

Subacute combined degeneration of the spinal cord concurrent with acute pulmonary embolism: a case report

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Xinyuan Pang¹ , Yulei Hao¹, Lushun Ma²,
La Zhuo¹, Lu Liu¹ and Jiachun Feng¹

Abstract

A 58-year-old male vegetarian presented with progressive numbness and weakness in the lower extremities. Laboratory examinations showed reduced vitamin B12 level with megaloblastic anaemia. Spinal magnetic resonance imaging (MRI) revealed hyperintensity within the posterior and lateral columns on T2-weighted imaging. The diagnosis of subacute combined degeneration (SCD) of the spinal cord was established. Unexpectedly, the patient developed transitory syncope on the second day after hospitalization. The diagnostic computed tomography pulmonary angiography (CTPA) confirmed multiple small pulmonary emboli. An isolated significantly elevated level of homocysteine (117.1 µmol/l) was documented when screening for hypercoagulable markers. Except for a long-term vegetarian diet, no other risk factors for hyperhomocysteinaemia (such as a family history of homocysteinuria) was found. The severity of the hyperhomocysteinaemia found in this current patient was unusual for patients with an insufficient intake of vitamin B12. In SCD patients, elevated homocysteine may increase the risk of thrombosis, which may exacerbate existing problems. Knowing the risk factors should help physicians choose appropriate diagnostic and therapeutic strategies.

¹Department of Neurology and Neuroscience Centre, The First Hospital of Jilin University, Changchun, Jilin Province, China

²Department of Gastrointestinal and Colorectal Surgery, China-Japan Union Hospital of Jilin University, Changchun, Jilin Province, China

Corresponding author:

Jiachun Feng, Department of Neurology and Neuroscience Centre, The First Hospital of Jilin University, 71 Xinmin Street, Changchun 130021, Jilin Province, China.

Email: fengjcf@126.com



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Keywords

Subacute combined degeneration of spinal cord, hyperhomocysteinaemia, acute pulmonary embolism, vitamin B12 deficiency

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Introduction

Subacute combined degeneration (SCD) of the spinal cord, a degenerative disease of the posterior and lateral columns of the spinal cord and peripheral nerves, is characterized by severe demyelination and axon degeneration and primarily caused by vitamin B12 deficiency.¹ Chronic vitamin B12 deficiency may also result in methionine cycle metabolism disorder manifested with elevated homocysteine (Hcy).²

Hyperhomocysteinaemia (HHcy), a condition defined as a plasma Hcy level of $>15\ \mu\text{mol/l}$,³ has been reported to be associated with venous thrombosis in multiple epidemiological studies.^{4,5} Data also show an association between Hcy and pulmonary injury.⁶ A meta-analysis found a 60% increase (odds ratio, 1.60; 95% confidence interval, 1.10, 1.34) in the incidence of venous thromboembolism (VTE) with a $5\ \mu\text{mol/l}$ increase in serum Hcy.⁷ Mildly ($16\text{--}30\ \mu\text{mol/l}$) to moderately ($31\text{--}100\ \mu\text{mol/l}$) elevated Hcy levels are caused by multiple factors, including nutritional deficiency of vitamin cofactors involved in Hcy metabolism; while severe HHcy ($>100\ \mu\text{mol/l}$) is only observed in rare cases of hereditary enzymatic defects of Hcy metabolism.⁸ The probability of SCD co-occurring with acute pulmonary embolism is very low, with no cases reported to date. This current case report describes a male vegetarian with SCD who developed acute pulmonary embolism in the setting of severe HHcy secondary to a poor diet.

Case report

A 58-year-old male patient presented to the Department of Neurology and Neuroscience Centre, The First Hospital of Jilin University, Changchun, Jilin Province, China with numbness in the lower extremities for the past 7 months in October 2019. Previously, a diagnosis of peripheral neuropathy was suspected and neurotrophic drugs were prescribed at a local hospital in May 2019. However, the patient's symptoms progressed and were accompanied by an unsteady gait described as 'stepping on cotton' within 1 month after the initial diagnosis. His medical history was reviewed and it was noted that he was a vegetarian that had adhered to the diet without meat for approximately 10 years. He had an unremarkable family history, and denied the use of tobacco, alcohol or other substance abuse. In addition, he denied any history of stomach disorders. After admission, a neurological examination revealed a loss of acupuncture sensation below the level of T4, impaired vibratory sensation and grade 4/5 weakness of the bilateral extremities. The tendon reflexes were brisk in the lower limbs and the bilateral Babinski sign was positive. Heart and lung auscultation revealed no major abnormalities. No oedema was observed in the lower extremities.

