DOI: http://dx.doi.org/10.18203/issn.0019-5359.IndianJMedSci20163535

LETTER TO EDITOR

CO-PRESENCE OF FACTOR V LEIDEN G1691A, MTHFR C677T AND XMN-1 – 158 $^{G}\Gamma$ (C → T) IN SICKLE CELL PATIENTS

Dear Editor,

Vascular complications are an important and perplexing aspect of the clinical spectrum of sickle cell anemia.[1,2] patients with sickle cell disease show activation of the blood coagulation, fibrinolytic systems, increased platelet activity and consumption of coagulation inhibitors during vaso-occlusive crises.[3-6] Due to importance of vascular complications in the physiopathology of sickle cell disease, a number of genetic polymorphisms associated with thrombophilia had reported as potential genetic modifiers of sickle cell disease. Inherited risk factors for vascular disease include factor V Leiden[7] (G1691A) and methylenetetrahydrofolate reductase (MTHFR) C677T[8] point mutations and in view of their role in enhancing thrombus formation, it was suggested that these mutations play a role in the pathogenesis of sickle cell disease.[9,10] The CT variation at position - 158 upstream of the Gγ globin gene affect HbF production which is detectable by the restriction enzyme Xmn-1.[11] Heterozygosity for presence of Xmn I site polymorphism is also likely to influence phenotype.[12] The Xmn1-$^{G}\gamma$ site is common in almost all population and it has little effect in normal individuals. However, under conditions of hemopoietic stress, as in homozygous β thalassemia and sickle cell disease, presence of the Xmn1- $^{G}\gamma$ site favors a higher HbF response.[13] We had recruited the sickle cell patient from outpatient department All India institute of Medical sciences for the study of various modulating factors. Diagnosis of sickle cell patients done by high performance liquid chromatography (HPLC- Bio-Rad-Variant™ Bio Rad, CA, USA). DNA extraction done by phenol-chloroform method. Molecular study for FV Leiden done according to Bertina RM[14] (1994) while MTHFR C677T genotypic study done according to Hanson NQ[15] (2001). Xmn-1 polymorphism study done according to Sutton M.[16] We evaluated 240 patients for the three modulating factor i.e. FV Leiden, MTHFR and Xmn1 polymorphism. Out of the 240 patents 17 were heterozygous and 3 were homozygous for FV Leiden mutation while 42 patients were heterozygous and 8 were homozygous for MTHFR C677T mutation. Xmn1 (C-T) present in 73 patients in heterozygous condition while 34 patients were homozygous for Xmn-1 polymorphism. Fifteen patients showed the presence of FV/MTHFR/Xmn-1 in heterozygous patients while 37 patients were carrier for MTHFR/Xmnn-1in heterozygous patients. Three homozygous patients were carrier for FV/MTHFR/Xmn-1 while 7 patients were carrier for MTHFR/Xmn-1 polymorphism. These observations suggest the co- presence of FV Leiden, MTHFR C677T and Xmn-1 in sickle cell patients is common; and emphasis on the hypothesis the interaction of various genetic factors had epistatic effect on phenotype of sickle cell disease.

SANJAY PANDEY, RAHASYA MANI MISHRA[1], SWETA PANDEY, RENU SAXENA
Department of Hematology, All India Institute of Medical Sciences, New Delhi, [1]Department of Environmental Biology, Awadhesh Pratap Singh University, Rewa, India

Address for correspondence:
Prof. Renu Saxena,
Department of Hematology, I.R.C.H. Building (1st Floor), All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India.
E-mail: pandeysanjaybtrediffmail.com

REFERENCES

1. Setty BN, Rao AK, Stuart MJ. Thrombophilia in sickle cell disease: The red cell connection. Blood 2001;98:3228-33.
2. Hebbel RP. Thrombogenesis or thrombogenic risk? J Lab Clin Med 2001;137:381-2.
3. Lourenço D, Sampaio MU, Kerbauy J, Sampaio CA. Estimation of plasma kallikrein in sickle-cell anemia, and its relation to the coagulation and fibrinolytic systems. Adv Exp Med Biol 1989;247B:553-7.
4. Peters M, Plaat BE, ten Cate H, Wolters HJ, Weening RS, Brandjes DP. Enhanced thrombin generation in children with sickle cell disease. Thromb Haemost 1994;71:169-72.
5. Key NS, Slungaard A, Dandelet L, Nelson SC, Moertel C, Styles LA, *et al*. Whole blood tissue factor procoagulant activity is elevated in patients with sickle cell disease. Blood 1998;91:4216-23.
6. Bayazit AK, Kilinc Y. Natural coagulation inhibitors (protein C, protein S, antithrombin) in patients with sickle cell anemia in a steady state. Pediatr Int 2001;43:592-6.
7. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, *et al*. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 1994;369:64-7.
8. Hanson NQ, Aras O, Yang F, Tsai MY. C677T and A1298C polymorphisms of the methylenetetrahydrofolate reductase gene: Incidence and effect of combined genotypes on plasma fasting and post-methionine load homocysteine in vascular disease. Clin Chem 2001;47:661-6.
9. Zimmerman SA, Ware RE. Inherited DNA mutations contributing to thrombotic complications in patients with sickle cell disease. Am J Hematol 1998;59:267-72.
10. Andrade FL, Annichino-Bizzacchi JM, Saad ST, Costa FF, Arruda VR. Prothrombin mutant, factor V Leiden, and thermolabile variant of methylenetetrahydrofolate reductase among patients with sickle cell disease in Brazil. Am J Hematol 1998;59:46-50.
11. Gilman JG, Huisman TH. DNA sequence variation associated with elevated fetal Gg globin production Blood 1985;66:783-7.
12. Panigrahi I, Agarwal S, Gupta T, Singhal P, Pradhan M. Pradhan hemoglobin E-beta Thalassemia: Factors affecting phenotype. Indian Pediatr 2005;42:357-62.
13. Garner C, Tatu T, Game L, Cardon LR, Spector TD, Farrall M, *et al*. A candidate gene study of F cell levels in sibling pairs using a joint linkage and association analysis. Gene Screen 2000;1:9-14.

14. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, *et al*. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 1994;369:64-7.
15. Hanson NQ, Aras O, Yang F, Tsai MY. C677T and A1298C polymorphisms of the methylenetetrahydrofolate reductase gene: Incidence and effect of combined genotypes on plasma fasting and post-methionine load homocysteine in vascular disease. Clin Chem 2001;47:661-6.
16. Sutton M. Polymerase chain reaction amplification applied to the determination of beta like globin gene cluster haplotypes. Am J Hematol 1989;32:66-9.