

Case Report

A CASE OF VENOUS THROMBOSIS AND INFERTILITY IN A MALE WITH A1298C MUTATION OF MTHFR GENE

***Sajit Varghese and Shaikh Asif**

Department of Medicine, Smt. N.H.L. Municipal Medical College, Ahmedabad, Gujarat, India

**Author for Correspondence*

ABSTRACT

Infertility affects about 10-15% of couples, of which half are due to the male factor, most common cause of which is spermatogenic failure. A possible cause for genetic susceptibility to oligozoospermia is 5,10-Methylene tetrahydrofolate reductase (MTHFR) gene polymorphisms. MTHFR is an important regulatory enzyme for folate and homocysteine metabolism, and different MTHFR gene mutations may lead to variable degrees of hyperhomocysteinemia. Hyperhomocysteinemia is an independent risk factor for stroke, coronary artery disease, peripheral vascular disease, venous thrombosis, colon cancer, acute leukemias and Neuro-psychiatric disorders. Here, we describe a unique case of cerebral venous sinus thrombosis in a male patient with oligozoospermia, found to have A1298C mutation of MTHFR gene.

Key Words: Infertility, MTHFR, Thrombosis

INTRODUCTION

MTHFR gene is located on chromosome 1 locus p36.3 and the two commonly recognized polymorphic gene variants are the 'thermolabile' C677T variant and the A1298C variant (Sibani *et al.*, 2000; Eloualid *et al.*, 2012). In the latter variant, adenine(A) is replaced by cytosine(C) at position 1298 of exon 7 in MTHFR gene, resulting in the normal glutamic acid being substituted by alanine codon (missense mutation), leading to mildly decreased MTHFR enzyme activity and mild hyperhomocysteinemia (Soltanpour *et al.*, 2011). MTHFR converts 5, 10-methylene THF to 5-methyl THF, which acts as co-substrate for remethylation of homocysteine to methionine. The above products are important components for DNA methylation and DNA synthesis, thus indirectly spermatogenesis. Hyperhomocysteinemia leads to an increased free radical-induced vessel and tissue injury (oxidative stress), hyperviscosity, as well as degradation of blood vessel wall protein and extracellular matrix components, thus being an important cause for arterial plaques and venous thrombosis (Rees *et al.*, 1993).

CASES

A 31 year old male was admitted with sudden onset left sided weakness, while he was resting at home in the afternoon. Soon after admission he developed generalized tonic-clonic convulsions with loss of consciousness. Past history was notably insignificant with no addictions, including alcohol. Family history revealed that he and his wife (married since 2 years) had recently undergone detailed infertility testing, which showed that he was having oligozoospermia (total spermatozoa 10 million/cc with only 20% actively motile and 50% sluggishly motile spermatozoa). Detailed clinical examination revealed the patient was stuporous with left complete sensory-motor hemiplegia (power 0/5) with right gaze deviation and unequal sluggish reactive pupils(left 0.5mm and right 1.5mm). Complete hemogram, renal function, liver function, random blood sugar, thyroid function, chest X-ray, ultra-sonography abdomen/pelvis, and echocardiography tests were within normal limits. Anti-nuclear antibody (ANA), anti-phospholipid antibody (APLA), lipid levels, serum VDRL tests were also normal. Homocysteine levels were high(>50) with normal vitamin B12 and RBC folate levels. MRI brain (Figure 1) showed subacute hemorrhagic infarct in right fronto-parietal lobe with minimal mass effect in form of leftward midline shift and right lateral ventricle compression. MR angiography (MRA) neck was normal while MRA brain showed diffuse arteriosclerotic changes in bilateral middle cerebral artery branches and right anterior cerebral artery. MR venography (Figure 2) confirmed superior sagittal venous sinus thrombosis. MTHFR gene

Case Report

polymorphism analysis showed wild type for C677T and heterozygous for A1298C (AC genotype) mutation.