Laboratory examination showed a decreased red cell count ($2.31 \times 10^{12}/\text{l}$) and haemoglobin level ($93\ \text{g/l}$), with an increase in mean corpuscular volume ($119\ \text{fl}$). The serum vitamin B12 level was very low

(<30 pmol/l; reference range, 174–878 pmol/l). Cerebrospinal fluid examination and electromyography showed no abnormalities. Cervical thoracic spine magnetic resonance imaging (MRI) revealed hyperintense lesions in the lateral and posterior columns (Figure 1). These findings were suggestive of vitamin B12 deficiency and macrocytic anaemia, which led to the diagnosis of SCD. The patient received an intramuscular injection of high dose vitamin B12 (1000 µg/day) immediately following diagnosis. Meanwhile, nutritional guidance was arranged.

However, on the second day of treatment, the patient suddenly fainted and lost consciousness for about 30 s while walking in the ward. Despite spontaneous recovery, he was extremely weak. He denied any associated chest pain, dyspnoea or tachypnoea. No tonic-clonic activity and

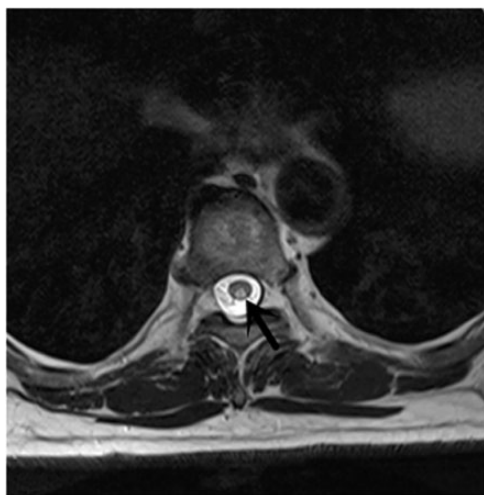


Figure 1. Spinal magnetic resonance imaging of a 58-year-old male patient that presented with numbness in the lower extremities for the past 7 months. The patient had adhered to a vegetarian diet without meat for approximately 10 years. Axial T2-weighted imaging of the spinal cord at the T3 level demonstrated bilateral symmetric signal intensity within the dorsal and lateral columns (inverted V sign) (arrow).

urinary incontinence were observed during the attack. Upon examination, his vital signs were normal. Initially, a syncope caused by neurological diseases or arrhythmia was considered. Holter, echocardiography, electroencephalogram, brain MRI and brain magnetic resonance angiography showed normal results. The room air oxygen saturation was 93% and arterial blood gas analysis revealed mild hypoxaemia ($PO_2 = 75$ mmHg). Notably, the level of D-dimer was high (2.79 mg/l; reference range, 0.00–0.50 mg/l). Although no positive results were detected by compressed venous ultrasonography of the extremities, computed tomography pulmonary angiography (CTPA) confirmed multiple emboli in small branches of the bilateral pulmonary arteries, which was consistent with a pulmonary embolism (PE) (Figure 2). Further examinations to assess the possible thrombophilic cause of the PE revealed an elevated Hcy level (117.1 µmol/l; reference range, 6.0–16.0 µmol/l). The levels of protein C, protein S, factor V Leiden, prothrombin mutation, cardiolipin antibody, anti B2 glycoprotein and lupus anticoagulant were all in the normal range. Also, genetic testing related to HHcy, including the methylenetetrahydrofolate reductase C677T gene mutation, showed negative results. Negative results were observed in tests for autoantibodies against gastric parietal cells and antibodies against intrinsic factors. Based on these results, the final diagnosis of severe HHcy-induced PE was made. The patient was administered anticoagulant therapy with 5000 units low-molecular-weight heparin administered subcutaneously once every 12 h for three consecutive days; and 2.5 mg warfarin was administered orally once every 12 h. After 3 days of combined anticoagulant therapy, 2.5 mg warfarin was administered orally every 12 h on a daily basis. In addition, he was administered 5 mg folic acid orally three times a day, 10 mg/day vitamin B6

