Young Onset Ischemic Stroke due to Two Heterozygous Mutations: A Case Report

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Abstract:

This report underscores the importance of a comprehensive approach involving various diagnostic modalities and the need for considering genetic factors as a cause for young onset ischemic stroke as mutation of these is a risk for thrombosis.

Keywords: stroke; ischemic strokes; factor V; mutation.

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1 INTRODUCTION

Factor V Leiden mutation is one of the important genetic risk factors known for spontaneous thrombosis.[1] Its mutation causes activated protein C resistance.[2] This mutation also potentiates the effect of methylenetetrahydrofolate reductase (MTHFR) causing hyperhomocysteinemia, a known risk factor for blood clot.[3] A combined mutation of both has been reported in 0.02%.[4] Although rare, it has been found to be associated with young individuals but the combined mutation has rarely been reported. To contribute to the understanding, we present a case of factor-V R506Q and methylenetetrahydrofolate reductase-C677T mutation with left lacunar thalamic infarction of a 25-year-old male who presented with twelve-hour history of ringing sensation of right side of his body who was managed with direct oral anti-coagulation drug which prevented further thrombosis and significant improvement of his symptoms.[5]

2 CASE PRESENTATION

A twenty-six-year-old male, resident of Kathmandu, Nepal, presented with chief complaint of ringing sensation of right side of his body for 16 hours which was aggravated by walking. His past medical history includes cervical spine tuberculosis from second to fourth cervical spine two years back for which he took anti-tubercular medications for a total duration of 12 months. Furthermore, he has a smoking history of five pack years.

His vitals were within normal limit and a complete neurological examination revealed a reduced power on his right arm (4/5) and right leg (4/5).

A diffusion-weighted magnetic resonance imaging (DWI) of brain was done which revealed abnormal high signal changes demonstrating restricted diffusion involving the corona-radiata, posterior limb of internal capsule and periventricular occipital lobe (Figure 1) on the left side which is consistent with left middle cerebral artery and posterior cerebral artery territory infarction.

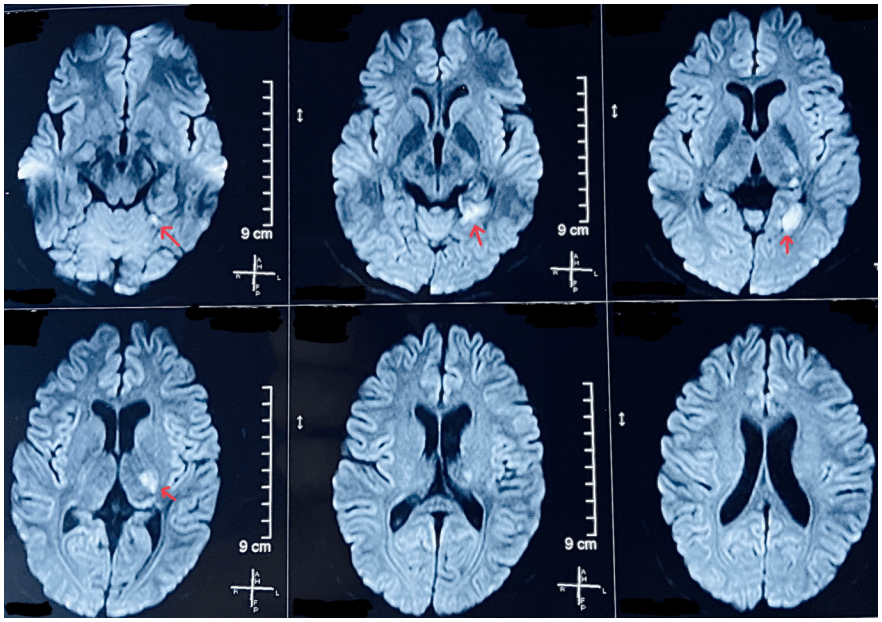

Figure 1: Diffusion-weighted magnetic resonance imaging of brain showing restricted diffusion involving posterior limb of internal capsule and occipital lobe.

Considering the above findings, a routine blood investigation was sent which was normal. An autoimmune panel was sent which was also normal. His echocardiography, doppler ultrasonography of bilateral lower limbs and electrocardiogram was also normal. Furthermore, a thrombotic panel was also sent.

He was initially initiated on tablet aspirin and tablet rosuvastatin. Later, his thrombotic panel revealed MTHFR-C677T heterozygous mutation (heterozygous C>T substitution at nucleotide position 677 in MTHFR gene resulting in replacement of alanine with valine at amino acid 222) and Factor V-R506Q heterozygous mutation (heterozygous G>A substitution was observed at nucleotide position 1691 in Factor V gene resulting in replacement of arginine with glutamine at amino acid 506). Thus, he was initiated with tablet rivaroxaban, a direct oral anti-coagulation drug. Subsequent follow up revealed no progression of his symptoms.

