Recurrent Unprovoked Venous Thromboembolism in a Young Female Patient with High Levels of Homocysteine

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Abstract

Keywords

- ▶ antifactor Xa
- ▶ cardiovascular risk factors
- ▶ deep vein thrombosis
- ▶ factor V Leiden
- ▶ hypertension
- ▶ thrombophilia

Hyperhomocysteinemia is a rare condition which predisposes to atherothrombosis. Recurrent venous thromboembolism (VTE) with hyperhomocysteinemia is known but extremely uncommon. Homocysteine levels of more than 22 $\mu\text{mol/L}$ can predispose to VTE in a middle-aged women. We describe a case of a middle-aged woman, community ambulant with recurrent VTE with intermediately high homocysteine levels. She had no other risk factors for recurrent venous thrombosis. In our article, we also discuss hyperhomocysteinemia and its link to VTE.

Homocysteinemia was diagnosed in 1962, when it was reported that people with genetic condition called homocystinuria were prone to develop severe cardiovascular disease in their teens and 20s.¹ Elevated homocysteine levels is a risk factor for developing atherosclerosis and blood clots in the arteries and veins. There is a correlation between total homocysteine levels and coronary artery disease, peripheral artery disease, stroke, or venous thrombosis.^{1–3} Hyperhomocysteinemia and its association with deep vein thrombosis (DVT) is known but is very rare.¹ We describe a young patient with intermediately high homocysteine levels and recurrent unprovoked DVT.

Case Report

Mrs. ABY is a 42-year-old Malay lady, community-ambulant, married with two children, with no abortions in past, had history of diabetes mellitus (DM), hypertension, and hyperlipidemia. She was noncompliant to her medications and her HBA1c in September 2011 was 14.8%. She was on insulin and metformin for her treatment of DM. She also had hypertension for which she was taking amlodipine and atenolol.

She had history of left leg femoral and popliteal vein thrombosis with pulmonary embolism in May 2010. Her computed tomography (CT) scan of the thorax showed that the cardiac chambers, main pulmonary trunk, and right and left pulmonary arteries are normally opacified. Filling defects were seen in the segmental branches of the right upper (apical and anterior) and lower (lateral and posterior) lobes suggestive of thrombosis. Filling defects were also seen in the left upper (apical, anterior, and lingular) and lower (main and posterior) segmental branches (▶ **Fig. 1**). She was treated with warfarin for 6 months.

She was admitted in September 2011 for right leg swelling which she developed over few weeks. There was no history of fever, ingestion of any new medications including contraceptive pills, recent surgery, or travel. There was no associated breathlessness.

On examination, she was afebrile, blood pressure was 130/70 mm Hg, heart rate was 70 beats per minute, systemic examination was normal. The right leg was warm, red, and swollen. Ultrasound Doppler scan showed DVT in right femoral and iliac vein.

Figure 1 Filling defects in the segmental branches of the right upper (apical and anterior) and lower (lateral and posterior) lobes suggestive of thrombosis.

Her blood work showed hemoglobin 14.2 g/dL, white blood cell $12.7 \times 10^9/L$, neutrophils 69.2%, lymphocytes 17.5%, monocytes 6.1%, eosinophils 6.7%, basophils 0.5%, platelets $196 \times 10^9/L$, activated partial thromboplastin time 29 seconds, prothrombin time 13.3 seconds, PT/International Normalized Ratio 1.02, sodium 130 mmol/L, potassium 4.4 mmol/L, creatinine 91 $\mu\text{mol/L}$, urea 6.8 mmol/L, free thyroxine 12 pmol/L, thyroid-stimulating hormone 1.75 mIU/L, cholesterol 7.3 mmol/L, low-density lipoprotein (LDL) 4.7 mmol/L, triglycerides 4 mmol/L, HbA1c 14.8%, antithrombin 109%, protein C 77%, protein S 100%, lupus anticoagulant absent, activated protein C resistance 0.82 (normal 1 to 1.3), factor V Leiden normal, anticardiolipin 1 gG 3 GPL U/mL, anticardiolipin 1 gM 2 MPL U/mL, homocysteine 36 $\mu\text{mol/L}$ (5 to 15 $\mu\text{mol/L}$). Her CT scan of the abdomen and pelvis showed no intra-abdominal or retroperitoneal mass lesion detected as per concern. Her mammography was normal. She was started on Clexane, warfarin. Folic acid was added due to high levels of homocysteine. The patient was discharged well and stable.

