Case Report

Vitamin B12 deficiency and hyperhomocysteinemia: A description of two cases with thrombosis

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Abstract: Elevated homocysteine levels are associated with venous and arterial thrombosis. This report describes two patients with low vitamin B12 levels due to pernicious anaemia and elevated homocysteine levels, one of whom presented with an arterial thrombosis (cerebrovascular event) and another with venous thrombosis (deep vein thrombosis) without any other apparent cause for their presentation. Although not routinely recommended, it may be of value to screen patients with unexplained arterial or venous thrombotic events for elevated homocysteine levels. However, the paradox remains, that while hyperhomocysteinaemia is associated with an increased risk of thrombosis, therapeutic strategies that lower homocysteine levels do not reduce the risk of thrombotic events.

INTRODUCTION

Hyperhomocysteinemia and thrombotic events have long been described but the association remains controversial with some meta-analyses finding a positive correlation and other studies disputing it. Thrombotic events in young patients, whether arterial or venous, usually triggers a workup for risk factors such as anti-phospholipid syndrome and inherited thrombophilias, but the measurement of homocysteine levels is not currently recommended.

CASE 1

Mrs PD is a 37-year-old woman, non-smoker with no co-morbidities and has 2 children with an uneventful obstetric history. She presented with a sudden onset dense left hemiplegia, associated with left facial weakness. A computed tomography (CT) scan of the brain confirmed a right middle cerebral artery territory infarct and CT angiogram revealed a partially occlusive thrombus of the right common carotid, with complete occlusion of the right internal carotid artery in the neck and the right external carotid artery occluded from its origin. A transthoracic echocardiogram did not show origin of the thrombus being cardiac and no structural heart disease was found.

Laboratory investigations showed a normal haemoglobin (14 g/dl) (normal 11.6–16.4) with an elevated mean corpuscular volume (MCV) of 116 fL (normal 78.9–98.5). The liver and renal function were normal with a normal lipogram. Vitamin B12 was reduced at 45 pmol/l (normal 156–672) with normal serum folate 31.5 nmol/l (normal 8.8–60.3). Antibodies to parietal cells and intrinsic factor were both positive and homocysteine levels were greater than three times the upper limit of normal, measuring 50 umol/l (normal 5.1–15.4). The antiphospholipid work up and Human Immunodeficiency Virus (HIV) testing was negative.

During the course of her hospital stay she regained mild power on the left side and could mobilise with the aid of a walking frame. Vitamin B12 replacement was initiated during her hospital stay with 1mg intramuscular injections daily for a week then weekly for a month as an out-patient. She was managed medically with aspirin, for the occlusive thrombus.

CASE 2

Mr AP is a 41-year-old man with no known comorbidities who was first diagnosed with an unprovoked deep vein thrombosis (DVT) of the right femoral vein in 2016. At the time, his haemoglobin was markedly reduced at 5.7 g/dl (normal 13.4 – 17.5) with an elevated MCV of 106 fL (normal 83.1 to 101.6) and reduced white cell count 1.3 X 10^9/L (normal 3.92 – 10.4) and thrombocytopenia of 117 x 10^9/L (normal 171 – 388). Renal function was normal and the auto-immune work up was negative (anti-nuclear antibodies, rheumatoid factor and anti-neutrophil cytoplasmic antibodies) and he was HIV negative.

He also had signs suggestive of sub-acute combined degeneration of the spinal cord with loss of fine touch and proprioception which was suspected to be due to low vitamin B12 levels of 37 pmol/l. The aetiology of this was also likely pernicious anaemia as he was found to have positive intrinsic factor antibodies (anti-parietal cells antibodies were negative). He was commenced on anticoagulation with vitamin K antagonist (warfarin). Homocysteine levels were elevated at 45 umol/l (normal 5.1 – 15.4). Intramuscular
vitamin B12 replacement was also commenced and repeat
haemoglobin after 6 months of treatment was normal with
increased vitamin B12 levels at 198 pmol/l and reduced
homocysteine levels at 21.9 umol/l.

Despite maintaining a therapeutic international normalised ratio (INR), there was re-demonstration of thrombus in the same distribution 2 years later. Repeat assessment in March 2021 remained unchanged with evidence of persistent DVT but no progression of the neurological deficit and the warfarin was continued.

