INVITED EDITORIAL

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SERPINE1 and MTHFR variants: key targets in the search for genetic determinants in ESUS?

Anetta Lasek-Bal

Medical University of Silesia, Katowice, Poland

The concept of embolic stroke of undetermined source (ESUS) was introduced to provide a well-defined diagnostic evaluation in patients with cryptogenic stroke (CS) [1]. ESUS is diagnosed when a ischemic stroke (IS) is identified as non-lacunar and no definitive cause of IS can be determined following a comprehensive standardized diagnostic evaluation. Such evaluation includes brain imaging, 12-lead electrocardiogram, transthoracic echocardiogram, a minimum of 24 hours of cardiac monitoring, and vascular imaging. While CS and ESUS are distinct entities by definition, it is important to emphasize that the majority of patients with CS also fulfill the criteria for ESUS. The use of advanced cardiac monitoring techniques, organ and vessel imaging, and molecular studies in ESUS patients enables us to determine stroke etiology in at least 59% of them [2, 3]. Since the average age of ESUS patients is lower than that of the general stroke patients, it is suggested that genetic factors play a more significant role in ESUS.

Genetic susceptibility to IS may be influenced by specific polymorphic variants that encode the markers of hemostasis and/or endothelial function, such as Factor V Leiden, Factor II G20210A, MTHFR, and genetic variants of SERPINE1. All these variants represent key targets in the search for genetic determinants in ESUS patients.

Plasminogen activator inhibitor-1 (PAI-1), a serine protease inhibitor, is a crucial regulator of the fibrinolytic system [4]. Under normal physiological conditions in healthy individuals, serine protease inhibitor, clade E, member 1 (SERPINE1) is essential for fibrinolysis, as well as angiogenesis and cell migration [4, 5]. Therefore, the SERPINE1 gene is a promising candidate to be investigated in terms of its role in the etiology of stroke. The gene is highly polymorphic. The c.-820G[(4_5)] variant regulate the biosynthesis, thereby influencing the circulating levels of PAI-1 [6]. The SERPINE1 gene polymorphism is based on four (4G) or five (5G) guanine nucleotide repeats, depending on the allele. Both the 4G and 5G alleles bind a protein that activates gene transcription. However, the 4G allele also binds to a repressor protein, leading to transcription inhibition. It was suspected that the 4G allele was associated with an elevated PAI-1 production and an approximately double risk of thrombosis [7–9].

Following a stroke of various etiologies, elevated FVIII activity is more often found in SERPINE1 c.-820G[(4_5)] carriers than in those who have not experienced a stroke [10, 11] Klajmon A et al. confirmed the associations between SERPINE1 variants and increased FVIII levels in ESUS patients [12]. What more, in their current study ESUS patients with the variants of SERPINE1 c.-820G[(4_5)] and MTHFR C665T were characterized by elevated Lp(a) and more prothrombotic fibrin clot phenotype compared to patients with the wild type SERPINE1 c.-820G[(4_5)] and mutant MTHFR C665T.

The methylenetetrahydrofolate reductase enzyme (MTHFR) plays a significant role in homocysteine metabolism by participating in the transformation of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is required for the conversion of homocysteine to methionine [13].

The MTHFR A1298C and MTHFR C677T polymorphisms influence the MTHFR enzyme. The substitution of cytosine by thymine at position 677 of the MTHFR gene (the C677T polymorphism) decreases enzyme activity leading to hyperhomocysteinemia in homozygotes. [5] Hyperhomocysteinemia is considered to be a weak risk factor for thrombotic events [5, 14]. Despite the suggested multidirectional adverse effects of excessive homocysteine levels on the endothelium, platelets and coagulation factors, the association between the C677T variant and thrombosis is quite controversial due to discrepancies in study results [5, 15–19]. A meta-analysis revealed that the MTHFR C677T mutation raised the risk of stroke by nearly 1.5 times in individuals aged over 18 years [18]. Among individuals older than 65, carriers of the MTHFR C677T allele also exhibit a significantly elevated risk of stroke [19].

Address for correspondence: Anetta Lasek-Bal, Medical University of Silesia, Katowice, Poland; e-mail: abal@sum.edu.pl
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The MTHFR C677T polymorphism was more frequently associated with early deterioration of neurologic status in stroke patients, which may indicate potential gene-environment interactions [20].

In a recent study, the MTHFR A1298C polymorphism showed an association with fibrin clot properties but was not associated with stroke, whereas the MTHFR C677T polymorphism was linked to an increased risk of stroke [21]. The molecular coincidence MTHFR C677T polymorphism and SERPINE1 c.-820G[(4_5)] variant in ESUS patients presented by Klajmon and al. may implicate new stroke prevention strategy in these patients [12].

According to the current guidelines, the antiplatelet therapy is recommended for all ESUS patients. However the subgroups of them can benefit specifically from anticoagulation therapy. Implantable cardiac monitoring seems effective to increase anticoagulant initiation and to lower stroke recurrence rates in patients with ESUS [22].

Further studies are needed to elucidate whether SERPINE1 and MTHFR variants carriers following ESUS might benefit from long-term anticoagulant treatment. The young ESUS patients who have risk factors for atherosclerosis but do not exhibit significant stenosis in carotid and cerebral arteries can be good candidates for SERPINE1 and MTHFR polymorphisms assessment.

While the tests to examine variants of a single gene may be of limited or little use, integrated results of genetic screening for congenital and acquired risk factors related to the coagulation system may prove more valid and useful.

Understanding the prevalence of genetic variants in ESUS patients may aid clinicians in managing these patients from both diagnostic and prognostic perspectives.

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