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Case Series

A Case Series Exploring Hyperhomocysteinemia as a Prothrombotic Risk Factor

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ABSTRACT

The role of hyperhomocysteinemia (Hhcy) as a prothrombotic risk factor has been researched and debated over many decades. Several prospective and retrospective studies have established the association of Hhcy as a modifiable risk factor in both arterial and venous thrombosis. This case series of nine patients with either recurrent or unprovoked thrombosis and thrombosis occurring at unusual sites aims to elucidate the association between Hhcy and thrombotic events as an independent risk factor. This study underscores the importance of screening for homocysteine (Hcy) levels for early management of high-risk patients and contributes to the existing evidence of the thrombogenic effects of Hcy, thereby highlighting future research to improve management guidelines and preventive protocols.

Keywords: Folic Acid, Homocysteine, Hyperhomocysteinemia, Thrombosis, Vitamin B12

INTRODUCTION

Homocysteine (Hcy) is an amino acid which is not found in the normal dietary intake and is released in the circulation after demethylation of dietary methionine intracellularly. Hcy is thereafter converted to methionine by remethylation or to cysteine by trans-sulfuration. Both pathways require folate, cobalamin and riboflavin as cofactors. Plasma Hcy level is determined by a large number of genetic and acquired factors.[1-3] Hyperhomocysteinemia (HHcy) has multiple effects on the endothelium and hemostasis.[4-7] Various studies have shown the association of HHcy with thrombosis at common sites like the leg veins, at unusual sites of the upper extremities,[8] cerebral venous thrombosis,[9,10,11,12] retinal vein thrombosis[13] as well as arterial thrombosis in young patients causing acute myocardial infarction[14] and ischemic stroke.[15]

CASE REPORTS

This case series aims to explore the relationship between Hhcy and thrombosis and contribute to the understanding of Hhcy as a prothrombotic risk factor by retrospective analysis of thrombotic events which were either recurrent or at unusual sites specially in patients with no other identifiable prothrombotic risk factors.

Case-1: (Central retinal artery occlusion)

42-year-old non vegetarian male was detected to have central retinal artery occlusion right eye during routine medical examination. His vision was normal in both eyes. First order sclerosed artery was seen in inferotemporal quadrant of right eye. Complete blood counts, biochemistry, ultrasound abdomen with CDFI renal vessels, 2D ECHO, MRI Brain with MR angiography, and EEG were normal. Carotid Doppler revealed a soft plaque in left common carotid artery bulb extending to left internal carotid artery at its origin causing 10 to 20% narrowing. Serum homocysteine level was 23.2 µmol/L (5.46-15), Vitamin B12: 465.10 pg/ml (211-946) and serum folate: 12.97 ng/ml (> 5.38). His thrombophilic profile revealed INR: 1.10 and antithrombin lll: 31.2mg/dL. Immunological profile (antiphospholipid antibody lgM and IgG, cANCA, pANCA) was negative. Fundus fluorescein angiography showed incomplete filling of second order inferotemporal and inferonasal artery with minimal capillary ooze at inferotemporal macula. He was treated with ecosprin, statins, methylcobalamine, folic acid and pyridoxine.

Case-2: (Cerebral venous sinus thrombosis)

31-year-old non vegetarian male presented with acute onset headache and a generalized tonic-clonic seizure (GTCS). He was afebrile and no signs of meningeal irritation or focal deficits were present. Fundoscopy showed papilledema. Hemoglobin was 16.6 g/dL, serum homocysteine: 26.53 µmol/L and procoagulant workup (ANA, ANCA and anticardiolipin antibody) was negative. MRI brain with MR venography revealed thrombosis of right superior sagittal sinus and right transverse sinus. He was managed with a course of oral anticoagulants and antiepileptics for three months followed by ecosprin and anticoagulants. He had recurrence of GTCS after 2 years. MRI brain showed encephalomalacia and gliosis in left corona radiata with near complete recanalization of superior sagittal sinus and right transverse sinus. EEG was normal. Therapy with antiepileptics and anti-platelets was continued.

Case-3: (non-obstructive coronary artery disease)

48-year-old vegetarian male with no cardiovascular risk factors presented with anginal chest pain. ECG showed ST depression in leads l, aVL and Q waves in lll and aVF. 2D ECHO did not reveal any regional wall motion abnormalities (RWMA) and ejection fraction was 60%. Treadmill test was positive for reversible ischemia at 10.6 METS. Stress MPI showed a small sized stress induced reversible myocardial ischemia of mild severity in the posterior segment. Coronary angiography revealed plaques in left anterior descending (LAD) and left circumflex (LCx) coronary arteries and slow flow in right coronary artery (RCA) suggestive of non-obstructive coronary artery disease. He was managed with dual anti platelet therapy and statins and his symptoms remained in NYHA ll for next four years. Repeat ECHO showed normal biventricular function with no RWMA. S. homocysteine level was 25.23 µmol/L. Stress MPI did not reveal any evidence of inducible ischemia and LV function was normal. Coronary angiography showed mild plaques in LAD and LCx, and slow flow in RCA. Medical management with folic acid, beta blockers, anti-platelet therapy and statins was continued.

