. The study protocol was approved by local research ethics committees and informed consent was obtained from all participants. Genotyping was performed blinded to subtype diagnosis and case/control status.

DNA was isolated from blood samples using a commercial kit (Nucleon), and a 366bp region of DNA surrounding the tPA –7351C/T polymorphism was amplified using PCR. Digestion with Ban II restriction endonuclease produced 1 of 2 characteristic sets of fragments, depending on the presence of a C or a T allele at the SNP. The restriction fragments were separated on a 2% Micro ABagarose gel.

Results were obtained for 611(98%) controls and 301(96%) cases. The genotypes distribution was in Hardy-Weinberg equilibrium (P=0.051). There was no association between the TT genotype and lacunar stroke before or after adjustment for age, gender, hypertension, diabetes, and smoking (before adjustment OR: 0.761; P=0.206; 95% CI, 0.499 to 1.162; after adjustment OR: 1.343; P=0.187; 95% CI, 0.866 to 2.084). This was also true for both subtypes (ILI before adjustment OR: 0.796; P=0.433; 95% CI, 0.451 to 1.406; after adjustment OR: 1.141; P=0.666; 95% CI, 0.626 to 2.081; ILA OR: 1.347; P=0.280; 95% CI, 0.785 to 2.310; after adjustment OR: 1.413; P=0.234; 95% CI, 0.800 to 2.497).

In conclusion, this study does not support the tPA polymorphism being a risk factor for lacunar stroke. It is most likely that the original association was a false-positive attributable to small sample size.

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