CASE SERIES

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Hyperhomocysteinaemia and Hypercoagulability: A Case Series from Darjeeling

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Abstract

Hyperhomocysteinaemia (HHcy) is a common metabolic disorder that predisposes to a procoagulant state and has emerged as an established risk factor for IHD, ischaemic stroke and DVT. Serum Vitamin B12 and folate concentrations play significant role in pathogenesis, as both are important co-factors in the methionine cycle. Nutritional deficiencies and enzyme defect in the methionine homocysteine pathway contributes to HHcy. We report here 4 cases of HHcy (AMI 1, ischaemic Stroke 2 and DVT 1), all in the age group of 18 to 40 years. We propose that HHcy is grossly under-reported in our country and all cases with ischemic pathology in younger age should be screened for HHcy.

Key words: Hyperhomocysteinaemia, methionine, vitamin B12.

Introduction

Hyperhomocysteinaemia (HHcy) is a common metabolic disorder characterised by systemic elevation of the thiol amino acid, homocysteine, formed as an intermediate of the methionine cycle[1]. Deficiencies of cofactors of the methionine cycle such as vitamin B6, B12, and folate, or defects of enzymes such as cystathionine beta-synthase (CBS) or methylenetetrahydrofolate reductase (MTHFR), contribute to the genesis of HHcy. HHcy is associated with premature atherosclerosis, endothelial dysfunction and arterial and venous thrombosis[2].

Case 1

BR, an 18-year-old, non-diabetic, non-hypertensive non-smoker male, vegetarian, student from Kalimpong, West Bengal, India, was admitted with chest pain of 7 hours duration. The chest pain was sudden in onset, constricting in nature, radiating to left arm, aggravated with activities, associated with profuse sweating and was not relieved with oral analgesics. The patient had no history of fever, palpitation, dyspnoea, cough or haemoptysis, denied any past or current addictions, and had no family history of sudden cardiac death. We received the patient in respiratory distress with pulse rate of 98/minute regular, and BP 110/74 mmHg over the right upper arm in supine position. He was tachypnoeic with respiratory rate of 26/min with normal SpO_2 in room air. ECG revealed lateral wall AMI without AF and the patient was thrombolysed with Tenecteplase (Fig. 1A). Repeat ECG after 1 hour showed >50% reduction of ST elevation. 2D ECHO showed hypokinetic postero-lateral wall, moderate systolic dysfunction with LVEF 41%. Coronary angiography revealed unremarkable D1/D2, thrombotic plaque at proximal D1, dominant RCA and totally occluded distal LCX (Fig. 1B). Blood tests suggested macrocytic anaemia and elevated serum homocysteine with decreased serum vitamin B12 levels (Table I). Other causes of a hypercoagulable state were ruled-out. We arrived at a final diagnosis of posterolateral AMI in a young male with HHcy and macrocytic anaemia due to vitamin B12 deficiency. Patient was treated with parenteral vitamin B12 supplementation 1000 µg IM weekly for 6 weeks, then monthly, along with folic acid supplementation. He had an uneventful recovery and is currently under regular follow-up.

Case 2

MT, 30-year-old non-diabetic, non-hypertensive, alcoholic male smoker, presented with sudden onset right-sided hemiparesis, simultaneously involving proximal and distal limbs. The weakness rapidly progressed to complete paralysis, within a span of 30 minutes without headache, fever, vomiting, convulsion, diplopia, or vertigo. The patient had slurring of speech and deviation of mouth towards the left side. There was no family history of stroke or sudden cardiac death. On arrival, his pulse was 96/minute, regular, and normal in volume, with no special character, all peripheral pulses well palpable, and no radioradial or radio femoral delay. The BP was 128/84 mmHg measured at left upper arm supine position, respiration 20/min, and Spo2 99% in room air. Neurological examination revealed complete right-sided hemiparesis. NCCT brain showed no hemorrhage (Fig 1C). Our stroke thrombolysis team was activated and thrombolysis was performed with