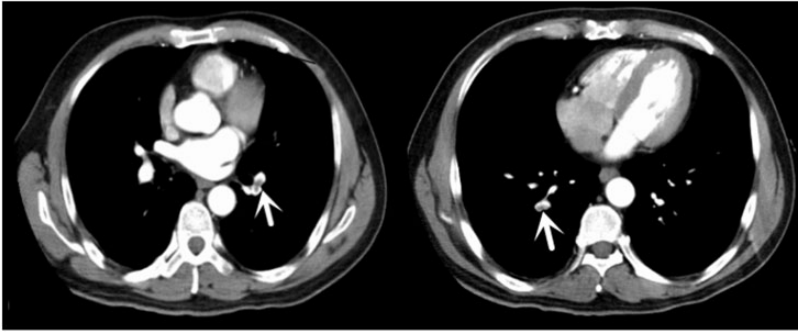


Figure 2. Computed tomographic pulmonary angiography images of a 58-year-old male patient that presented with numbness in the lower extremities for the past 7 months showing signs of nodular filling defects in double lower pulmonary arteries (arrows).

orally and 1000 $\mu\text{g}/\text{day}$ vitamin B12 1000 administered intramuscularly. After 2 weeks of treatment, his neurological symptoms subsided and the Hcy level was normalized to 12.5 $\mu\text{mol}/\text{l}$. The patient continued to receive oral warfarin, vitamin B6 and folic acid supplements as described above with 0.5 mg vitamin B12 orally three times a day for 3 months after discharge. There was no sign of PE recurrence during the follow-up of 6 months.

The Independent Institutional Review Board of the First Hospital of Jilin University provided verbal consent for this case report. The patient described in this report provided verbal informed consent for publication.

Discussion

In the present case, the patient was initially diagnosed with SCD based on their medical history, clinical features, laboratory results and MRI findings. However, on his second day of hospitalization, the patient suddenly developed syncope, which complicated the diagnosis and treatment. It is worth noting that the new symptom of syncope facilitated the diagnosis of acute PE. CTPA was applied to detect filling defects in the bilateral pulmonary artery branches. The results

revealed that the damaged pulmonary blood perfusion decreased the filling of the left ventricle and disturbed cerebral circulation, consequently resulting in transitory syncope.⁹ Since the patient's clinical manifestations differed from those of typical PE (e.g. chest pain, dyspnoea or haemoptysis), the clinical diagnosis was difficult. This patient's 10-year experience of a vegetarian diet had contributed greatly to chronic vitamin B12 insufficiency. Detecting no other major risk factors for thrombosis, it is our opinion that severe HHcy, which was caused by vitamin B12 deficiency, was the most plausible causative factor for PE. To the best of our knowledge, this is the first report on the co-occurrence of SCD and PE that was effectively treated with anticoagulant and Hcy-lowering therapy.

The metabolism of vitamin B12 (also known as cobalamin) plays an important role in maintaining neurological functions.¹⁰ Vitamin B12, as an enzyme cofactor, converts methylmalonyl coenzyme A to succinyl coenzyme A, and Hcy to methionine.¹¹ Succinyl coenzyme A and methionine participate in methylation of myelin protein (Figure 3).¹¹ Deficiency in vitamin B12, caused by either intrinsic factor antibodies or exposure to nitrous oxide, can inhibit the conversion of Hcy and

