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PAI mutation 4G/5G- Coagulopathy Risk Factor for Stroke or Multiple Sclerosis

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ABSTRACT

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system (CNS) with difficult differential diagnosis. The new trials show the importance of PAI-1 in etiology of neuroinflammation and neurodegeneration in multiple sclerosis. PAI mutation of 4G/5G is a risk factor for thrombotic events in young adults. We present a prospective study with patient diagnosed with MS and examined for thrombophilia, especially PAI mutation 4G/5G. Observational study was performed to evaluate the incidence of PAI mutation in patients with ischemic stroke and healthy control group. A comparison analyses was done in the three groups of patients. PAI mutation could play a role as a risk factor for neuroinflammation in MS.

Keywords: Multiple Sclerosis; Thrombophilia; PAI Mutation; Ischemic Stroke

Abbreviations: CNS: Central Nervous System; PAI-1: Plasminogen Activator Inhibitor-1; tPA: Type Plasminogen Activator; PTE: Pulmonary Thromboembolism; BBB: Blood Brain Barrier; PAS: Plasminogen Activation System

Introduction

Thrombophilia is defined as a predisposition to abnormal clot formation. It is a polygenic disorder with variable expressivity. A predisposition to thrombosis may result from genetic factors, acquired changes in the clotting mechanism, or more commonly, an interaction between them. Homozygous carrier or the combination of two or more heterozygous abnormal factors for thrombophilia can lead to thrombotic disorders in youngers. Homozygous carring of the PAI mutation, 4G/4G is clinical significance for thrombotic events. Increased plasma activity of PAI-1 leads to reduced fibrinolytic activity and increased risk of arterial and venous thrombosis. Plasminogen activator inhibitor-1 (PAI-1) is the primary tissue-type plasminogen activator (tPA). Decreased fibrinolytic capacity due to increased plasma levels of PAI-1 plays an important role in the pathogenesis of thrombotic events [1]. Individuals who are homozygous for the 4G allele have increased plasma PAI-1 concentrations compared to those with the 5G allele [2]. This polymorphism has been studied extensively. In some studies, the prevalence of the 4G allele has been found to be higher in coronary artery disease, meningococcal septic shock, osteonecrosis, severe preeclampsia, pulmonary thromboembolism (PTE) [1,3,4]. The SERPINE1 gene is responsible for the production of PAI-1. PAI-1 is involved in hemostasis by inhibiting the action of plasminogen activators. These proteins, including urokinase plasminogen activator (u-PA) and tissue-type plasminogen activator (t-PA), convert plasminogen to its active form, plasmin. Plasmin is involved in fibrinolysis. By inhibiting the conversion of plasminogen to plasmin, PAI-1 prevents fibrinolysis. The 4G allele is associated with higher plasma PAI-1 activity.

Elevation of plasma PAI-1 activity leads to decreased fibrinolytic activity and increased risk for arterial and venous thrombosis [5]. In different populations, plasma levels of the PAI-1 antigen are associated with the 4/5 guanosine (4G/5G) polymorphism in the promoter region of the PAI-1 gene [6]. Homozygous carriers of the 4G allele have the highest levels of PAI-1 [7,8]. In multiple sclerosis (MS), malfunction of the plasminogen activation system (PAS) and blood brain barrier (BBB) disruption are pathological processes that might lead to an abnormal fibrin(ogen) extravasation into the parenchyma. Fibrin(ogen) deposits, usually degraded by the PAS, lead an autoimmune response and following demyelination. However, the PAS disruption is not well understood in this disorder [9,10]. Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) because of genetic and environmental factors.

Recently, evidence for role of fibrinolysis in the pathogenesis of MS were found. Proteolysis could be a possible mechanism which affect the breakdown of the blood-brain barrier. Extracellular proteolytic enzymes could be considered as important factors in multiple sclerosis [11]. Plasminogen activators/plasmin (PA) system is involved in fibrinolysis and extracellular proteolyses. Tissue-type plasminogen activator (t-PA) and its inhibitor (PAI-1) is a part of PA system. Fibrinolytic potential in demyelinating MS lesions is reduced because of formation- t-PA and PAI complexes [12]. The reduced level of t-PA because of formation of the t-PA/PAI-1 complexes reduce the ability of t-PA receptors to produce plasmin, which reduces the fibrinolytic capacity in MS lesions, which result in increased axonal fibrin involvement and neurodegeneration [13,14].

