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Factor XIII Val 34 Leu polymorphism and migraine

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Abstract

At present, it is contradictory to determine if the combination of certain prothrombotic polymorphisms and migraine and also the risk to develop ischaemic vascular disease. Recently, the common Val34Leu polymorphism of the A-chain factor XIII gene, associated with variations in factor XIII activity, has been suggested to play a significant role in the development of arterial and venous thrombotic disorders.

Our study analysed the incidence of genetic polymorphism Factor XIII (V34L) in a sample of migraineurs and a control group of the patients with ischemic cardiopaty.

In this study 70 consecutive patients aged 10-66 years (mean age 39.2 years), suffering from migraine [**1**] (58 migraine without aura, 12 migraine with aura, ICHD-II criteria) and 70 patients aged 36-71 years (mean age 45.8 years), with ischemic cardiopathy [**2**] were studied with Polymerase Chain Reaction (PCR) for genetic polymorphism Factor XIII (V34L).

Factor XIII (V34L): 42 subjects (60%) [**1**] and 27 (38.5%) [**2**] were heterozygous; 2 subjects (3%) [**1**] and 2 (2.85%) [**2**] were mutated.

These data evidenced that the incidence the factor XIII Leu 34 allele in two population studied not evidenced meaningful differences. Therefore a role in the pathogenesis of such disturbances is hypothetical and deserves ulterior deepenings in more important casuistries.

Key words: Factor XIII Val 34, gene polymorphisms, migraine

Introduction

Factor XIII (FXIII) has a pivotal role in the coagulation process. Activated FXIII catalysed the formation of covalent ã-glutamyl-å-lysine bonds between fibrin monomers, and is involved in the formation of these bonds between other proteins, such as fibronectin and collagen. All these effects increase resistance of fibrin to degradation by plasmin, and improve clot adherence to the vessel wall (1). The relevance of FXIII is demonstrated by the severe bleeding tendency of patients with congenital FXIII deficiency (2). Recently, it has been identified one common polymorphism (G/T) in exon 2 of the FXIII A-subunit gene causing a Val34Leu amino acid change (3). The Leu 34 variant associates with increased FXIII specific activity (3). Interestingly, the Leu 34 allele has been suggested to play a significant role in the development of arterial and venous thrombotic disorders (4–7).

Stroke is a multifactorial disorder in which the influence of genetic and environmental factors could affect the risk of a thromboembolic disease (8). Among the recognized risk factors for stroke, migraine has been considered an independent risk factor for ischaemic cerebrovascular disease (CVD) (9, 10). At present, it is contradictory to determine if the combination of certain prothrombotic polymorphisms and migraine increase the risk to develop CVD (11, 12).

The objective of this study was to evaluate the role of the recently characterized FXIII V34L polymorphism in migraine, and specially to analysee the incidence of genetic polymorphism Factor XIII (V34L) in a sample of migraineurs and a control group of the patients with ischemic cardiopaty.

Patients and Methods

The study was performed and approved by Neurophysiopatology Service, Headache Centre, S. Luca Hospital, Vallo della Lucania (SA), Italy.

In this study 70 consecutive patients aged 10-66 years (mean age 39.2 years), suffering from migraine (58 migraine without aura, 12 migraine with aura, ICHD-II criteria) and 70 patients aged 36-71 years (mean age 45.8 years), with ischaemic cardiopathy were studied with Polymerase Chain Reaction (PCR) for genetic polymorphism Factor XIII (V34L).

Diagnosis of migraine was achieved according to the International Headache Society (15).

Genotype analysis

Genomic polymerase chain reaction (PCR) of the FXIII exon 2 gene was performed using the following primers: 5' gaccttgtaaagtcaaaaatgtc 3' and the mutagenic 5' tggtgcccggggcgtcaacctgcaag 3' (corresponding to nucleotides 67–89, and 215–238, respectively. Nucleotide number according to Grundmann et al.) (16). The mutated nucleotide in the reverse primer (bold underlined) allowed the identification of the 214 G/T (Val34Leu) polymorphism of the FXIII gene by restriction of the PCR product (148 base pairs-bp-) with Bsa HI (New England Biolabs, Beverly, MA, USA), followed by electrophoresis in acrylamide gels stained with AgNO3 (17). The G allele (Val 34) displayed a band pattern of 119 bp, whereas the presence of a 134-bp band was distinctive of the T allele (Leu 34).

The χ^2 test was used to compare frequency distributions. The strength of the association between the polymorphism and migraine with the occurrence of CVD was estimated by calculation of the odds ratio (OR) with the EpiInfo software and the Cornfield method for the calculation of 95% confidence intervals (CI).

Results

We have developed a rapid, simple, and reproducible method to identify the 214 G/T (Val34Leu) polymorphism of the factor XIII gene. The use of a mutagenic primer in the PCR amplification allows the identification of the genotype by a simple restriction assay with Bsa HI. Thus, we avoid the use of more complex and less reproducible techniques of genetic identification (SSCP, allele-specific PCR,

of solid-phase minisequencing).