Discussion

Homocysteinemia is a rare condition which is associated with risk of developing atherosclerosis and blood clots in the arteries and veins. 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.¹⁻³

Homocysteinemia is graded by Kang and coworkers 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.^{4,5} Homocystinuria and severe hyperhomocysteinemia are caused by rare inborn errors of metabolism resulting in marked elevations of plasma and urine homocysteine concentrations. Cystathionine β -synthase deficiency is the most common genetic cause of severe hyperhomocysteinemia. The homozygous form, also

known as congenital homocystinuria, can be associated with plasma homocysteine levels as high as 400 mmol/L during fasting.⁶ The homozygous trait is rare (occurring in 1 in 200,000 births) and clinical manifestations include ectopia lentis, skeletal deformities, mental retardation, thromboembolism, and severe, premature atherosclerosis.⁶ Atherothrombotic complications frequently develop in young adulthood in homozygotes and are often fatal.⁷ Around 50% of untreated patients with homocystinuria will have a thromboembolic event before the age of 30 years and mortality is as high as 20%. Heterozygotes typically have much less marked hyperhomocysteinemia with plasma homocysteine concentrations in the range of 20 to 40 mmol/L, approximately two to four times greater than the normal concentration of homocysteine in plasma.⁷⁻¹⁰ 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.¹¹ 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.^{12,13} The other causes of high homocysteine is seen typically in chronic renal failure.^{14,15} The presence of elevated plasma homocysteine concentrations may partially explain the observed acceleration of atherosclerosis in end-stage renal disease. Hyperhomocysteinemia may also be seen in patients with hypothyroidism and pernicious anemia. Elevated homocysteine concentrations have been reported in association with several types of carcinoma, including breast, ovarian, and pancreatic cancer, and acute lymphoblastic leukemia.¹⁶⁻¹⁸ Levels of homocysteine can be elevated by several drugs. methotrexate, phenytoin interfere with folate, the cosubstrate for methionine synthase, and causes a transient increase in plasma homocysteine concentrations.^{16,19} On the other hand theophylline, a phosphodiesterase inhibitor, may cause hyperhomocysteinemia by antagonizing the synthesis of pyridoxal phosphate (vitamin B₆).²⁰ Cigarette smoking also interferes with the synthesis of pyridoxal phosphate and increases homocysteine levels.

Elevated homocysteine levels has a toxic effect on the vascular endothelium and on the clotting cascade.^{16,21} Hyperhomocysteinemia may be associated with abnormal methionine metabolism that affects the methylation of DNA and cell membranes.¹² Homocysteine is rapidly auto-oxidized in plasma to homocysteine thiolactone. This combines with LDL, causing LDL-homocysteine thiolactone aggregate which can cause endothelial damage, proliferation of vascular smooth muscle cells, and increase atherothrombosis. Even moderate hyperhomocysteinemia is a risk factor for DVT in the general population.^{5,22-25}

The association between mild hyperhomocysteinemia and venous thrombosis was noted to be similar in degree to that reported for hyperhomocysteinemia and arterial vascular disease. Odds ratio for development of DVT increased to four times if the homocysteine levels were more than 22 $\mu\text{mol/L}$, seven times for women between the age 30 and 50 years compared with women who had normal

homocysteine levels and was roughly twice as high for women as for men with homocysteine levels above 22 $\mu\text{mol/L}$.^{5,25}

As our patient had homocysteine levels of 36 $\mu\text{mol/L}$, which are in the intermediate range of Kang's classification, she was at a risk of thrombosis. She was treated with folic acid supplement but it is not known whether homocysteine-lowering therapy such as folic acid, vitamin B₆, or vitamin B₁₂ is useful in prevention of recurrent venous thrombosis.^{2,5,22-24}

Conclusion

Hyperhomocysteinemia and its association with DVT is well-known though not as common as arterial thrombosis. Hyperhomocysteinemia in the intermediate range, especially in women between the ages 30 and 50 years, carries a high risk of VTE.

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