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Plasminogen Activator Inhibitor-1 (PAI-1) Gene Polymorphism and Its Clinical Significance in Ischemic Stroke

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ABSTRACT

Plasminogen activator inhibitor-1 (PAI-1) is the primary physiological inhibitor of tissue-type (t-PA) and urokinase-type (u-PA) plasminogen activators, which play a central role in fibrinolysis. Genetic polymorphisms in the PAI-1 gene, particularly the common 4G/5G variant in its promoter region, have been associated with altered plasma PAI-1 levels and susceptibility to thrombotic events. This study investigates the relationship between PAI-1 4G/5G polymorphism and ischemic stroke (IS) in patients under the age of 50, with a focus on its role as a risk factor compared to other inherited thrombophilias.

Abbreviations: IS: Ischemic Stroke; PAI: Plasminogen Activator Inhibitor; u-PA: Urokinase-Type; t-PA: Tissue-Type; IS: Ischemic Stroke; GCS: Glasgow Coma Scale; mRS: Modified Rankin Scale; BI: Barthel Index; PTE: Pulmonary Thromboembolism

Introduction

The fibrinolytic system is a key regulator of thrombus resolution, where plasminogen activators convert plasminogen into plasmin, leading to fibrin degradation. PAI-1 inhibits this process, thereby contributing to a prothrombotic state when excessively expressed. Elevated PAI-1 levels have been linked to ischemic stroke (IS), with both genetic and environmental determinants, including triglyceride levels. The 4G allele of the PAI-1 4G/5G polymorphism has been reported to increase transcriptional activity, leading to higher circulating PAI-1 concentrations and impaired fibrinolysis.

Materials and Methods

A prospective study was conducted among 101 patients aged 18–50 years admitted with a first ischemic stroke to Tokuda Hospital, Sofia, between 2010 and 2017. A control group of 69 individuals of similar age, without history of stroke but evaluated for thrombophilia due to venous thromboembolism, was included. Genetic testing for common thrombophilia markers, including PAI-1 4G/5G, MTHFR C677T, MTHFR A1298C, and prothrombin G20210A, was performed. Stroke severity was assessed with the NIH Stroke Scale (NIHSS), Glasgow Coma Scale (GCS), modified Rankin Scale (mRS), and Barthel Index (BI).

Results

Comparison and Analysis of Thrombophilia Factors Between Controls and the Patient Group

The thrombophilia factors in both groups of patients were analyzed, and their role in relation to MI was also determined. Among patients with IS, the highest percentage of heterozygous carriers of the MTHFRC677T mutation is 44.4% (28), as well as heterozygous carriers of the PAI mutation - 43% (27) and the MTHFR A1298C mutation - 41.9% (26), this carrier has no clinical significance. Double heterozygous carrier of the MTHFR A1298C and C677T mutations has clinical significance in terms of the thrombotic process. It occurs

only in two of the patients in the group with MI. A statistically significant difference is obtained for the following factor for thrombophilia: homozygous carrier of the PAI mutation. In the group of patients with IS, the frequency of homozygous carrier of the PAI mutation is 32.8% (22) (p=0.017) (Figures 1 & 2). In the control group, the frequency of these factors is as follows: with homozygous carriership of the PAI mutation, it is 7.2% (5) for the 4G allele. According to the literature, factor V Leiden is the most common form of hereditary thrombophilia, accounting for 40-50% of cases. Its frequency varies depending on the genetically differentiated populations. Heterozygous carriership occurs in 3-8% of the general population in Europe. Only five of the patients with IMI are heterozygous carriers of factor V Leiden (7.7%).