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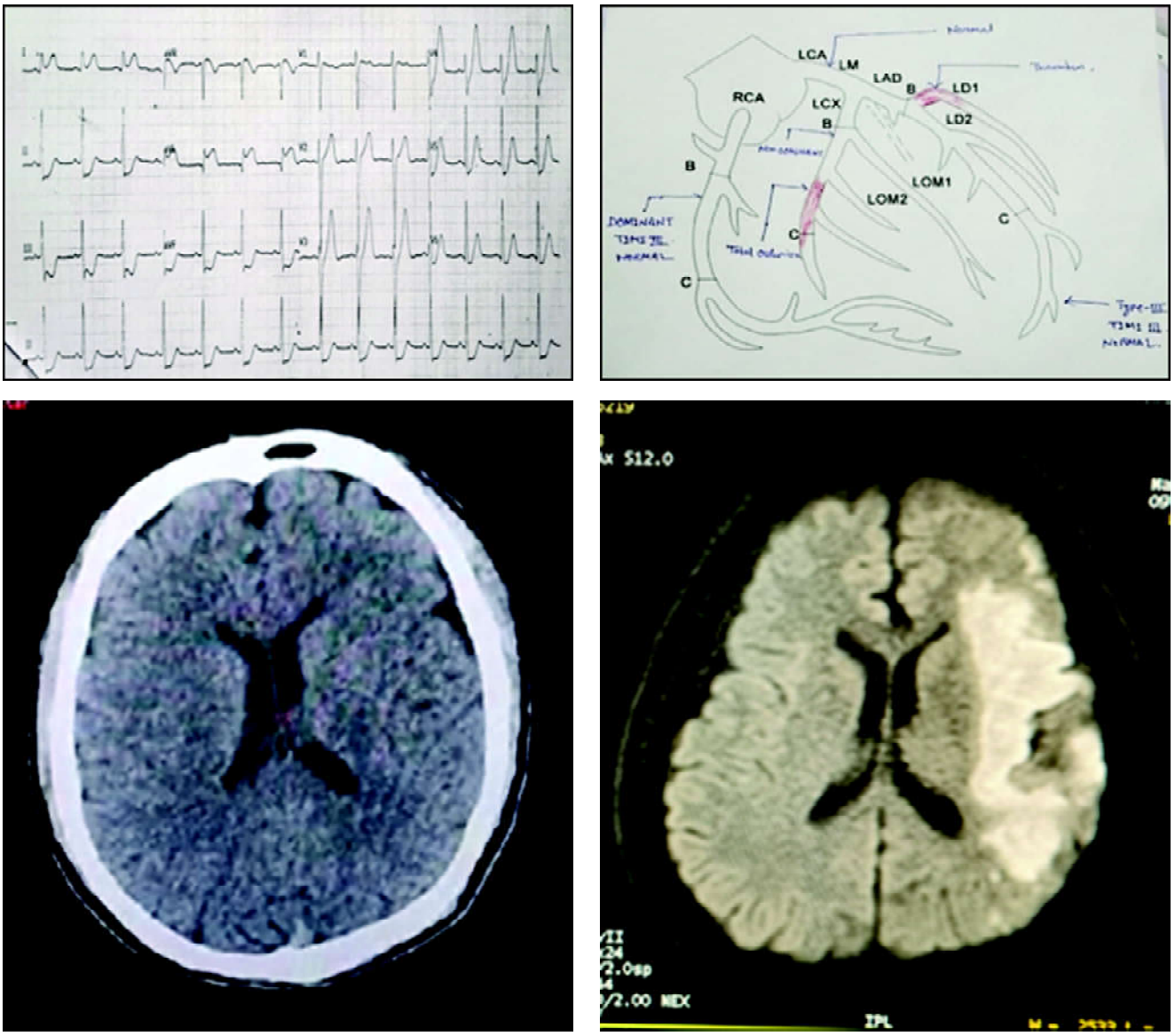

Fig. 1: *Showing investigation findings of contributing cases. 1A: ECG from Case 1 showing STEMI involving anterior wall; 1B: Diagrammatic representation of coronary angiography findings of Case 1; 1C: NCCT brain from Case 2, prethrombolysis; 1D: MR DWI showing large left MCA territory infarct from Case 3.*

Tenecteplase. Two hours after thrombolysis, the NIHSS score reduced from 12 to 7, and was zero after 24 hours of thrombolysis. Carotid artery Doppler showed a 5.5 x 3.0 mm non-occlusive thrombus in the left ICA, which was confirmed by MR angiography. Blood tests documented ANA seronegativity and elevated homocysteine levels with normal blood levels of protein C, protein S and antithrombin III (AT III) (Table I). ECG 12 lead showed sinus rhythm. The upper GI endoscopy was non-contributory. We considered a final diagnosis of complete right-sided hemiparesis due to atheroembolic stroke on the background of HHcy and normal vitamin B12 level, possibly due to an enzyme defect or deficiency in the methionine homocysteine metabolism cycle (Fig. 2). The patient was treated with antiplatelet therapy and is presently on physical rehabilitation care.