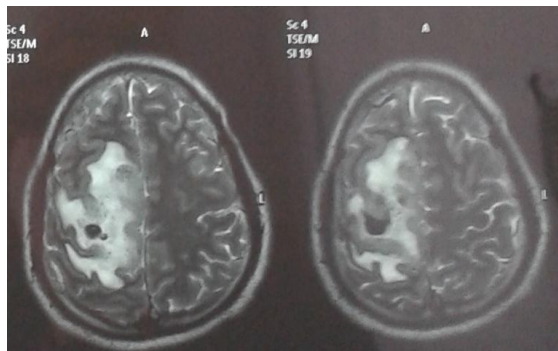


Figure 1: MRI brain

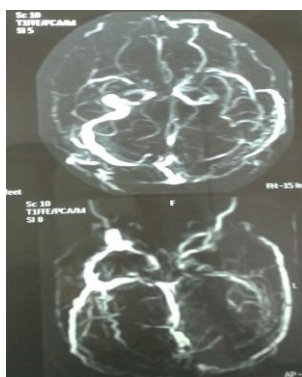


Figure 2: MR venography

We treated the patient with mannitol (intravenous, in tapering doses for 3 days), enoxaparin (0.6 mg subcutaneous twice a day, for 5 days), valproic acid (500 mg twice a day), parenteral and oral multivitamin supplements containing pyridoxine along with folic acid and vitamin B12, and oral warfarin to titrate INR in the range of 2 to 3. Patient improved considerably over 1 week and only the motor deficit was present on discharge, for which physiotherapy was explained.

DISCUSSION

The above case depicts a dramatic clinical recovery in this unique patient, on applying the proper treatment guidelines of venous sinus thrombosis due to hyperhomocysteinemia. The patient was a non-alcoholic, non-smoker and a non-vegetarian too.

Vitamin B12 and folic acid deficiency have been indirectly associated with hyperhomocysteinemia, which is also found to be more in alcoholics, smokers, and those who are predominantly food faddists and strict vegetarians. No family history of infertility was found, except in the patient himself, who affirms the association of A1298C heterozygous mutation for oligozoospermia, and this is proved by the few discrete studies on this mutation (Singh *et al.*, 2010).

Hyperhomocysteinemia may not only be the cause of the sagittal sinus thrombosis here, it may also be partly or mainly responsible for the diffuse arteriosclerotic changes in middle and anterior cerebral arteries of this patient.

Also, it is notable that the heterozygous A1298C mutation is known to be associated with mild hyperhomocysteinemia, while in this patient, the homocysteine levels are much higher. This may be explained by unknown genetic, ethnic and environmental factors, relevant to the Indian population (Guo *et al.*, 2009).

Case Report

Conclusion

A severe form of cerebral venous sinus thrombosis with mass effect and midline shift was reverted with the timely diagnosis of hyperhomocysteinemia and the clinical suspicion of a probable genetic susceptibility explaining the associated infertility.

REFERENCES

- Eloualid A, Abidi O and Charif M et al., (2012).** Association of the MTHFR A1298C Variant with Unexplained Severe Male Infertility. *PLoS ONE* 7(3) e34111.
- Guo H, Chi J, Xing Y and Wang P (2009).** Influence of folic acid on plasma homocysteine levels & arterial endothelial function in patients with unstable angina. *The Indian Journal of Medical Research* 129(3) 279–84.
- Mohammad Soleyman Soltanpour, Zahra Soheili and Ali Akbar et al., (2011).** The A1298C mutation in methylenetetrahydrofolate reductase gene and its association with idiopathic venous thrombosis in an Iranian population. *Labmedicine* 42(4) 213-16.
- Rees MM and Rodgers GM (1993).** Homocysteinemia: association of a metabolic disorder with vascular disease and thrombosis. *Thrombosis Research* 71 337-359.
- Sibani S, Christensen B and O'Ferrall E et al., (2000).** Characterization of six novel mutations in the methylenetetrahydrofolate reductase (MTHFR) gene in patients with homocystinuria. *Human Mutation* 15(3) 280–7.
- Singh K, Singh SK and Raman R (2010).** MTHFR A1298C polymorphism and idiopathic male infertility. *Journal of Postgraduate Medicine* 56(4) 267-269.