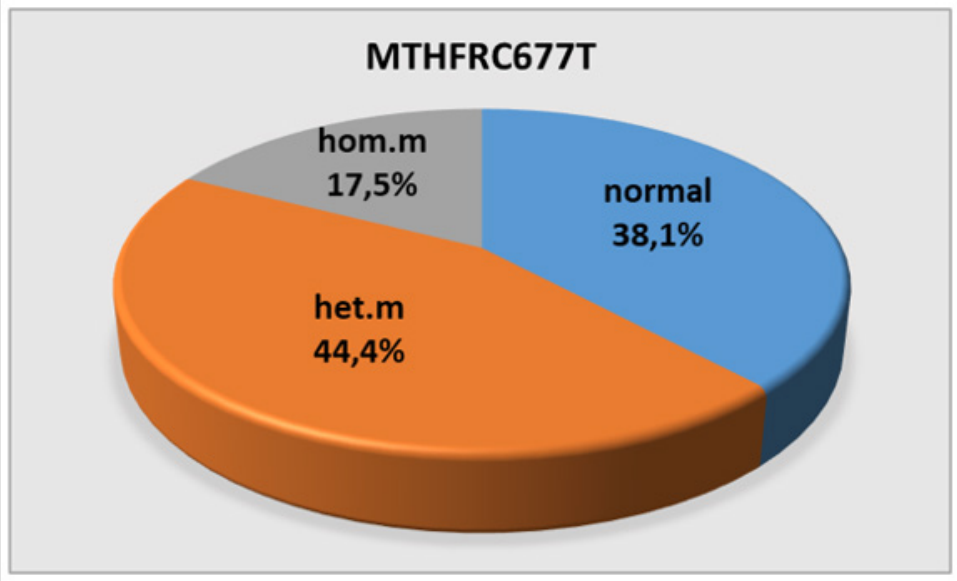

Figure 1: Mutation MTHFR C677T.

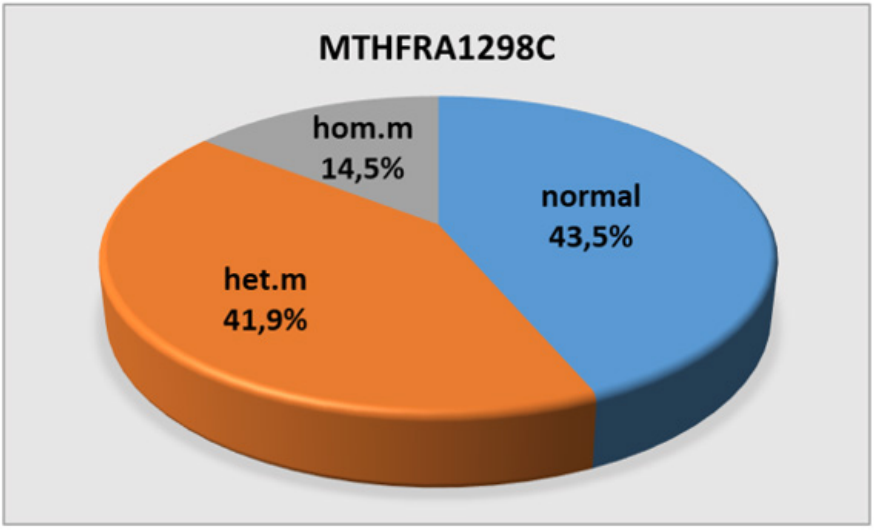

Figure 2: Mutation MTHFR A1298C.

The results obtained showed that homozygous carriership of the PAI mutation has clinical significance for IS. Individuals who are homozygous for the 4G allele have increased plasma PAI-1 concentrations compared to those with the 5G allele [1]. This polymorphism has been studied extensively, and some studies have found that the prevalence of the 4G allele is higher in coronary artery disease, meningococcal septic shock, osteonecrosis, severe preeclampsia, type 2 diabetic nephropathy, pulmonary thromboembolism (PTE), and arterial thrombosis [2-4]. A statistically significant difference was found for two other risk factors for thrombophilia in the two groups of patients. These are protein S and antiphospholipid antibodies. The low level of protein S has clinical significance for DVT, its frequency is higher in the control group - 25.6% (10), with $p < 0.001$, and in the group with IS - in only two of the patients. A statistically significant difference ($p<0.001$) was found for this factor, but not as a factor for IS, but for DVT in the control group, for which the frequency of experienced thrombophlebitis was also the highest. Hereditary defects or disorders of the natural anticoagulant proteins C, protein S and antithrombin are approximately 10 times less common than factor V Leiden, with a combined prevalence of 1% of the population [5] for the other thrombophilia factors (prothrombin mutation, MTHFR mutations, factor V Leiden, low protein C and antithrombin levels), no such statistically significant difference was found for these risk factors between the two groups of patients with regard to IS. In our study, homozygous PAI mutation carriership was found to be a statistically significant factor for IS, among the thrombophilia factors.