Case 3

RT, a 28-year-old non-diabetic, non-hypertensive, non-smoker, non-alcoholic male from Darjeeling, presented with right-sided hemiparesis of acute onset, along with slurring of speech and deviation of mouth towards left side, 2 days back. He had no headache, fever, vomiting, convulsion, diplopia, vertigo, or sensory symptoms. There was no positive family history of stroke or sudden cardiac death. Initial assessment revealed normal vital parameters including pulse 90 bpm regular, BP 120/74 mmHg. Neurological examination revealed right-sided complete

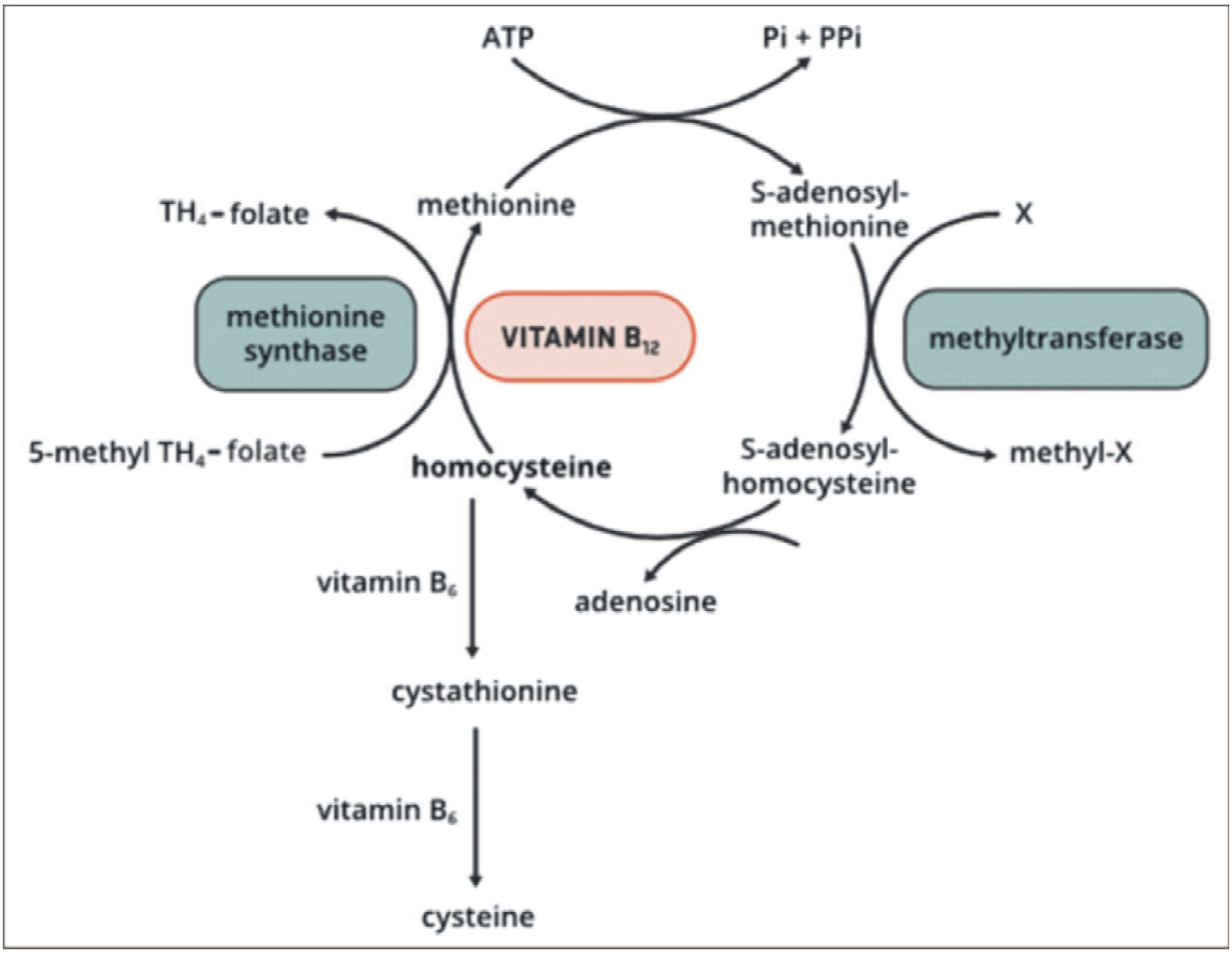

Fig. 2: *Methionine homocysteine metabolism cycle.*

hemiparesis with characteristic UMN features. CT scan revealed hypodensity in left temporo-parietal region, suggestive of acute infarct. MRI brain revealed large acute infarct involving left MCA territory (Fig. 1D). MR angiography and carotid artery Doppler were normal. ECG 12 lead showed sinus rhythm. Blood tests were normal, except for high EPO level characteristic of residence at high altitude, and macrocytosis arising out of diminished serum vitamin B12 and folate levels, along with elevated homocysteine. Other causes predisposing to hypercoaguability were ruled-out (Table I). He was diagnosed to be a case of ischaemic stroke in young with HHcy contributing to a hypercoaguable state. The patient received aspirin, rosuvastatin, B12 and folate supplementation and was discharged with follow-up at the Physical Medicine and Rehabilitation Department.

Case 4

AS, a 40-year-old non-diabetic, non-hypertensive, non-smoker, non-alcoholic, vegetarian female presented with recurrent right-sided lower limb swelling for last 2 years. She had a pulse rate of 104/minute regular, with good volume and all peripheral pulses being well palpable. All other vital parameters were normal. Doppler study revealed an echogenic thrombus at right popliteal vein extending up to right common femoral vein. Doppler of all other limbs, as well as the ECG and echocardiography, was normal. Blood biochemistry including tests for protein C, protein S and AT III was normal, except for high homocysteine and reduced vitamin B12 (Table I). We entertained a diagnosis of recurrent DVT of right popliteal vein without evidence of embolic sequel, on the background of HHcy leading to a thrombophilic state.