3 DISCUSSION

Thrombophilia, as genetic inheritance, is one of the causes for young onset ischemic stroke. Factor V is one of the most important factors responsible for dual role for the regulation of the coagulation cascade.[6] Factor V Leiden mutation trait shows autosomal dominant inheritance.[1] The single point mutation in factor V gene (guanine to adenine at nucleotide 1691) would lead to replacement of arginine with glutamine at amino acid 506. This abolishes the Arg506 cleavage site for activated protein C (APC) in factor V and factor Va. This enhances the procoagulant role of factor Va and reduction in anticoagulant role of factor V.[7] This also potentiates the effect of MTHFR. Heterozygous inheritance usually doesn't have clinical thrombotic complications unless a convergence with other inherited predisposition or an acquired thrombogenic stimulus to thrombosis is present.[8] MTHFR, a folate dependent enzyme, plays an important role in regulating plasma homocysteine level. A C677T point mutation has been linked to an increased risk of ischemic stroke. This variant contributes to decreased enzyme activity, leading to increased hyperhomocysteinemia which ultimately leads to ischemic stroke.[9] Although the homozygous factor V Leiden mutation incidence predominates by higher degree, the heterozygous factor V Leiden mutation is also somehow the cause for thrombosis.[6] The prevalence of heterozygous Factor V R506Q mutation has been reported to be less than 5% and that of heterozygous MTHFR mutation being less than 50% individually.[4] Interestingly, the mutations

of both of them occurring simultaneously in a symptomatic patient with a median age of 65.5 years has been seen is 0.02% cases.[4] The genetic predisposition for the combined heterozygous factor V Leiden R506Q and MTHFRC677T suggested reason for the young onset ischemic stroke along with other risk factor like smoking. The management of patients with dual genetic mutation depends on recurrence of thromboembolic events, family history and associated risk factors like smoking, obesity, etc. The prophylactic anticoagulant therapy is indicated in patients who have developed a thrombotic event. The duration of treatment depends on unprovoked or provoked reasons of thrombosis, site of thrombosis, family history, risk factors involved and type of thrombophilia, ranging from six months to lifelong treatment.[10]

4 CONCLUSION

Our case report has its own limitations to find the association of ischemic stroke with other possibilities due to the very low frequency of young onset ischemic stroke. However, the evidence of this case report will warrant for further study of genetic mutation in detail for young onset ischemic stroke and also advice clinicians to maintain a high index of suspicion for genetic screening and genetic predisposition in such a situation.

References:

1. Zuber M, Toulon P, Marnet L, Mas J-L. Factor V Leiden Mutation in Cerebral Venous Thrombosis [Internet]. Stroke [Internet]. 1996;27(10):1721–3. Available from: https://www.ahajournals.org/doi/abs/10.1161/01.STR.27.10.1721

2. Slusher KB. Factor V Leiden: a case study and review. Dimens Crit Care Nurs. United States 2010;29(1):6–10.

3. Bansal P. Factor V Leiden and MTHFR mutations as a combined risk factor for hypercoagulability in referred Patients population from Western India. Molecular Cytogenetics. 2014 p. P28.

4. Lalouschek W, Aull S, Serles W, Schnider P, Mannhalter C, Pabinger-Fasching I, et al. C677T MTHFR mutation and factor V Leiden mutation in patients with TIA/minor stroke: a case-control study. Thromb Res. United States 1999 Jan;93(2):61–9.

5. Terni E, Giannini N, Brondi M, Montano V, Bonuccelli U, Mancuso M. Genetics of ischaemic stroke in young adults. BBA Clin. Netherlands 2015 Jun;3:96–106.

6. Ghalaut PS, Duhan J, Chaudhary V, Dahiya HK, Kaushik S, Sharma M, et al. Ischemic stroke in a patient with hetrozygous factor v leiden mutation: an uncommon association. Indian journal of hematology & blood transfusion : an official journal of Indian Society of Hematology and Blood Transfusion. India 2014 p. 335–7.

7. Hamedani AG, Cole JW, Cheng Y, Sparks MJ, O'Connell JR, Stine OC, et al. Factor V leiden and ischemic stroke risk: the Genetics of Early Onset Stroke (GEOS) study. J stroke Cerebrovasc Dis Off J Natl Stroke Assoc. United States 2013 May;22(4):419–23.

8. Investigation and management of heritable thrombophilia. Br J Haematol. England 2001 Sep;114(3):512–28.

9. Chang G, Kuai Z, Wang J, Wu J, Xu K, Yuan Y, et al. The association of MTHFR C677T variant with increased risk of ischemic stroke in the elderly population: a meta-analysis of observational studies. BMC Geriatr. England 2019 Nov;19(1):331.

10. Kearon C, Crowther M, Hirsh J. Management of patients with hereditary hypercoagulable disorders. Annu Rev Med. United States 2000;51:169–85.