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Case Report

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Treatment of Venous Thrombosis in Young Patient with Moderately Severe Homocysteinemia – is Long Term Anticoagulation with Direct Oral Anticoagulation Effective Along with Folate and B12 Supplementation

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Keywords:

Homocysteine; Vascular injury

1. Background

Homocysteine is a sulfhydryl-containing amino acid formed during the metabolism of methionine. Recent evidence links elevated homocysteine levels to thrombosis via several mechanisms such as increased tissue factor expression, attenuated anticoagulant processes, enhanced platelet reactivity, increased thrombin generation, augmented factor V activity, impaired fibrinolytic potential, and vascular injury, including endothelial dysfunction [1-4]. Thus, higher total plasma homocysteine concentration is associated with increased risk of coronary artery disease, stroke, and venous thromboembolism.

Homocysteinemia is currently considered a weak prothrombotic factor and it is still unclear whether administration of vitamins like folate and B12, that reduce homocysteine levels acting as cofactors of the enzymes involved in the methionine metabolism, may decrease the risk of arterial and/or venous thromboembolic events [2,3,5].

In this case report, we describe a young patient admitted at Tan Tock Seng Hospital in Singapore, with homocysteinemia and venous thrombosis and response to direct oral anticoagulation (DOAC) with vitamins supplementation of folate and B12.

2. Case Presentation

A 23-year-old Indian male, non-smoker, and non-drinker with past medical history of Right Anterior Cerebral Artery-Middle Cerebral Artery watershed infarct in May 2019, and childhood seizure disorder on Keppra.

On admission in March 2020, he presented with right sided headache of 2 days duration and developed seizures in the hospital. He was on medications such as Keppra and Plavix. He was non-compliant to treatment.

In the emergency room, vital signs were stable with documented tachycardia with heart rate 100/minute. Physical examination findings were unremarkable with no new focal neurologic deficits.

His investigations showed full blood count and electrolytes were normal (Table 1) However, folate and B12 is significantly low. MRI Brain Stroke protocol showed cerebral venous sinus thrombosis and CT Angiogram showed acute thrombosis in the superior sagittal sinus (Figure 1). CT scan of abdomen and pelvis showed no masses or malignancies.

In his previous admission in March 2019, for young stroke workup was done and showed high homocysteine level >50 umol/L. The rest of the investigations were unremarkable. (ANA, dsDNA, anticardiolipin, LAC, antithrombin III, protein C and protein S, B2- glycoprotein- normal). Family was not keen for N-methylenetetrahydrofolate reductase deficiency testing.

His homocysteine levels were repeated on 20 March 2020 and showed high homocysteine level (>50 umol/L) (Table 2). He was graded intermediate high based on Kang and Coworkers classification for homocysteinemia (Table 3). Homocysteine levels in a healthy person is around 5 to 15 micromoles per liter (umol/L).

The following are the grading for homocysteinemia: Moderately high: 15–30 umol/L; Intermediate high: 30–100 umol/L and Severe: Above 100 umol/L [7].

Patient was managed as acute thrombosis in the superior sagittal sinus and cortical veins with homocysteinemia. There was no convincing evidence of atherosclerotic disease on the CT scan, and Neurologist had advice that there was no role of antiplatelet therapy and that the previous mechanism of stroke in 2019 remains as a prothrombotic state, hence anticoagulation monotherapy is sufficient. Plavix was stopped eventually and was continued on anticoagulation. SC Clexane 1 mg/kg BD was given and bridged to Apixaban 5 mg BD. He was given oral folate and B12 supplementation. He was discharged well and stable. He was counselled on compliance to both anticoagulation and folate/B12 supplementation as he was previously noted non adherent to his medications.

Patient had remained well with no more headaches. In 26 August 2020, an MR Venogram was performed and showed recanalization of the venous sinuses (Figure 2). He was continued long term anticoagulation with DOAC. He was given Rivaroxaban 20 mg once a day. He tolerated anticoagulation and on last follow up with Vascular Medicine Clinic in Tan Tock Seng Hospital in January 2023, he was given advised to continue medications with compliance to both anticoagulation and folate/B12 supplementation.

3. Discussion

Homocysteinemia is a rare condition which is associated with risk of developing atherosclerosis and blood clots in the arteries and veins. 2,3,4 More than 75 clinical and epidemiological studies have shown a relation between total homocysteine levels and coronary artery disease, peripheral artery disease, stroke, or venous thrombosis [5- 7] (Figure 3).

Homocysteinemia is graded by Kang and co-workers (Table 3) as moderate, intermediate, and severe as per the plasma homocysteine concentrations in fasting. Kang and coworkers have classified hyperhomocysteinemia as moderate (homocysteine concentration, 15 to 30 mmol/L), intermediate (30 to 100 mmol/L), and severe (100 mmol/L) on the basis of concentrations measured during fasting.

