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QUIZ CASES

Subacute combined degeneration of the spinal cord is associated with tripterygium glycoside tablet usage

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Abstract

Background Subacute combined degeneration (SCD) is a neurodegenerative disease caused by vitamin B_{12} deficiency. The lesions mainly involve the posterior cord, lateral cord, and peripheral nerves. Occasionally, the lesions also involve brain white matter and optic nerves in severe cases. Reports of drug-induced impaired absorption and metabolism of vitamin B_{12} resulting in SCD are scarce.

Introduction A patient developed SCD after long-term use of tripterygium glycoside tablets in the treatment of glomerulonephritis. However, after discontinuation and vitamin B_{12} treatment with tripterygium glycoside tablet, the symptoms of SCD were significantly resolved.

Conclusion Drug-induced SCD is a less commonly reported cause of the disease. Tripterygium glycoside tablets can induce adverse reactions in the digestive system, causing damage to absorption and metabolism of vitamin B_{12}. Physicians should be aware of the possibility of tripterygium glycoside tablet-induced SCD after excluding more common causes such as inadequate dietary intake and impaired absorption due to gastrointestinal diseases or genetic disorders.

Keywords Subacute combined degeneration · Tripterygium glycoside tablets · Vitamin B_{12}

Introduction

Tripterygium wilfordii is a traditional Chinese herb used for the treatment of "fire-wind-dampness" syndrome. Tripterygium glycoside tablets as a patent medicine were approved by the State Food and Drug Administration of the People's Republic of China, in which the main component is extracted from the rhizome of *Tripterygium wilfordii* [1]. The main bioactive components of tripterygium glycoside tablets are triptolide, tripterylide glycol, tripterone, and alkaloids, which have a variety of signal pathway activities. The anti-inflammatory, immunosuppressive, anti-neoplastic, antioxidative, antimicrobial properties, and other effects of tripterygium glycoside tablets have been increasingly recognized. Clinical trials have shown that tripterygium glycoside tablets have a significant effect on the treatment of rheumatoid arthritis [2]. The tripterygium glycoside tablets have been used as the effective drug for malignancy such as Crohn's disease and HIV/AIDS due to its various pharmacological activities [3, 4]. Moreover, tripterygium glycoside tablets have also been used in kidney disease because it can significantly reduce proteinuria and preserve renal function [5]. Tripterygium glycoside tablets are showing more therapeutic potential [5]. But it should be noted that tripterygium glycoside tablets have a high incidence of adverse reactions, including gastrointestinal discomfort, diarrhea, reproductive toxicity, hematological disorders, and liver damage [6]. Since tripterygium glycoside tablets have a narrow therapeutic window, its clinical application is often restricted by safety concerns [7]. Both the therapeutic

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and toxic effects of tripterygium glycoside tablets are mediated by the same mechanisms that induce apoptosis, oxidative stress, and the release of lactate dehydrogenase [8]. A meta-analysis conducted by Chi Zhang et al. showed that the main side effects of tripterygium glycoside tablets were gastrointestinal symptoms (13.3%), adverse reproductive outcomes (11.7%), skin reactions (7.8%), and hematological and cardiovascular events (6.5%) [9]. Some studies have shown that liver damage caused by tripterygium glycoside tablets has a dose-dependent relationship [10]. However, reports on digestive system adverse reactions are relatively rare and there are no reports on the effects of tripterygium glycoside tablets on gastrointestinal absorption and metabolism. In this article, we reported for the first time a patient who suffered from subacute combined degeneration of the spinal cord (SCD) because of vitamin B_{12} deficiency due to long-term use of tripterygium glycoside tablets.

Case summary

A 63-year-old man complained of subacute progressive bilateral hand numbness for more than 2 months and lower limb weakness for half a month. The patient's upper limb numbness gradually progressed in an incremental manner and was subsequently associated with a symptom of astereognosis. Half a month ago, the patient developed bilateral lower limb weakness and unsteadiness, which were more severe at night. The patient also complained about the recent memory impairment. He had a history of hypertension (well controlled with oral nifedipine and valsartan), type 2 diabetes mellitus (on long-term insulin aspart subcutaneous injection), and IgA nephropathy (treated with oral tripterygium glycoside tablets 10 μg twice daily for about 10 years). He did not have chronic diarrhea and stomach surgery. The patient was not a vegetarian and had a balanced diet. The patient had a history of smoking and drinking for over 20 years, with smoking about 10 cigarettes and drinking about 100 ml alcohol daily. But he had quit smoking and abstained from alcohol for more than 10 years. Cranial nerve examination results showed no abnormal sign. The patient had mild distal lower limb weakness (Medical Research Council grade 4+) with generalized hyporeflexia and bilateral positive Babinski sign. He had impairment of light touch, bilateral proprioception, pinprick sensation, and temperature sensation over bilateral lower limbs. He had no apparent cerebellar signs, and he walked with a stomping gait. He had a mild cognitive impairment.