Discussion

The essential amino acid methionine is usually present in diet far in excess of physiological needs. Excess methionine

is degraded by the methylation cycle to homocysteine, which can be remethylated back to methionine or catabolised by transulfuration to cysteine. In this metabolic cycle, activation of methionine generates S-adenosylmethionine (SAM), which serves as the "universal methyl donor" for numerous methylation reactions. The recycling of Homocysteine back to methionine requires the enzyme methionine synthase (also known as 5-methyltetrahydrofolate-homocysteine methyltransferase), along with folate in the form of 5-methyltetrahydrofolate as the methyl donor and vitamin B12 in the form of methylcobalamin as a cofactor (Fig. 1).

Table I: Laboratory data with normal values.

	Normal value	Case 1	Case 2	Case 3	Case 4
BMI	18.5 - 23 kg/m^2	19.4	22.2	20.7	21.5
Hb	13 - 15 g/dL	11.0	14.8	16.9	9.8
MCV	80 -100 μm^3	103	92	100	112
WBC	4,000 - 10,000/μL	13,300	7,000	6,100	9,800
Platelet count	150 - 500/μm	218	206	95	187
FBS	<100 mg/dL	85	93	98	105
TSH	0.7 - 5.2 mIU/L	1.6	2.1	1.8	2.4
Creatinine	0.6 - 1.2 mg/dL	0.5	0.9	0.5	0.7
LDL Cholesterol	<100 mg/dL	52	81	55	104
Triglyceride	50 - 150 mg/dL	36	163	109	134
Uric Acid	3.6 - 7 mg/dL	4.7	4.0	8.7	6.2
Serum Protein	6.0 - 8.3 mg/dL	7.4	6.8	7.0	7.2
Serum Albumin	3.5 - 5.5 mg/dL	4.2	3.9	4.1	5.0
Serum B12	120 - 914 pg/mL	67.83	239	106	51
Serum Folate	3.1 - 19.9 ng/mL	4.82	6.2	2.0	3.2
Homocysteine	3.3 - .2 μmol/L	30.82	48.54	>50.00	41
Lipoprotein (a)	0 - 30 mg/dL	18.35	9.5	25.5	20
Protein C	65 - 135 IU/dL	92.4	97.2	110.6	104.7
Protein S	60 - 160 IU/dL	77.2	87.3	105.8	95.8
Antithrombin III	80 - 130%	96%	102%	113%	88%
ANA	Negative	Negative	Negative	Negative	Negative
APLA	Negative	Negative	Negative	Negative	Negative
ANCA	Negative	Negative	Negative	Negative	Negative
24 hour urinary protein	<30 mg	12	23	27	14
Echocardiography		Hypokinetic postero - with LVEF 41%	No RWMA with LVEF 68%	No RWMA with LVEF 65%	No RWMA with LVEF 70%

