Thrombotic CV Stroke in a Young Male with Hyperhomocysteinemia and Protein S Deficiency: A Case Report

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INTRODUCTION:

Globally, stroke is the second commonest cause of mortality [1] and the fourth leading cause of disease burden.[2] Stroke is a leading cause of death and disability in elderly, however stroke in young adults is also observed. WHO defines stroke as an event caused by the interruption of the blood supply to the brain, usually because a blood vessel bursts or is blocked by a clot. This cuts off the supply of oxygen and nutrients, causing damage to the brain tissue.[3] Common causes of stroke in young person are valvular heart disease , arterial dissection, AV malformation, hypercoagulable state, sickle cell disease, pregnancy and venous thrombosis.[4]

CASE REPORT:

An 18 year old male presented to emergency department with complaint of right sided weakness and dysarthria for 10 hours, headache since 3 days without any significant past, family and personal history.

On presentation, patient's heart rate was 80/min (regular) and blood pressure was 110/80 mmHg. On neurological examination, patient had motor aphasia with right conjugate deviation of eye. Patient had right sided limb hypotonia , areflexia and grade zero power with loss of all sensations and absent plantar reflex. His hematological and biochemical profile were as follows: Hemoglobin- 13.4 gm%, hematocrit-43.5%, total count-7820/mm^3, differential count- 70/24/3/2/1 % respectively, platelet count- 2.4 lac/mm^3 , serum sodium-139 mEq/L, serum potassium-4.2 mEq/L, blood urea-24.2 mg%, serum creatinine-0.78 mg% , serum bilirubin-0.8 mg%, SGPT- 34 mg% and prothrombin time-11.4 seconds with INR 0.84. CT scan report was suggestive of infarct in left cerebellar hemisphere. Conservative management was started in form of Tab. Aspirin 325 mg stat followed by 150 mg OD, Tab. Clopidogrel 75 mg OD, Inj. Mannitol 1mg/kg IV 8 hourly and general nursing care. Further investigations were planned. MRI angiography was done which was suggestive of large acute infarct in left temporo-right perisylvian region- left lentiform nucleus-left parietal-left frontal region, left posterior cerebellar infarct, thrombosis and occlusion of left internal carotid artery with blockage of left middle cerebral artery and its branches from its origin (images 1 and 2). Lipid profile, ECG and 2D Echocardiography were normal. Sickling test, anti cardiolipin antibody, RA factor, Antinuclear Antibody, C Reactive Protein and ASO titre were also negative.

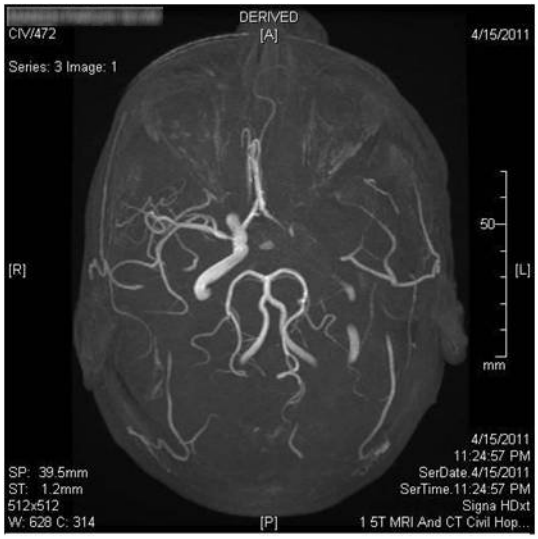

Image 2: MRI angiography showing left MCA block.

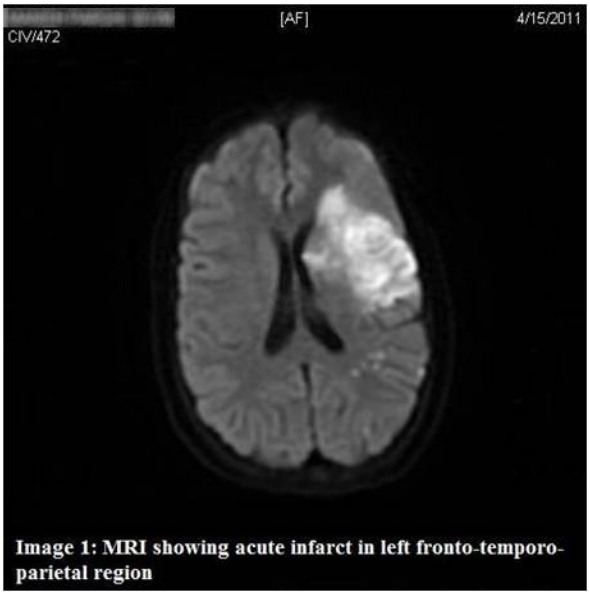

Image 1: MRI showing acute infarct in left fronto-temporo-parietal region

However his serum homocysteine level was 94.8 µmol/L (3-15) which was significantly higher. His serum B12 level was 316 pmol/L and Folic acid level was 260 µg/L . Protein C level was normal but Protein S level was 36% (47-143) which was significantly lower. Treatment was added in form of Inj. Enoxaparin 1mg/kg SC BD for 3 days, and along with Tab. Warfarin 2 mg/day was started with overlapping period of 3 days. Dose of warfarin was adjusted according to PT INR. Tab. Folic acid 20 mg/day was also given.