Laboratory test results showed lower serum vitamin B_{12} level (103 pg/ml, normal range 180–914 pg/ml), albumin/globulin ratio (1.48%, normal range 1.5–2.5%), and high-density lipoprotein (0.95 mmol/l, normal range 1.08–1.91 mmol/l). In addition, indicators such as folic acid (20.88 ng/ml, normal range 3.1–19.9 ng/ml), mean corpuscular volume (108.3 fl, normal range 82.9–95 fl), mean corpuscular hemoglobin (35.3 pg, normal range 27–31 pg), carcinoembryonic antigen (5.48 ng/ml, normal range 0.01–5.0 ng/ml), neuron-specific enolase (23.35 ng/ml, normal range 0.01–17.0 ng/ml), glycosylated hemoglobin (6.2%, normal range 4.0–6.0%), and the number of neutrophils (8.81×10^9/l, normal range $1.8–6.4 \times 10^9$/l) were abnormally elevated. The other indicators were within the normal range. Regular etiologies of vitamin B_{12} deficiency such as anemia, malnutrition, malabsorption, and other causes of SCD such as N_2O were excluded due to patient history and laboratory tests. Differential diagnosis excluded diseases such as demyelinating, infectious, neoplastic, autoimmune, and nutritional diseases. The patient had no discomfort in the gastrointestinal tract, so there was no gastrointestinal endoscopy and pathological examination. Moreover, magnetic resonance imaging (MRI) of the cervical cord showed hyperintensity on the dorsal column and intervertebral disc herniation of cervical C2–C6 levels (Fig. 1a, b). Considering the patient's clinical impairment of pyramidal tract, dorsal column, and peripheral nerves, as well as his neuroimaging results and low serum vitamin B_{12} level, he was diagnosed as SCD.

The patient's bilateral lower limb motor function defects were improved 1 month after the cessation of tripterygium glycoside tablet administration and treatment with vitamin B_{12}. The vitamin B_{12} treatment lasted for 8 weeks with a daily injection dosage of 1000 μg. The vitamin B_{12} levels were gradually increased with improvement of the patient clinical symptoms. Eight weeks after the discontinuation of tripterygium glycoside tablets, the measurement of laboratory

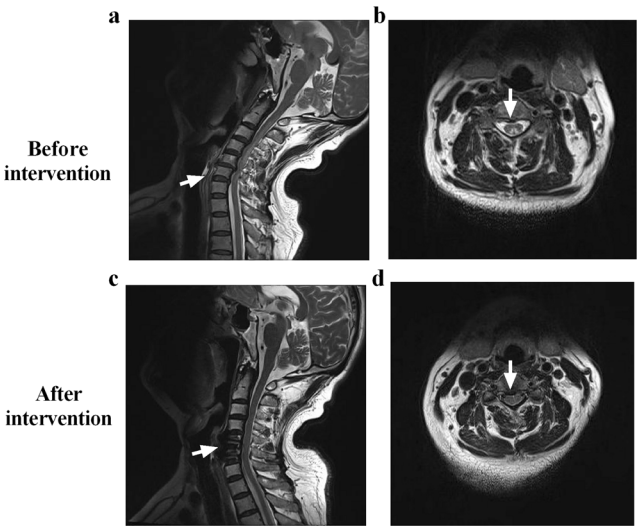

Fig. 1 MRI of a patient presenting with subacute combined degeneration before and after intervention. The patient presenting with SCD depicts hyperintensity involving the posterior part of the cervical spinal cord on sagittal (**a**) image and inverted "V" sign on axial section (**b**, arrow). After intervention, there was disappearance of the hyperintensity involving the posterior part of the cervical spinal cord on sagittal (**c**) image and inverted "V" sign on axial section (**d**, arrow)

indicators and MRI was performed. The results showed that the patient had a normal range of serum vitamin B12 levels (680 pg/ml), mean red blood cell volume (88.9 fl), and mean red blood cell hemoglobin (29.3 pg). Furthermore, the MRI results showed that the horizontal signal of cervical C2–C6 was normalized (Fig. 1c, d), suggesting that the lesion disappeared after the discontinuation of tripterygium glycoside tablets followed by supplementation of vitamin B_{12}. Thus, we inferred that SCD is associated with tripterygium glycoside tablets usage. The patient was discharged after 6 weeks and after 6 months follow-up, no recurrence was observed.