It is now well accepted that elevations of homocysteine in the blood arise from genetic defects in homocysteine transsulfuration or re-methylation, or in the transport, delivery or metabolism of cofactors, B12 and folate being the most clinically important. Cystathionine β-synthase deficiency leading to impaired metabolism of homocysteine, MTHFR deficiency leading to impaired 5-methyl tetrahydrofolate generation subsequently leading to reduced availability of methyl groups for the remethylation of homocysteine, and disorders of vitamin B12 absorption, transport, and metabolism, are the primary causes of HHcy in clinical settings[3]. In this series of 4 cases of HHcy, 3 patients had B12 deficiency (Cases 1, 3 and 4), and the remaining patient had clinical suspicion of an enzyme defect (Case 2). Case 3 also had associated folate deficiency which might be contributory to the genesis of HHcy. We excluded prothrombotic states due to protein C and protein S deficiency, dyslipidaemia and hypothyroidism, as well as those arising from common autoimmune settings (Table I).

Elevated plasma homocysteine is associated with an increased risk of myocardial infarction, stroke, and venous thromboembolism.[4] A meta-analysis found that for every 2.5 μmol/L increase in plasma total homocysteine, the risk of myocardial infarction increases by about 10% and the risk of stroke increases by about 20%[5]. It has been suggested that HHcy may be a late stage predictor of CVD, implying elevated homocysteine levels may not be a primary risk factor for atherosclerosis and CVD, but may increase the risk of clinical disease in those with an atherosclerotic background[6].

The issue of elevated plasma homocysteine levels as predisposition to cerebrovascular disease appears less distinct in the world literature. In the British Regional Heart Study of 5665 men aged 40 to 59 years, baseline homocysteine levels in those who suffered a first stroke during 12.8 years of follow-up were significantly higher. In the same study it was observed that comparison of homocysteine levels of 15.4 μmol/L or more with levels less than 10.3 μmol/L yielded a multivariate relative risk of stroke of 4.7[7]. Accordingly it may be concluded that HHcy is likely to confer a significantly high-risk of stroke.

Elevated homocysteine has a documented association with unprovoked, deep vein thrombosis (DVT) and pulmonary embolism (PE)[8]. In a study of 60 patients with DVT from Turkey, mean homocysteine was significantly higher in patients over the age of 40 years[9]. In our series, all patients were between 18 to 40 years and the questionable issue of homocysteine elevations with age, does not appear to influence our findings.

Considering hypercoagulable states seems clinically judicious when encountering stroke, CVD or DVT in young. Thomas proposed the mnemonic CALMSHAPES to remember the clinically important hypercoagulable states: Protein C deficiency, Antiphospholipid syndrome, factor V Leiden mutation, Malignancy, protein S deficiency,

hyperhomocysteinaemia, antithrombin III deficiency, prothrombin G2021A mutation, factor eight excess, and Sticky Platelet syndrome[10]. With better understanding and refined diagnostics, all these are being picked up more frequently in recent years.

Conclusion

We conclude that HHcy confers an independent predisposition to a hypercoagulable state, and in the appropriate metabolic milieu, can lead to premature prothrombotic clinical events, as exemplified by our cases. Increasing physician awareness to consider this often neglected procoagulant risk factor is the central purpose of this case series.

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