Materials and Methods

Materials

Healthy control group, group of patients with ischemic stroke, group of patients with MS.

Method 1

(I) MRI

(II) Laboratory tests for thrombophilia,

(III) Neurological exams.

Statistical Analysis

Statistical methods: chi square, standard deviation, statistical significance $p<0.05$.

Results

Result A

We present a prospective clinical trial of 54 patient with multiple sclerosis, 69 healthy controls and 101 patients with ischemic stroke. A total of number of 101 patients with ischemic stroke under 50 years were screened, 67 were examined for PAI mutation. From all patients 32 were females, 69 were males (Table 1). The average age was 42.27 years (min 18, maximum 50 years, SD ± 6.632). The healthy control group consists of 44 women and 25 men, with a mean age of 40.45 years (SD±8.23) (Table 2). In 40.3% (27) of experienced stroke patients were heterozygous carriers of the PAI 4G/4G mutation 40.3% (13). Homozygotes for the 4G/4G mutant allele were 32,84 % (22) of patients, and homozygotes for the normal allele were 26.9% (18) (Table 3). Regarding thrombophilia factors, homozygous carrier of the PAI mutation 4G/4G variant was found to increase the chance of stroke 3.00 times [OR=3.00; CI: (0.70-12.93)]. In central nervous system, PAI-1 is produced predominantly by astrocytes and its main function is to suppress t-PA [15]. We conducted a study in patients with a proven diagnosis of multiple sclerosis and healthy controls regarding a genetic polymorphism in the Pai-1 gene.

Table 1: Patients with Ischemic Stroke.

Gender	n	%	Age		
			Average	Standard deviation	Min
Female	32	31,7	41,66	7,196	19
Male	69	68,3	42,55	6,388	18
Total	101	100	42,27	6,632	18

Note: n- Sample size.

Table 2: Healthy control group.

Group	N	Age				t	df
		Mean	Standard deviation	Min	Max		
Healthy controls	69	40,45	8,23	18,00	50,00	5,09	168
Patients with stroke	101	42,27	6,63	18,00	50,00		
Total	170	39,91	7,84	18,00	50,00		

Note: DF- Degrees of freedom, t- t test, n- sample size.

Table 3: Experienced Stroke Patients with Examined PAI mutation.

PAI-1	N	%
Normal variant	18	26,9
Heterozygous carrier	27	40,3
Homozygous carrier 4G/4G	22	32,8
Total	67	100,0

Note: n- sample size.