Case-4: (Acute anterior wall ST elevation myocardial infarction with LV clot and cerebral venous sinus thrombosis)

31-year-old male with no known cardiovascular risk factors presented with acute anterior wall ST elevation myocardial infarction. Thrombolysis was done with injection tenecteplase. Echocardiography revealed apical hypokinesia with LVEF of 50%. CAG showed a mid-LAD 100% thrombotic occlusion. PCI to LAD was done with drug eluting stent (2.25 x 23mm Xience Prime) and he was managed on ecosprin and ticagrelor. He developed holocranial headache and photophobia three days later. Wernike's aphasia was present and CE-MRI brain and MRV revealed thrombosis of left internal jugular vein, left transverse and sigmoid sinuses, left temporal lobe hematoma and multiple small embolic infarcts in right parieto-occipital and frontal lobes. 2D ECHO showed apical hypokinesia and a LV clot. Thrombophilia profile was negative (Antithrombin: 110% (80-120), Protein C: 119 IU/dL (60-140), Factor V Leiden Mutation: not detected, Prothrombin gene mutation: not detected, MTHFR mutation: not detected, lupus anticoagulant: negative, B2 glycoprotein lgG/lgM: 6.7 SGU/ml/ 4.19 SMU/ml (< 20), Cardiolipin lgG/lgM: 11.79 GPL/ 12.26 GPL (< 12.5)). Serum homocysteine was 25 µmol/L. He improved with dual anti platelets, anticoagulants, anti-epileptics and decongestant therapy and was advised a course of folic acid, antiepileptics and oral anticoagulant for 6 months.

Case-5: (Recurrent deep venous thrombosis with Pulmonary thromboembolism)

33-year-old non vegetarian male a known case of DM II and chronic DVT right lower limb for 10 years had discontinued anticoagulation for 6 months when he developed painful swelling of left lower limb. CDFI left lower limb showed acute DVT involving SFV, popliteal and posterior tibial veins. Chronic DVT was present in right lower limb. He was treated with low molecular weight heparin and anticoagulation but he developed sudden onset palpitations and pleuritic pain left chest. ECG showed RV strain pattern and CT Pulmonary Angiography (CTPA) revealed a hypodense thrombus in the right and left main pulmonary artery extending into its superior and inferior divisions and subsegmental branches suggestive of pulmonary thromboembolism with severe thrombus burden. D dimer level was 4756.90 FEU. Thrombophilia profile was negative (Anti beta 2 glycoprotein lgG/ IgM: 1.22SGU/ 2.0 SMU (< 20), Cardiolipin antibody lgG/ IgM: 8.70 GPL (< 15)/ 8.64 GPL (< 12.50), Lupus Anticoagulant: not detected, Factor V Leiden, Prothrombin gene and MTHFR gene mutations were not detected). Serum homocysteine was 39.46 µmol/L and vitamin B12 level was 145 pg/ml. He improved significantly with a course of injection low molecular weight heparin (LMWH) 80 mg subcutaneously BD for 15 days followed by anticoagulation with rivaroxaban. He had recurrence of swelling left lower limb a month later followed by chest pain and breathlessness. Repeat CTPA revealed a saddle thrombus in pulmonary artery bifurcation extending to bilateral pulmonary arteries and into lobar and segmental branches. Signs of RV dysfunction was seen with increased RV/LV ratio. In view of recurrent DVT with unprovoked VTE he was advised long term anticoagulation.

Case-6: (Pulmonary thromboembolism)

29-year-old male developed insidious onset, gradually progressive dyspnea on exertion a month after deinduction from a high-altitude area (21000 ft). He remained symptomatic for next 2 months followed by a syncopal attack. Serial ECGs, cardiac biomarkers and 2D ECHO were normal. CT Pulmonary Angiography (CTPA) showed a partial focal filling defect at subsegmental branch of left lower lobe pulmonary artery suggestive of partial acute pulmonary thromboembolism (PTE). FDP level was 52.51µg/ml (<10). He improved with a course of LMWH and oral anticoagulants. He remained asymptomatic at 6 months follow-up and serum homocysteine was 43.09 µmol/L. CTPA revealed complete resolution of PTE and he is on long term oral anticoagulation.