Table I summarizes genotype and allele distribution in all established groups of patients. In the goup of migraineurs patients were revealed 26 (37%) with wild type genotype, 42 (60%) heterozygous and 2 (3%) mutated. In the group with ischaemic cardiopathy were revealed 41 (58%) with wild type genotype, 27 (38.5%) heterozygous and 2 (3%) mutated. The comparison of the results shows a higher proportion of wild type in cardiac patients (58% vs 37%), an equal percentage of mutated patients (3% vs 3%) and a higher proportion of heterozygous patients in the migraine group (60% vs 38.5 %). (See Figure 1)

Discussion

It is now well demonstrated that the FXIII V34L polymorphism associates with FXIII specific transglutaminase activity, due to the thrombin-activation rate of FXIII (3, 18–22). Paradoxically, the less frequent Leu 34 allele has been identified as a protective genetic factor against coronary artery disease (4, 5) and venous thrombosis (6, 7). Also, a preliminary study indicated a slightly higher incidence of the FXIII Leu 34 variant in 62 patients with primary intracerebral haemorrhage compared with controls (23). However, contradictory results have been obtained by our group including more patients with primary intracranial haemorrhage (24), coronary heart disease, and venous thrombosis (25) that do not support the previous conclusion.

Our results in ischemic cardiopathy patients suggest that FXIII Leu 34 allele does not play a protective role in ischemic cardiopathy patients from our area, independently of the aetiologic varieties. However, stroke is a multifactorial disorder, genetic and environmental factors act additively to determine the risk of an individual of developing thrombosis (8). Recent studies have suggested that migraine (an independent risk factor for ischemic cardiopathy) could be synergistic with other risk factors for thrombosis (9, 10). We speculated that FXIII Leu 34 when combined with migraine could increase the likelihood of ischemic cardiopathy. Firstly, we found that this polymorphism has no a significant role in the development of migraine (with or without aura). Finally, our data suggest that the Leu 34 allele does not protect against ischemic cardiopathy in patients with coexisting migraine.

Considering the present study, several points should be borne in mind when interpreting results. First, the study was performed in survivors. Therefore, a survival bias cannot be avoided in the disease-association study, and likely early mortality from ischemic cardiopathy in patients could lead to an underestimation of the prothrombotic polymorphism. Second, our study has been performed in Caucasian subjects from the Mediterranean area. Since the prevalence of this polymorphism could vary geographically, and it is linked to other FXIII polymorphisms also associated with the activity of FXIII, the FXIII Val34Leu polymorphism may have a different predictive value for thromboembolic disease in diverse populations. Therefore, these data could not exclude the possibility of association between the Val34Leu FXIII and thrombotic risk in other populations, and consequently, the relevance of FXIII polymorphism should be further investigated in other populations, and with prospective and family studies. Third, the size of our sample is small, and thus, new studies including more patients should be performed

References

1. Lorand L, Losowsky MS, Miloszewski KJ, . Human factor XIII. fibrin-stabilizing factor. Prog Hemost Thromb1980; 5:245–90.
2. Mikkola H, Palotie A, . Gene defects in congenital factor XIII deficiency. Sem Thromb Haemost1996; 22:393–8.
3. Anwar R, Gallivan L, Edmonds SD, Markham AF.. Genotype/phenotype correlations for coagulation factor XIII. Specific normal polymorphisms are associated with high or low factor XIII specific activity. Blood1999; 93:897–905.
4. Wartiovaara U, Perola M, Mikkola H,Tötterman K, Savolainen V et al. Association of FXIII Val34Leu with decreased risk of myocardial infarction in Finnish males. Atherosclerosis1999; 142:295–300.
5. Kohler HP, Stickland MH, Ossei-Gerning N, Carter A, Mikkola H, Grant PJ. Association of a common polymorphism in the factor XIII gene with myocardial infarction. Thromb Haemost1998; 79:8–13.
6. Catto AJ, Kohler HP, Coore J, Mansfield MW, Stickland MH, Grant PJ. Association of a common polymorphism in the

