Hyperhomocysteinemia, Deep Vein Thrombosis and Vitamin B12 Deficiency in a Metformin-treated Diabetic Patient

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Vitamin B12 deficiency may be induced by long-term use of metformin, which may in turn lead to hyperhomocysteinemia. Thus, hyperhomocysteinemia may increase the risk of vascular thrombosis in diabetic patients, when metformin is used and a homozygous methylenetetrahydrofolate reductase (MTHFR) C677T mutation is present. We report a 65-year-old Taiwanese diabetic woman who was treated with metformin for 6 years and who had suffered from swelling of the left lower extremity for 3 months. Ascending venography confirmed the diagnosis of proximal deep vein thrombosis, while hyperhomocysteinemia, megaloblastic anemia caused by vitamin B12 deficiency, and a homozygous C677T mutation of the MTHFR gene were also found. She had no identifiable venous thrombotic risk factors other than hyperhomocysteinemia, which seemed to be caused by both MTHFR C677T homozygous mutation and vitamin B12 deficiency. With the substitution of insulin injection for metformin, short-term supplement of vitamin B12, and anticoagulant therapy for the deep vein thrombosis, her anemia and hyperhomocysteinemia recovered rapidly. The deep vein thrombosis also responded well. Our findings highly suggested the role of metformin in causing vitamin B12 deficiency, which may serve as an additional risk factor for venous thrombosis in diabetic patients. Our report also highlights the need to check vitamin B12 levels during metformin treatment. [J Formos Med Assoc 2007;106(9):774–778]

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Hyperhomocysteinemia is known to be associated with an increased risk of arterial and venous thrombosis.1 The most common genetic defect that may result in hyperhomocysteinemia is a C677T homozygous mutation in the methylenetetrahydrofolate reductase (MTHFR) gene.2 Hyperhomocysteinemia associated with this mutation is more pronounced when low plasma levels of folate, vitamin B6 or vitamin B12 coexist.3 Long-term use of metformin has been shown to be able to induce vitamin B12 deficiency.4,5  

Herein, we report a metformin-treated diabetic patient who presented with deep vein thrombosis, hyperhomocysteinemia and megaloblastic anemia, which appeared to be related to metformin-induced B12 deficiency. The patient was treated successfully. This report further confirms the relationships among hyperhomocysteinemia, MTHFR C677T homozygous mutation and vitamin B12 deficiency, and highlights the need to test vitamin B12 levels during metformin treatment.
Case Report

A 65-year-old Taiwanese woman was admitted on June 22, 2004 because of swelling of her left thigh and calf for 3 months, and a pale appearance, generalized weakness and exertional breathlessness for 1–2 months. She was found to have type 2 diabetes mellitus and had been treated with metformin (500 g twice daily) and glibenclamide (10 mg twice daily) since 1998. She had also suffered from myasthenia gravis associated with thymoma, which was diagnosed in April 1999 and treated with thymectomy followed by the use of pyridostigmine bromide. Bilateral palmar numbness sensations were experienced for several years. She could not recall any remarkable thromboembolic events in her life or among her close relatives. She had not received any hormone replacement therapy, nor was any evidence of malignancy found at admission.

Physical examination revealed nothing abnormal except for a pale face and swelling of the left lower extremity in addition to the sensation of numbness in both hands. Her hyperglycemia had been well controlled, as reflected by her HbA1c value of 5.8% at admission. Ascending venography of her left lower extremity showed an intraluminal filling defect at the left popliteal vein and occlusion of the superficial femoral vein with multiple collateral circulation at the proximal region, as well as non-opacification of the left external iliac vein and faint opacification of the left internal iliac vein (Figure). These findings were compatible with deep vein thrombosis. The laboratory data before and after admission are shown in the Table. The main abnormal laboratory findings were an elevated D-dimer value, macrocytic anemia, an increased level of fasting total homocysteine (measured by fluorescence polarization immunoassay on an Abbott IMX analyzer), and a decreased level of vitamin B12 (assayed on an Abbott AxSYM system based on a microparticle enzyme immunoassay). No deficiencies in protein C (114%; normal range, 70–140%), protein S (81.5%; normal range, 70–123%) or antithrombin III (102.5%; normal range, 70–140%) were detected. Lupus anticoagulant test was negative, and the anticardiolipin antibodies (IgG and IgM) were within normal ranges. Her folic acid level was normal. The lactate dehydrogenase level was increased (276 U/L; normal range, 103–193 U/L). Her haptoglobin level and transferring saturation were normal. An MTHFR C677T homozygous gene mutation was detected using the method described by Frosst et al.2 Bone marrow aspiration showed notable erythroid megaloblastic change and giant metamyelocytes, consistent with a diagnosis of megaloblastic anemia. Antiparietal cell antibody was negative. Stomach biopsy showed no evidence of atrophic gastritis.