The frequency of this factor in the group of patients with MI is as follows: homozygous PAI mutation carrier is 32.8% (22) ($p=0.017$). In the control group, the frequency of these factors is as follows: homozygous PAI mutation carrier is 11.5% (8). The results obtained showed that homozygous PAI mutation carrier has clinical significance for IS. Although there is a relationship between the polymorphism of the PAI-1 gene and stroke, most studies have not confirmed this relationship [6-8]. The insufficient number of patients may lead to false negative results and differences between populations (e.g. allelic heterogeneity). In ischemic stroke, there is a complex interaction between genetic factors, lifestyle, social and environmental factors. Therefore, genetic factors may have a different impact in a given population due to the action of non-genetic risk factors for stroke. The PAI-1 4G/5G polymorphism and stroke risk have shown a clinically significant association between the PAI-1 4G/5G genotype and the risk of future ischemic stroke [9]. The 4G allele, which has a higher transcriptional activity than the 5G allele, is associated with increased plasma PAI-1 activity [10]. In addition to the impaired fibrinolytic capacity due to high levels of circulating PAI-1, local tissue effects are not fully understood, but PAI-1 influences smooth muscle cell proliferation processes as well as protection against atherothrombosis [11] (Figure 3). Fisher's exact test showed that there was a statistically significant association between the PAI mutation and the occurrence of recurrent IS ($p=0.010$) in the sampled population. The mean value of the NIHSS scale for the homozygous carriers of the PAI-4G/5G mutation is 8.17, median- 5.50, standard deviation- 4.86 (min-3.00, max-18.00). Regarding functional independence, for homozygous carriers of the PAI-4G/5G mutation, the BI at 3 months had an arithmetic mean of 72.50, median of 90.00, standard deviation of 35.36 (min-0, max-100). The modified Rankin scale at 3 months. for homozygous carriers of the PAI-4G/5G mutation it is 1.88, median 1.00, standard deviation- 2.10 (min-0, max-6.00).

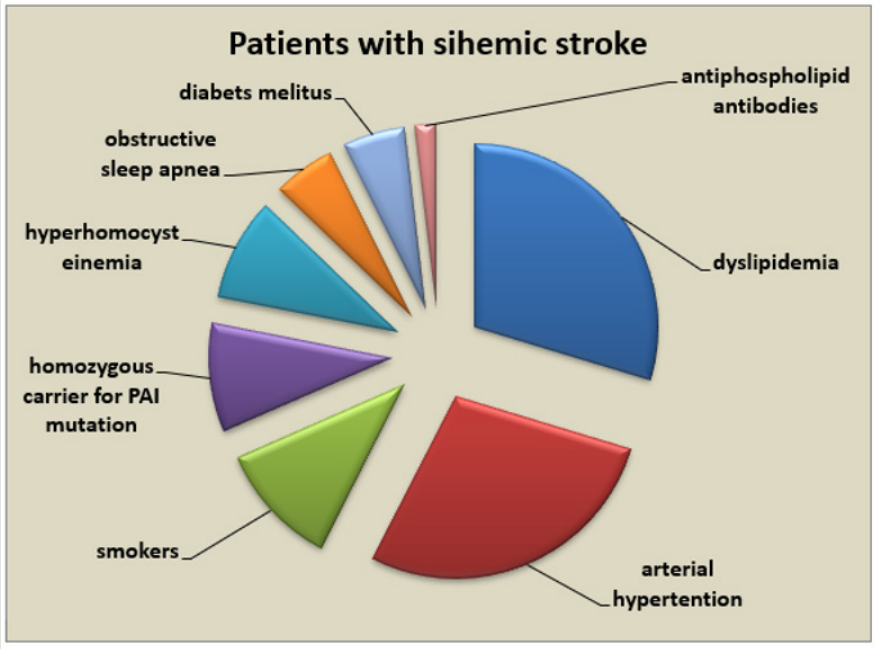

Figure 3: Risk factors for stroke in the group of patients with IS.

