International Journal Dental and Medical Sciences Research
Volume 4, Issue 6, Nov-Dec 2022 pp 499-501 www.ijdmsrjournal.com ISSN: 2582-6018

Young Stroke caused by Heterozygous MTHFR Mutation A1298C: a Case Report

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Submitted: 25-11-2022 Accepted: 08-12-2022

ABSTRACT
Ischemic stroke at young age is concerning in both developing and developed countries owing to its rising incidence, high morbidity and mortality and long- term psychological, physical and social consequences. The etiology of young stroke is heterogenous and mainly attributed to metabolic and coagulation defects. Here, we present a case of young stroke caused by a rare entity that is Methylenetrahydrofolate reductase (MTHFR A1298C) mutation causing hyperhomocysteinemia. Patient was managed conservatively with anti-platelet medication, vitamin supplementation, physiotherapy and recovered well. This case highlights the need to consider rare causes of stroke in young patients and importance of family screening in such patients.

Keywords: Young stroke, hyperhomocysteinemia, Methylenetrahydrofolate reductase (MTHFR A1298C), heterozygous mutation

I. INTRODUCTION

Stroke in the younger population is less common than in elderly but has a major impact on individuals and society. Furthermore, Stroke is the leading cause of disability. Approximately 10% to 15% of all strokes occur in adults aged 18 to 50 years [1]**.** Incidence of young ischemic stroke differs considerably worldwide and is generally higher in developing countries than in industrialized countries [2]. The etiology of young stroke is mainly attributed to genetic mutations in coagulation and metabolic pathways.

MTHFR (Methylenetrahydrofolate reductase) is a key enzyme that is required for folic acid metabolism in vivo. MTHFR polymorphism results in deregulated folate metabolismand hyperhomocysteinemia. C677T and A1298C are two common mutants in MTHFR. Their missense mutations result in the replacement of 677 base C with T and the substitution of A with C in 1298, which change the amino acid structure of MTHFR leading to reduction in MTHFR enzyme activity [3-4]. Homocysteine cannot be converted into methionine normally, which causes a significant rise in the homocysteine levels in the blood, escalating susceptibility to stroke [5].

II. CASE REPORT

A 21-year-old male with no addictions and comorbidities presented to the medical emergency with complaints of headache, sudden onset weakness in the right half of body and inability to speak. He had no history of trauma, seizures or loss of consciousness. He was afebrile with a blood pressure of 150/80 mm of Hg, pulse rate of 80/minute which had a regular rhythm and saturation of 98% on room air. General examination did not reveal pallor, icterus, cyanosis, clubbing, lymphadenopathy and pedal edema. Neurological examination suggested a Glasgow Coma Scale of 11 (E4V1M6), pupils were equal in size and reactive to light. Broca's aphasia was present. On motor examination the upper limb and lower limb had grade 0 power on the right side and grade 5 power on the left side. Tone was reduced on the right side; deep tendon reflexes were absent on the right side and were normal on the left side. Plantar reflex was mute bilaterally. Sensory examination was normal. There were no signs of meningeal irritation or cerebellar involvement. Other systemic examination did not reveal any abnormalities.

Random Blood Sugar was 134 mg/dl, non-Contrast computed tomography of head was done and suggestive of ill-defined hypodensity in left frontal and temporal lobe. Later Magnetic Resonance Imaging of the brain was done and revealed acute infarct in cortical, subcortical region of left fronto-temporo-parieto-occipital regions and left basal ganglia and striated terminalis regions.

Routine blood investigations (hemogram, liver function test, kidney function test) were within normal limits. Echocardiogram and Holter monitoring were done and came out to be normal.

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Carotid doppler revealed type II plaque in the left carotid bulb (>70% of diameter).

Considering young stroke, the patient was investigated for vasculitis and APLA for which he tested negative. Homocysteine level was found to be high (>65 micromoles/liter), vitamin B12-222pg/ml and folic acid -14 pg/ml. Lipid profile was suggestive of dyslipidemia (high triglycerides, low High-Density Lipoproteins, high Low-Density Lipoproteins). Thrombophilia profile revealed a heterogeneous mutation of MTHFR gene (A1298C). Protein C, Protein S, Antithrombin III levels were normal and factor V Leiden mutation was absent.

Patient was started on antiplatelets, statins, anti-edema measures along with other supportive treatment. He was also prescribed vitamin B6 (pyridoxine), folic acid and vitamin B12 supplements. The patient is now being followed up in OPD and is doing well with a marked improvement in his limb power and speech. Family screening for homocystinemia revealed elevated level in his asymptomatic younger sister.

III. DISCUSSION

Stroke is the second leading cause of death and the third leading cause of disability worldwide [6]. The impact of stroke is greatest when it affects young bread earners of the family.

Khan JA et al. reported in a study that 68/260 (26%) of their patients were 15-45 years of age [7]. Vohra et al. reported that 34% of their patients in stroke case series were under the age of 50 years [8].

Some risk factors for stroke are non-modifiable such as age, gender, andfamily history while other risk factors, such as hypertension, diabetes, and hyperlipidemia can be managed. Seventy percent of strokes are due to known risk factors [9]. Homocysteinaemia is also one of the modifiable risk factors of stroke [9]. In one study, moderate hyperhomocysteinemia was an independent stroke risk factor seen in 30% of a group of Malaysian ischemic stroke patients [9].

Homocysteine is metabolized by one of two pathways: transsulfuration and remethylation. Vitamins are necessary in the metabolism of homocysteine. Elevations in plasma homocysteine levels can result from genetic factors, most commonly a thermolabile variant of MTHFR with reduced enzymatic activity; vitamin deficiencies, specifically deficiency of folate, vitamin B6, or vitamin B12; chronic kidney disease, which can increase homocysteine levels due to decreased renal removal and impaired metabolism; certain drugs, including fibrates, nicotinic acid, methotrexate and cigarette smoking.

Meta-analyses of case-control studies have found an odds ratio of 2.5 to 3.0 for Venous thromboembolism in patients with markedly elevated homocysteine levels of more than two standard deviations above the mean value of control groups [10-11].

Two types of missense mutation exist: C677T and A1299C. Amongst these two mutations, most of the studies are done only on the C677T mutation.

Xiabo Dong et al. did a meta-analysis in 2021 and found that there was correlation between MTHFR A1298C polymorphism and stroke susceptibility, especially in adults and ischemic stroke [12].

A case similar to ours was reported from Maharashtra by Jimil H shah et al- a 21-year-old male with heterozygous MTHFR mutation causing cerebral sinus thrombosis in 2016 [13].

Our patient was positive for heterozygous MTHFR A1298C mutation and responded well to vitamin supplements and stroke management. His younger sister was also screened and was found to have hyperhomocysteinemia suggestive of hereditary susceptibility. Therefore, this highlight primary prevention in the family.

IV. CONCLUSION

Hyperhomocysteinemia is now a widely recognized risk factor for vascular disorders and ischemic and thromboembolic stroke. The role of heterozygous A1298C mutation in prothrombotic state is still unclear and further larger studies are needed.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms in which the patient has given his consent for images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due effort will be made to conceal his identity.

Financial support and sponsorship

Nil

Conflicts of interest

There are no conflicts of interest.

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