Metformin-induced vitamin B12 deficiency was highly suspected. Therefore, insulin injection was substituted for metformin to control her hyperglycemia. The megaloblastic and macrocytic anemia was corrected after vitamin B12 supplementation was given. Her hyperhomocysteineemia was also rapidly converted to a normal level (Table). The symptoms and signs of deep vein thrombosis responded well to anticoagulant therapy. Little improvement was seen in her palmar...
numbness, which may have resulted from cervical radiculopathy, as confirmed by magnetic resonance imaging study, rather than from vitamin B12-deficiency-related neuropathy.

Discussion

Deep vein thrombosis is known to be associated with many risk factors. Acquired contributing risk factors, such as previous thromboembolic events, immobilization, recent surgery, malignancy, antiphospholipid antibody, myeloproliferative disorder, and hormone replacement therapy, were not present in this patient. No deficiencies in protein C, protein S, or antithrombin III were detected. The two most prevalent hereditary risk factors for venous thrombophilia in Caucasians, i.e. factor V Leiden and prothrombin 20210A, are extremely rare or even absent in Taiwanese, so these two mutations were not tested for in this patient. The only significant prothrombotic risk factor identified in our patient was hyperhomocysteinemia.

Whether or not hyperhomocysteinemia is associated with an increased risk of venous thrombosis has been investigated and reviewed extensively. Although our previous study indicated that hyperhomocysteinemia is possibly not an important risk factor for venous thrombophilia in Taiwanese, the results of recent meta-analyses support the notion that hyperhomocysteinemia is an independent risk factor for venous thrombosis.

The plasma level of total homocysteine is confounded by many factors, such as age, sex, nutrition status, smoking, drugs, and diseases. Our previous multivariate analysis in healthy subjects revealed that total plasma homocysteine levels tended to increase with age, and with decreasing plasma levels of folate and vitamin B12, which are common genetic mutations in Taiwanese. The total plasma homocysteine level in our patient would be elevated to a higher value when vitamin B12 deficiency is also present. That vitamin B12 supplementation rapidly restored the hyperhomocysteinemia to a normal level supported the role of vitamin B12 deficiency in contributing to hyperhomocysteinemia in this patient.

The vitamin B12 deficiency-induced megaloblastic anemia seen in our patient was considered not to be pernicious anemia, based on the fact that there was no evidence of atrophic gastritis and an absence of antiparietal cell antibodies. In fact,
Deep vein thrombosis in a metformin-treated patient

Megaloblastic anemia due to vitamin B12 malabsorption associated with long-term metformin treatment has been previously reported. It has been estimated that 10–30% of patients taking metformin will develop evidence of vitamin B12 deficiency. Metformin seems to have an effect on calcium-dependent membrane action, and the cobalamine-intrinsic factor complex uptake by ileal cell surface receptors is known to be calcium-dependent. Other proposed mechanisms include a bacterial overgrowth in diabetics on biguanides, leading to increased binding of the intrinsic factor–vitamin B12 complex to bacteria, thus decreasing the absorption of vitamin B12. Therefore, the vitamin B12 deficiency in this patient was very likely to have been induced by long-term metformin use. After substituting insulin for metformin, her B12 and hemoglobin levels were still normal 2 years later (Table), even though no further supplementation of vitamin B12 was given. These results also support the role of metformin in causing vitamin B12 deficiency, and indicate the need to test vitamin B12 levels during metformin treatment.

Diabetes mellitus is well known to be associated with an increased risk for arterial thrombosis. It is important to note that hyperhomocysteinemia may serve as an additional independent risk factor for vascular thrombosis in diabetic patients when metformin is used and a MTHFR homozygous C677T mutation is present.

In conclusion, the deep vein thrombosis in this diabetic patient was very likely a result of hyperhomocysteinemia caused by a metformin-induced vitamin B12 deficiency and a MTHFR C677T homozygous gene mutation. The successful treatment confirmed this proposition. Our findings emphasize the need to regularly test vitamin B12 levels during metformin treatment.

References