Discussion

This study demonstrates a statistically significant association between homozygous PAI-1 4G/5G polymorphism and increased risk of ischemic stroke in young patients. These findings are consistent with previous population studies from Northern Europe, which also identified the 4G allele as a genetic risk factor for ischemic events, particularly in the presence of elevated triglycerides. The higher transcriptional activity of the 4G allele leads to elevated PAI-1 plasma levels, impaired fibrinolysis, and a prothrombotic state [12]. Interestingly, other classical genetic thrombophilia factors such as factor V Leiden and prothrombin G20210A mutation did not show significant differences between patients and controls in this cohort. This observation highlights the heterogeneity of ischemic stroke etiology and supports the notion that arterial thrombosis may be influenced by distinct mechanisms compared to venous thrombosis. The interaction between genetic predisposition and environmental factors such as hypertension, diabetes, and dyslipidemia likely plays a critical role in determining individual stroke risk. Limitations of this study include the relatively small sample size and restriction to a single-center population, which may limit the generalizability of the findings. Nevertheless, the consistent association between homozygous PAI-1 mutations and ischemic stroke observed here suggests that genetic screening could be valuable in identifying high-risk individuals, particularly younger patients without conventional risk factors [9].

Conclusion

Homozygosity for the PAI-1 4G allele is a significant genetic risk factor for ischemic stroke in young adults. In contrast, other thrombophilia markers such as factor V Leiden and prothrombin G20210A did not show clinical relevance in this cohort. These findings emphasize the importance of considering genetic predisposition, especially in younger stroke patients, and suggest a potential role for PAI-1 genotyping in risk stratification and prevention strategies.

References

1. Eriksson P, Kallin B, Båvenholm P, F M vant Hooft, A Hamsten (1995) Allele-specific increase in basal transcription of the plasminogen-activator inhibitor 1 gene is associated with myocardial infarction. Proc Natl Acad Sci U S A 92(6): 1851-1855.
2. Kohler H, Grant P (2000) Mechanisms of disease: plasminogen-activator inhibitor type 1 and coronary artery disease. New Engl J Med 342(24): 1792-1801.
3. Westendorp R, Hottenga J, Slagboom P (1999) Variation in plasminogen-activator-inhibitor-1 gene and risk of meningococcal septic shock. Lancet 354(9178): 561-563.
4. Zoller B, Garcia de Frutos P, Dahlback B (1998) A common 4G allele in the promoter of the plasminogen activator inhibitor-1 (PAI-1) gene as a risk factor for pulmonary embolism and arterial thrombosis in hereditary protein S deficiency. Thromb Haemost 79(4): 802-807.
5. Coppola A, Tufano A, Cerbone A, Giovanni Di Minno (2009) Inherited thrombophilia: implications for prevention and treatment of venous thromboembolism. Semin Thromb Hemost 35(7): 683-694.
6. Catto A, Carter A, Stickland M, J M Bamford, J A Davies, et al. (1997) Plasminogen activator inhibitor-1 (PAI-1) 4G/5G promoter polymorphism and levels in subjects with cerebrovascular disease. Thromb Haemost 77(4): 730-734.
7. Hindorff L, Schwartz S, David S Siscovick, Bruce M Psaty, W T Longstreth, et al. (2002) The association of PAI-1 promoter 4G/5G insertion/deletion polymorphism with myocardial infarction and stroke in young women. J Cardiovasc Risk 9(2): 131-137.
8. Hoekstra T, Geleijnse J, Kluft C, Erik J Giltay, Frans J Kok, et al. (2003) 4G/4G genotype of PAI-1 gene is associated with reduced risk of stroke in elderly. Stroke 34(12): 2822-2828.
9. Per Gunnar W, Nilsson N, Ardnor S, Per Eriksson, Lars Johansson, et al. (2005) Plasminogen Activator Inhibitor-1 4G/5G Polymorphism and Risk of Stroke. Replicated Findings in Two Nested Case–Control Studies Based on Independent Cohorts. Stroke 36(8): 1661-1665.
10. Panahloo A, Mohamed Ali V, Lane A, F Green, S E Humphries, et al. (1995) Determinants of plasminogen activator inhibitor 1 activity in treated NIDDM and its relation to a polymorphism in the plasminogen activator inhibitor 1 gene. Diabetes 44(1): 37-42.
11. Roest M, Banga J (2003) Editorial comment-genetic make-up for increased PAI-1 expression protects against stroke. Stroke 34(12): 2828-2829.
12. Binder B, Christ G, Gruber F, Grubic N, Hufnagl P, et al. (2002) Plasminogen Activator Inhibitor 1: Physiological and Pathophysiological Roles. Physiology 17(2): 56-61.

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