Patient gradually started improving after 10 days and was discharged with advice of continuation of medications, physiotherapy and speech therapy. At the end of 3 months patient had complete recovery. Repeat levels of protein S and homocysteine were not done due to financial issues of the patient.

DISCUSSION:

According to some studies in India, there is a high incidence (approximately 24–35%) of stroke in young population. Long after acute cerebral ischaemia, an imbalance in the haemostatic system and a minor but significant degree of inflammation was detected in young patients. The mechanisms behind haemostatic imbalance seem to be enhanced thrombin generation, platelet activation and depressed fibrinolysis.[5] Multiple factors causing hypercoagulable state can determine thrombosis in both arterial and venous territory but according to the etiological factor there is a predominance of either of them as shown in the table.[6]

	Arterial thrombosis	Venous thrombosis
Acquired factors	Atherosclerosis Diabetes mellitus Tobacco smoking Oral contraceptives Polycythemia Thrombocytosis Paroxysmal nocturnal hemoglobinuria Sickle cell anaemia Heparin induced thrombocytosis Antiphospholipid syndrome	Prolonged immobilization Trauma Surgery Pregnancy Post partum Oral contraceptives Neoplasia Cancer chemotherapy Antiphospholipid syndrome
Inherited disorders	Hyperhomocysteinemia High Lp(a) Prothrombin G2O210A mutation Protein S deficiency	Antithrombin deficiency Protein S deficiency Protein C deficiency Factor V resistance to activated protein C Prothrombin G2O210A mutation Plasminogen deficiency t-PA deficiency or PAL -1 increase

Homocysteine is an amino acid formed during the metabolism of methionine along two major enzymatic pathways, either remethylation or transsulfuration, which require folate and vitamine B12 or vitamine B6 respectively. High plasma homocysteine levels occur in mutations in one of the enzymes involved in its metabolism. Recent studies have now demonstrated that homocysteine causes endothelial cell dysfunction and induces apoptotic cell death in cell types relevant to atherothrombotic disease, including endothelial cells and smooth muscle cells.[7] Furthermore, a direct causal relationship between induction of Hyper-homocysteinemia and accelerated atherosclerosis has been reported in apolipoprotein E (apoE)-deficient mice with diet- and/or genetic-induced high homocysteine levels are seen in people with vitamin B or folate deficiency, kidney disease, low levels of thyroid hormones, psoriasis, and with certain medications (such as antiepileptic drugs and methotrexate).[8] It has been recognized that some people have a common genetic variant (called methylenetetrahydrofolate reductase, abbreviated MTHFR) that impairs their ability to process folate. This defective gene leads to elevated levels of homocysteine in some people who inherit MTHFR variants from both parents.[7] In our set up it was not possible to get done genetic analysis for MTHFR , and also our patient was vegetarian by diet and was having low levels of Vitamin B12 and Folic acid so we considered giving supplements for the same.

Congenital Protein C or S deficiency is an inherited disorder. Congenital Protein S deficiency is autosomal dominant disorder and occurs in about 1 in 20,000 people. Venous

thromboembolic is more common with Protein S deficiency , however there are studies that suggest an association with arterial thrombus formation also.

Protein S exists in the body in two primary forms, free form and protein bound form. Only the free form of Protein S is able to interact with Protein C. There are three classifications of Protein S deficiency : type I, II and III. Type I Protein S deficiency results from an inadequate amount of Protein S present in both the free and bound forms. Type II Protein S deficiency is characterized by defective Protein S molecules. Type III Protein S deficiency is characterized by a low amount of free Protein S, but an overall normal amount of total Protein S.

This case is of great interest because of association between two factors, one of them inherited Protein S deficiency and other hyperhomocysteinemia (in our patient it was not possible to rule out inherited cause). The prothrombotic activity of the first factor became clinically evident in the presence of second one. It is possible that if any of the two risk factors were independent they could not have generated such a significant thrombotic process like complete occlusion of left internal carotid artery and middle cerebral artery .Regardless of whether there is a MTHFR mutation in both genes or not, the treatment for elevated homocysteine is the same—dietary intervention and supplementation with folic acid and vitamins B_6 and B_{12}. The amount of each of these supplements should be adjusted on the basis of the degree of homocysteine elevation, not the genetic status.[7] In our patient the two major identifiable causative factors for CV Stroke were hyperhomocysteinemia and Protein S deficiency and so the mainstay of therapy for him was folate supplement, and Vitamin B complex supplement to decrease the elevated homocysteine levels and anticoagulation therapy to compensate for inherited Protein S deficiency which resulted in complete recovery of the patient. Though regular follow up is required in such cases.

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