Case-7: (Portal vein thrombosis)

27-year-old male was detected to have cavernous transformation of portal vein and splenomegaly (13.3 cm) suggestive of portal hypertension (sequelae of portal vein thrombosis) on routine ultrasound abdomen done during evaluation of plasmodium vivax malaria. No clinical or biochemical evidence of chronic liver disease was present and UGI endoscopy was normal. Thrombophilic profile (ANA, APLA panel, CALR mutation) was negative. Serum homocysteine level was 29.65 µmol/L, vitamin B12: 362.4 pg/ml and serum folate: 5.27 ng/ml. UGI endoscopy and fibroscan were normal and he was treated with tab propranolol 40 mg bd.

Case-8: (Upper limb arterial thrombosis with cerebral venous sinus thrombosis)

45-year-old male was diagnosed to have acute limb ischemia left upper limb with absent flow in left subclavian, axillary, brachial, radial and ulnar arteries based on clinical examination and CDFI left upper limb. Left trans-brachial thrombectomy was done following which he did not have any residual neurovascular compromise and was advised long term anticoagulation. Two years later he developed headache and diplopia. Bilateral papilledema and left VI cranial nerve palsy was present. CT venography, MRI brain and MRV revealed cerebral venous thrombosis in superior sagittal sinus, right transverse sinus, sigmoid sinus and superficial cortical veins. His procoagulant workup was normal. Serum homocysteine was 27.80 µmol/L, vitamin B12: 228.10 pg/ml and serum folate: 5.05ng/ml. He was managed with LMWH overlapped with oral anticoagulation. He remained symptomatic and repeat MRI brain and MRV after 2 years of regular anticoagulant therapy revealed near total occlusion of superior sagittal sinus and patchy recanalization of left transverse sinus with dural collaterals. CDFI (arterial) left upper limb-showed normal PSV flow in left subclavian, axillary and brachial arteries. Triphasic flow was present in left radial artery. The caliber of proximal left ulnar artery was reduced with low velocity biphasic flow and the distal half was obliterated with echogenic luminal contents. Long term anticoagulation was advised.

Case-9: (Central retinal vein occlusion)

51-year-old hypertensive male, presented with one year history of painless, progressive diminution of near vision left eye followed by impairment of distant vision. He had grade II hypertensive retinopathy in both eyes and central retinal vein occlusion (CRVO) with macula edema in left eye. Serum homocysteine was 39.19 µmol/L. Two doses of intraocular ranibizumab injection was administered at one month interval and he was advised pyridoxine and folic acid supplementation.

DISCUSSION

HHcy results from genetic, age and gender related, racial, nutritional, epigenetic, and iatrogenic causes. It is classified as mild (15-30 µmol/L), moderate (30-100 µmol/L) and severe (> 100 µmol/L). There is a high prevalence of HHcy in healthy Asian Indian population and ethnic related excess of plasma homocysteine levels has been seen in Asian Indians living in the United States as compared to Caucasians.[16] A global trend of vegetarianism in Asia, Central and South America, Mexico and parts of Africa predisposes to vitamin B12 and folate deficiency, an acquired cause of HHcy. HHcy as a risk factor for thrombosis has undergone intense investigation in the past and its role in thrombosis has many unexplored avenues.

The proposed mechanism of HHcy induced vascular injury is through oxidative stress, overproduction of free radicals, mitochondrial dysfunction, endothelial injury, atherosclerosis, DNA dysfunction, increased proliferation of vascular smooth muscle and low-grade inflammation.[17] Mild elevations of Hcy levels increase the risk of DVT in the general population. Several studies have shown Hhcy as an independent risk factor for CVD which is the leading cause of death worldwide.[18-20] Wu et al in their retrospective study have shown an independent correlation of Hhcy with obstructive CAD with 93.1% sensitivity, 90% accuracy and 86.1% specificity.[21] Sun et al in their study on young Chinese adults with ACS revealed that Hhcy was associated with severe CAD, multi vessel involvement and ST elevation myocardial infarction.[22] Aday A W et al in the largest prospective study have shown the association of Hhcy with increased risk of future venous thromboembolism (VTE), specially unprovoked pulmonary embolism and DVT.[23] Hhcy is considered a risk factor for venous thrombosis at unusual sites like cerebral, retinal, upper extremity, portal and splanchnic veins. Although current guidelines do not recommend screening for homocysteine in healthy individuals for primary prevention

and assessment for both CVD and VTE, screening of high-risk patients for thrombosis would be beneficial. The conventional and effective mode of treatment of Hhcy is with supplementation of vitamin B6, B12 and folic acid.

CONCLUSION

To conclude, Hhcy has been found to be a modifiable risk factor in thrombosis, however it's exact pathological mechanisms and clinical implications remain incompletely understood, therefore, future research to study Hcy as a prothrombotic biomarker, accurate risk assessments, polygenic risk scores and stratification of patients would enable healthcare providers to initiate preventive protocols for optimization of thromboprophylaxis in the form of dietary interventions, lifestyle modifications and pharmacological treatment to improve clinical outcomes in high risk cases.

Informed Consent

Written informed consent was taken from all patients for publication of this case series

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