factor XIII gene with venous thrombosis. Blood1999; 93:906–8.
7. Franco RF, Reitsma PH, Lourenco D, Maffei FH, Morelli V et al. Factor XIII Val34Leu is a genetic factor involved in the aetiology of venous thrombosis. Thromb Haemost1999; 81:676–9.
8. Wolf PA, Cobb JL, D'Agostino RB et al. Epidemiology of Stroke. In Yatsu FM , editor. Stroke Pathophysiology, Diagnosis, and Management. New York: Churchill Livingstone, 1992:3–27.
9. Merikangas KR, Fenton BT, Cheng SH, Stolar MJ, Risch N. Association between migraine and stroke in a large-scale epidemiological study in the United States. Arch Neurol1997; 54:362–8.
10. Rothrock J, North J, Madden K, Lyden P, Fleck P, Dittrich H. Migraine and migrainous stroke: risk factors and prognosis. Neurology1993; 43:2473–6.
11. Kontula K, Ylikorkala A, Miettinen H, Vuorio A, Kauppinen-Mäkelin R et al. Arg506Gln Factor V mutation (Factor V Leiden) in patients with ischaemic cerebrovascular disease and survivors of myocardial infarction. Thromb Haemost1995; 73:558–60.
12. Corral J, Iniesta JA, González-Conejero R, Lozano ML, Rivera J, Vicente V. Migraine and prothrombotic genetic risk factors. Cephalalgia1998; 18:257–60.
13. National Institute of Neurological Disorders and Stroke. Special report: Classification of cerebrovascular diseases III. Stroke1990; 21:637–76.
14. White HD, Simes RJ, Anderson NE, Hankey GJ, Watson JD et al. Pravastatin therapy and the risk of stroke. New Engl J Med2000; 343:317–26.
15. Headache Classification Committee. The International Classification of Headache Disorders, 2nd Edition. Cephalalgia 2004;24:1-160..
16. Grundmann U, Aman E, Zettlmeissl G, Kupper HA. Characterization of a cDNA coding for human factor XIIIa. Proc Natl Acad Sci USA1986; 83:8024–8.
17. Corral J, Iniesta JA, González-Conejero R, Vicente V. Detection of factor V Leiden from a droop of blood by PCR-SSCP. Thromb Haemost1996; 76:735–7.
18. Kangsadalampai S, Board PG. The Val34Leu polymorphism in the A subunit coagulation factor XIII contributes to the large normal range in activity and demonstrates that the activation peptide plays a role in catalytic activity. Blood1998; 92:2766–70.
19. Ariëns RAS, Philippou H, Nagaswami C, Weisel JW, Lane DA, Grant PJ. The factor XIII V34L polymorphism accelerates thrombin activation of factor XIII and affects cross-linked fibrin structure. Blood2000; 96:988–95.
20. Wartiovaara U, Mikkola H, Szöke G, Haramura G, Kárpáti L et al. Effect of Val34Leu polymorphism on the activation of the coagulation factor XIII-A. Thromb Haemost2000; 84:595–600.
21. Balogh I, Szöke G, Kárpáti L, Wartiovaara U, Katona È et al. Val34Leu polymorphism of plasma FXIII. Biochemistry and epidemiology in familial thrombophilia. Blood2000; 96:2479–86.
22. Kohler HP, Ariens RA, Whitaker P, Grant PJ . A common coding polymorphism in the FXIII A-subunit gene (FXIIIVal34Leu) affects cross-linking activity. Thromb Haemost1998; 80:704.
23. Catto AJ, Kholer HP, Bannan S, Stickland MH, Carter A, Grant PJ et al. Val34Leu. A novel association with primary intracerebral hemorrhage. Stroke1998; 29:813–6.
24. Corral J, Iniesta JA, González-Conejero R, Villalón M, Rivera J, Vicente V. Factor XIII Val34Leu polymorphism in primary intracerebral haemorrhage. The Hematol J2000; 1:269–73.
25. Corral J, González-Conejero R, Iniesta JA, Rivera J, Martýìnez C, Vicente V. The FXIII Val34Leu polymorphism in venous and arterial thromboembolism. Haematologica 2000; 85:293–7

Allele	Migraineurs patients	Patients with ischaemic cardiopathy
Wild type	26 (37%)	41 (58%)
Heterozygous	42 (60%)	27 (38.5%)
Mutated	2 (3%)	2 (3%)

Table I: Allele distribution for factor XIII genotype

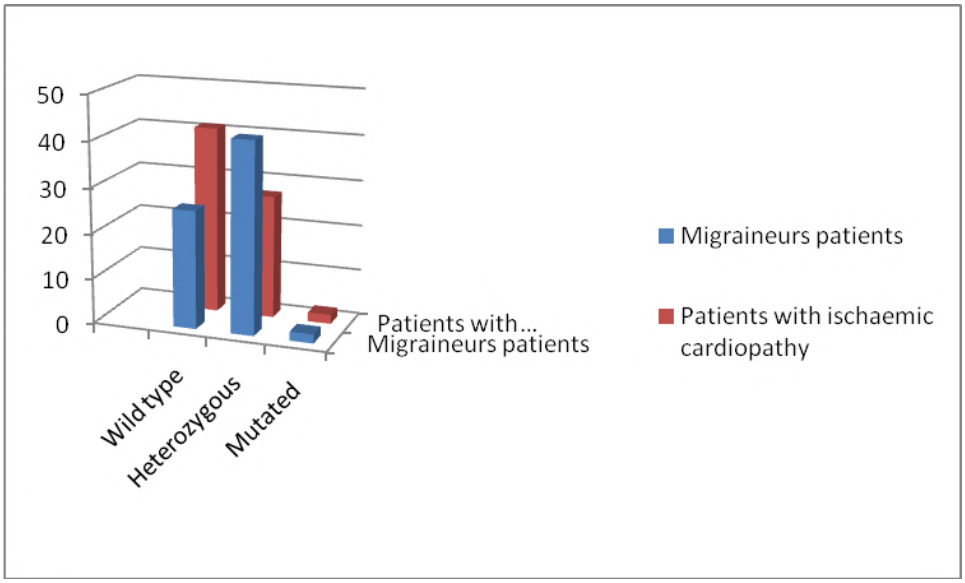

Figure 1: Comparative data for patients groups