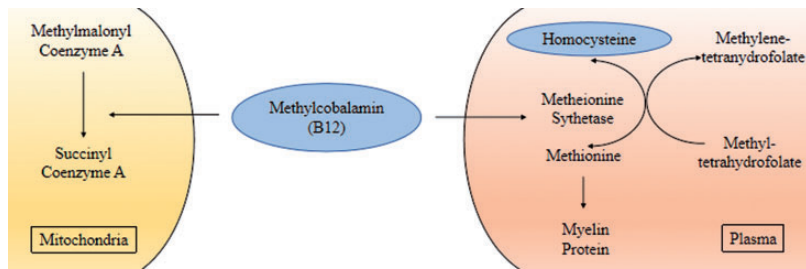


Figure 3. Pathways of vitamin B12 and homocysteine metabolism.

methylmalonyl coenzyme.^{12,13} Specifically, excessive drinking, gastrectomy and a vegetarian diet have been recognized as risk factors for vitamin B12 deficiency.¹⁴ The daily requirement of vitamin B12 for adults is 2 µg.¹⁵ Vitamin B12 deficiency resulting from an improper diet can lead to demyelination of the central and peripheral nervous system.¹⁴ The spinal MRI of this patient showed typical lesions involving both posterior and lateral columns, but his electromyography was normal. A clinical study found no direct correlation between clinical, electrophysiological and MRI abnormalities in their SCD patients.¹⁶ Additionally, it is reported that only 36 cases (54.5%) had abnormal nerve conduction among the 66 cases of vitamin B12 deficiency.¹⁷ Transcranial magnetic stimulation, which can stimulate the central and peripheral nerves painlessly, is worth considering in such cases to detect positive results.¹⁸

Severe HHcy (plasma Hcy >100 µmol/l) is normally caused by rare genetic mutations or enzyme deficiency in the metabolism of methionine, folate or vitamin B12, but it also can occur in individuals with severe vitamin B12 deficiency due to pernicious anaemia.¹⁹ Thrombotic events, such as atherosclerosis, arterial occlusive disorders and VTE, have been reported to be related to elevated Hcy levels.^{20,21} A meta-analysis showed that HHcy was an independent risk factor for VTE.²² HHcy affects

haemostatic processes and alters the balance in favour of the prothrombotic state by different pathways.²³ HHcy contributes to vascular damage, primarily through promoting oxidant stress to cause endothelial vasomotor dysfunction, or by affecting smooth muscle cell proliferation directly.²⁴ These conditions lead to abnormal vascular function and structure.²⁵ Furthermore, HHcy produces a prothrombotic state, which is manifested by enhanced platelet activation and coagulation, likely as a consequence of increased tissue factor expression.²⁶ Alternatively, *in vitro* and *in vivo* studies indicate that HHcy can also impair fibrinolysis, an additional prothrombotic factor, by altering the fibrinogen structure or affecting the level of fibrinolytic factor in plasma.²³ It should be noted that in a rat model, chronic HHcy has been demonstrated to induce lung oxidative stress, which plays a vital role in the pathogenesis of pulmonary damage elicited by this amino acid.²⁷ The above-mentioned findings provide the theoretical basis for the following hypothesis. In this current case, PE resulted from the HHcy-induced endothelial injury and thrombus formation, along with the vitamin B12 deficiency-caused demyelination of the nervous system. Interestingly, isolated vitamin B12 deficiency due to poor diet has not been reported to directly cause such an unusual elevation of Hcy. The alleviated symptoms and normalized Hcy level in the patient after only 2 weeks of

parenteral vitamin supplementation, together with the absence of other causes of HHcy, strongly support that vitamin B12 deficiency due to a long-term vegetarian diet was the underlying cause of his severe HHcy.

In conclusion, this is the first reported case of a vegetarian individual with severe HHcy that suffered bilateral PE after the diagnosis of SCD. This case demonstrates that diet-related vitamin B12 deficiency may lead to SCD and severe HHcy, which in turn can induce PE. Medical professionals should consider the possibility of acute thromboembolism in the case of worsened symptoms in SCD patients with HHcy, or the sudden occurrence of new symptoms. In such cases, early supplementation of B vitamins and folic acid, which can rapidly correct the Hcy level, could be effective. A balanced diet and a comprehensive evaluation of risk factors for vascular events to identify and prevent life-threatening thrombotic events at an early phase is strongly recommended.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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ORCID iD

Xinyuan Pang  <https://orcid.org/0000-0001-9938-6932>

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