Result B

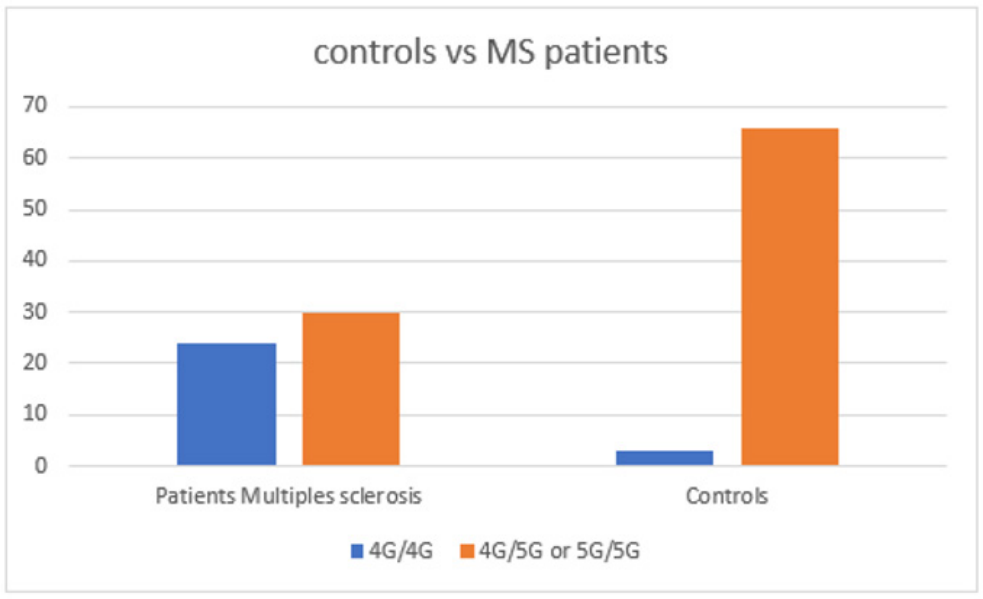
The examined patients with multiple sclerosis were 54, with the majority of female - 39, and male - 15. The average age was 32.8 years (min 18, maximum 50 years) with a standard deviation of 10.5, as it is presented in (Table 4). It is noteworthy that the frequency of homozygotes for the mutant allele of the PAI-1 gene in patients with multiple sclerosis is significantly higher than in healthy controls. We detected PAI 4G/4G in 24/54 MS patients, compared to only 3/69 in healthy controls. The results are statistically significant as chi-square is 28.4268 and p-value is < 0.00001 as presented in (Table 5) and Graphic 1. When chi-square statistic is performed with Yates correction, the value is 26.1346 and the p-value is still < 0.00001. We compared the groups of patients with stroke and multiple sclerosis to evaluate prevalence of PAI-1 mutation in both cohorts. We found that no matter of slightly higher count of PAI-1 homozygous carriers in patients with multiple sclerosis, the chi-square is 1.71 and the p-value is 0.190985, which is not significant. The chi-square statistic with Yates correction showed similar result- 1.2528 and the p-value is 0.263011, which is not significant (Table 6).

Table 4: Comparison of Age Between Controls and Patient Group.

Group	count	Age		
		Mean	Standard deviation	Min
Control	69	40,45	8,23	18,00
MS	54	32.796296	10.51572	18,00

Table 5: Comparison and Analysis of PAI 4G/ 4G Between Controls and Patient Group with MS.

	Mutant 4G/4G	Normal 4G/5G or 5G/5G	Marginal Row Totals
MS	24	30	54
Control	3	66	69



Graphic 1: Controls via MS patients.

Table 6.

	Mutant 4G/4G	Normal 4G/5G or 5G/5G	Marginal Row Totals
Stroke	22	45	67
MS	24	30	54

Discussion

Although ischemic stroke is a vascular disorder and multiple sclerosis is autoimmune inflammation disease, disfunction of the plasminogen activation system and blood brain barrier disruption are common pathological processes that might lead to an abnormal fibrinogen extravasation. These deposits lead to an autoimmune response and following demyelination or atherosclerosis. A couple of previous trials showed the importance of PAI-1, resulted with overexpression of reactive astrocytes leading to dys fibrinolysis in MS and thrombogenesis in patients with ischemic stroke [11]. According to our study, PAI-1 mutation could be a risk factor for the development of multiple sclerosis (p-value < 0.00001) and ischemic stroke at a young age (p<0.05), and the difference between the two groups and healthy controls is statistically significant. However, between the ischemic stroke and multiple sclerosis patient groups, the difference in PAI-1 mutation rates was not statistically significant(p-value-0.190985). All the conventional risk factors reported to be associated with MS such as reduced physical activity, smoking, endothelial dysfunction, platelet activation, thrombophilia, and hyper-homocysteine are proved pro-thrombotic conditions [12]. A lot of evidence supports a significant existence of local and systemic thrombotic events in MS for both its inflammatory and coagulant components. An assessment of risk factors is necessary for patients with ischemic stroke. At a young age genetic factors play a leading role in most cases of thrombotic event. The correct determination of risk factors for cerebrovascular accidents, including the presence of thrombophilia, plays a role in the effective prevention.

Conclusion

PAI mutation could play a role as a risk factor for development of demyelinating disease like MS. Further studies should be performed to evaluate the role of PAI mutation in MS. In the future examination of patients with MS for PAI mutation could play role for the choice of treatment and prevention of invalidation of these patients.

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