DISCUSSION

Vitamin B6 and B12 are essential in the metabolism of
homocysteine, and are required for the conversion of
homocysteine to methionine. Folic acid is a cofactor in this pathway. There are various causes of vitamin B12 deficiency with the most common being pernicious anaemia whereby antibodies are directed against intrinsic factor or parietal cells. Other causes include a vegan diet, malabsorption disorders, metabolic surgery and the use of drugs such as metformin. Vitamin B12 deficiency leads to elevated homocysteine levels, as does folate (vitamin B9) or vitamin B6 deficiency.

Markedly elevated homocysteine levels can also be genetic, either due to a rare autosomal recessive disorder due to deficiency of methionine synthase or from a severe deficiency of the enzyme methylenetetrahydrofolate reductase (MTHFR). Both lead to a severe elevation of homocysteine in blood and urine. This manifests as developmental delay, severe premature atherosclerosis, ocular abnormalities, osteoporosis and venous thromboembolism. 5-7% of the population have a less marked elevation of homocysteine levels without any of those clinical manifestations and occasionally may be due to renal disease, hypothyroidism, certain drugs (fibrates, nicotinic acid, metotrexate) or smoking.(1)

Elevated homocysteine is associated with atherogenic and prothrombotic properties and can manifest with cardiovascular events via mechanisms such as attenuated anticoagulant processes, increased platelet and thrombin reactivity, impaired fibrinolysis and endothelial dysfunction. Some studies have also found an association of elevated levels of homocysteine with venous thrombosis and recurrent thromboembolic events.

Remacha et al. (2) studied the association of acquired vitamin B12/folate deficiency and the risk of thrombosis in a case control study using 193 patients with vitamin deficiency and 87 controls. A multivariate analysis found that vitamin B12/folate deficiency was a significant risk factor for arterial thrombosis. However, when adjusted for hyperhomocysteinemia, vitamin B12/folate deficiency was no longer a risk factor suggesting that hyperhomocysteinemia was responsible for arterial thrombotic risk in these patients.

A prospective cohort study (Women's Health Study) of 27555 women over 45 years of age without cardiovascular disease and venous thromboembolism (VTE) were assessed for baseline homocysteine concentration and future risk of VTE. This study concluded that elevated homocysteine levels were associated with unprovoked pulmonary embolism and deep vein thrombosis but not provoked events.(3) A second cohort of 2672 women in the Women's Antioxidant and Folic Acid Cardiovascular Study also corroborated the findings that elevated homocysteine levels were associated with VTE events. Their data also supported a joint association of BMI with homocysteine, as women with elevations in both BMI and plasma homocysteine concentration were at highest risk.(3)

In a case-control analysis of 269 patients with first DVT in the Leiden Thrombophilia Study, a homocysteine concentration above the 95th percentile was associated with a 2.5-fold increased odds of VTE.

A meta-analysis showed for each 5 umol/L increase in homocysteine level there was a 20-50% increase in CAD independent of the Framingham risk factors and concluded a combined risk ratio for coronary events 1.18 (95% CI) for each 5umol/L increase in homocysteine level.(4)

The impact on management of patients remains controversial due to the findings of studies looking at the effect of homocysteine lowering interventions (HLI) for preventing cardiovascular events. A Cochrane review of controlled trials concluded that compared to placebo there is no difference in the prevention of myocardial infarction with the use of HLI (6.0% versus 7.1%) but there was reduced stroke incidence in patients using HLI (4.3%) versus placebo (5.1%). There was no difference if the HLI was given as vitamin B6, 9 and 12 alone or in combination for MI but for stroke events there was a small difference favouring either supplement alone rather than in combination. (5) In addition, the Vitamins and Thrombosis (VITRO) study investigated the effect of homocysteine lowering by daily supplementation of B vitamins on the risk reduction of deep vein thrombosis (DVT) and pulmonary embolism (PE) and found that homocysteine lowering by vitamin B supplementation did not prevent recurrent venous thrombosis compared to placebo.(6)

Other prospective intervention studies have also shown that despite lowering homocysteine levels with vitamin supplementation, there was no significant impact on the risk of recurrence of venous or arterial disease.(7)

LIMITATION

There is paucity of local data on the incidence of secondary hyperhomocysteinemia in patients with vitamin deficiencies and routine monitoring would help create a registry of patients who could be followed up prospectively to gauge the number of thrombotic events and target intervention studies accordingly.
CONCLUSION
Despite a controversial association of homocysteine with thrombotic events, our patients had no other identifiable cause for their presentation except hyperhomocysteinemia. Hyperhomocysteinemia represents a potentially reversible procoagulant state which should be considered when other investigations do not elicit aetiology of the thrombosis, especially in young patients or thromboses at unusual sites.

REFERENCES