Severe hyperhomocysteinemia occurs in homozygous deficiency of N, N10-methylenetetrahydrofolate reductase, the enzyme involved in the vitamin B12-dependent remethylation of homocysteine to methionine, may also lead to severe hyperhomocysteinemia [4,5]. Patients with this type of deficiency tend to have a worse prognosis than those with cystathionine β-synthase deficiency, in part because of the complete lack of effective therapy. Family of our patient was not keen for N, N-methylenetetrahydrofolate reductase deficiency testing. Patients with this type of deficiency tend to have a worse prognosis than those with cystathionine β-synthase deficiency, in part because of the complete lack of effective therapy.

Patient had high homocysteine levels of >50 μmol/L, which are in the intermediate range of Kang's classification, at a risk of thrombosis. Anticoagulation was continued long term, in view of homocysteinemia, as patient had very high chance of thrombosis recurrence since it is a risk factor for both arterial and venous thrombosis.

The B vitamins, including folate and B12, play vital roles in the metabolism of homocysteine. Deficiency of these B vitamins can lead to an elevated circulating level of total homocysteine, which has been implicated in the development of cardiovascular disease.5,6 Patient was treated with folic acid and B12 supplement, but it is not known whether homocysteine-lowering therapy such as folic acid, or vitamin B12 is useful in prevention of recurrent venous thrombosis [5-7].

4. Conclusion

Homocysteinemia in the intermediate range, especially in very young patient, carries a high risk of thrombosis. Any young patient presenting with thrombosis should have homocysteine level checked . DOAC can be used as a long-term option along with Vitamin B12 and folate supplementation for treatment of thrombosis in this setting.

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Table 1:

Routine Blood tests: (20 March 2020)
Full blood count: Haemoglobin 16.1 g/dL WBC 8.9 x10^9/L Platelet 150 x10^9/L
Coagulation profile: PT 14.5 secs PTT 27.7 secs
ECG: Normal Sinus Rhythm
Electrolytes: Sodium 136 mmol/L Potassium 3.7 mmol/L corrected Calcium 2.35 mmol/L
Magnesium 0.7 mmol/L Phosphate 1.0 mmol/L
Albumin 47 g/L Urea 3.5 mmol/L Creatinine 70 umol/L
Folate 7 nmol/L B12 88 pmol/L
Anti-IF 2 negative, Anti-parietal cell positive

Table 2: Thrombophilia screen

ANA<80 IU/mL Anti-ds-DNA<25 IU/mL
Anti-thrombin III 80 IU/mL
Protein C 76 IU/dL Protein S 84 IU/dL
Anti B2 glycoprotein, anti-cardiolipin IgM and IgG- negative
Factor V Leiden negative
Lupus anticoagulant -negative
Anti-cardiolipin IgM/IgG, lupus anticoagulant -negative
Anti-B2cglycoprotein -negative
Homocysteine > 50 umol/L

Table 3: Kang and co-workers homocysteinemia severity grading [7].

On the basis of concentrations measured during fasting
1. **Moderate (15 to 30 mmol/L)**
2. **Intermediate (30 to 100 mmol/L)**
3. **Severe (100 mmol/L)**

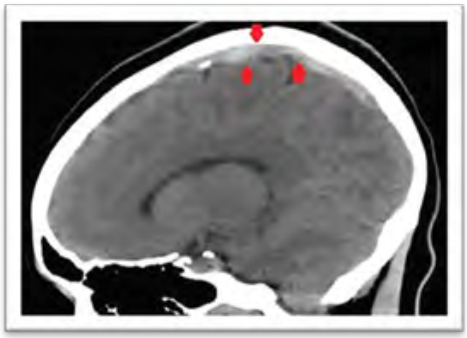

Figure 1: CT Angiogram in March 2020

Figure 1.1: Hyper density is seen in the superior sagittal sinus (SSS), in the anterior half, as well as in the cortical veins at the high frontal region. There are associated filling defects in the SSS on the delayed phase of the CT angiogram, in keeping with acute Dural sinus thrombosis and cortical vein thrombosis.

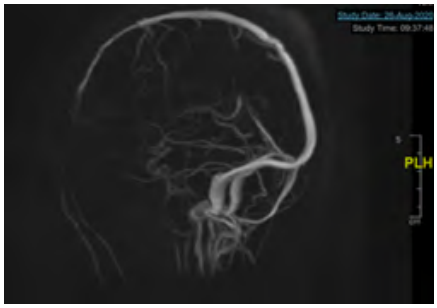

Figure 2: MRV in August 2020

Recanalization of the previously occluded Dural sinuses and cortical veins. No evidence of Dural or deep venous thrombosis on the current study.

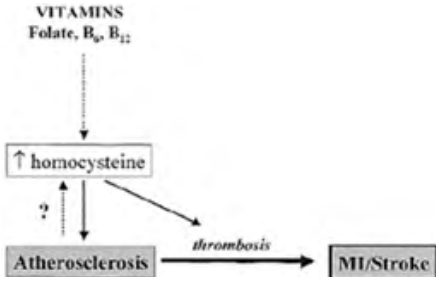

Figure 3: Elevated homocysteine levels – Toxic effect on the vascular endothelium