Discussion

SCD is a neurodegenerative disease induced by vitamin B_{12} deficiency. The lesions mainly involve the posterior cord, lateral cord, and peripheral nerves, but in some serious cases, the lesions will also affect the brain white matter and optic nerve [11]. Vitamin B_{12} in the human body can only be ingested through animal food, and there are three kinds of vitamin B_{12} cofactors in the body, which can be used as coenzyme for the metabolism of folic acid (one carbon unit) and the tricarboxylic acid cycle [12]. In 1981, Scott et al. found that supplementation with methionine could effectively prevent the development of SCD in monkeys exposed to N_2O, which provided proof that the neurological impairment caused by vitamin B_{12} deficiency were related to impaired methylation [13]. It is well-known that any factor affecting the synthesis and activity of methyl vitamin B_{12} and adenosine vitamin B_{12} may result in SCD.

The main causes of vitamin B_{12} deficiency are genetic disorders affecting the metabolism of vitamin B_{12}, insufficient intake of vitamin B_{12}, which is mostly seen in vegetarian diet, malabsorption caused by gastrointestinal disorders, as well as improper use of drugs. The latter three causes-induced vitamin B_{12} deficiencies can be quickly and effectively treated by vitamin B_{12} supplementation. Normally, the body stores up about 2 to 5 μg of vitamin B_{12} and about 0.1 to 0.2% of stored vitamin B_{12} is used daily. Therefore, it usually takes 3 to 6 years for serious defects to occur [14].

Our patient was not a vegetarian and had a balanced diet, with no history of gastrointestinal or related genetic disorders, but he still developed vitamin B_{12} deficiency, which led to SCD. He did not frequently take metformin, and further analysis of his drug history showed that tripterygium glycoside tablets were the cause of vitamin B_{12} deficiency. It is likely that long-term use of tripterygium glycoside tablets may lead to vitamin B_{12} malabsorption, resulting in vitamin B_{12} deficiency and complications caused by vitamin B12 deficiency.

Tripterygium glycoside tablets are a fat-soluble mixture extracted from the rhizome of *Tripterygium wilfordii*, and its pharmacological activity is produced by various components, including diterpenoids, triterpenoids, and sesquiterpene alkaloids [15]. It has been found that tripterygium glycoside tablets have anti-inflammatory, immunosuppressive or immunoregulation, anti-neoplastic, and antimicrobial effects. Tripterygium glycoside tablets have been proven to have therapeutic value in the treatment of rheumatoid arthritis, glomerulonephritis, systemic lupus erythematosus, and other autoimmune diseases. Studies have shown that tripterygium glycoside tablets have significant therapeutic effects on nephrotic syndrome, IgA nephropathy, and chronic glomerulonephritis, but it is often accompanied by frequent adverse reactions [5]. Tripterygium glycoside tablets exert significant toxic effects on the reproductive system of male SD rats, and the toxicity is time- and dose-dependent [16, 17]. Furthermore, tripterygium glycoside tablets lead to acute hepatic injury, myocardial damage, and gastrointestinal inflammatory changes [18, 19]. Tripterygium glycoside tablets and its preparations also have obvious gastrointestinal toxicity, mainly manifested as nausea, diarrhea, and liver impairment [9]. Clinical studies have confirmed that tripterygium glycoside tablets can affect a variety of metabolic pathways, including lipid metabolism, tricarboxylic acid cycle, digestion, and absorption [20–22]. High dose of tripterygium glycoside tablets can cause a time-dependent toxicity, such as disorder of the metabolic regulation network, enhancement of amino acid and choline metabolism, and alteration of the intestinal flora [23]. Based on the many side effects of tripterygium glycoside tablets, especially gastrointestinal inflammatory and toxicity, thus, long-term use of tripterygium glycoside tablets may cause damage to normal gastrointestinal mucosal, resulting in malabsorption. Moreover, the toxicity of tripterygium glycoside tablets is different between normal and hyperimmune bodies [20]. These side effects of tripterygium glycoside tablets on gastrointestinal structure and intestinal flora may be one of the possible mechanisms leading to malabsorption and thus vitamin B_{12} deficiency. Metabolic profiling indicated that a significant increase in the content of urinary amino acids such as leucine, lysine, acetyl-lycine, tyrosine, and glutamine after long-term high-dose use of tripterygium glycoside tablets suggests that tripterygium glycoside tablets can cause abnormal amino acids metabolism [24]. Furthermore, it is also a possible factor that may lead to SCD [22]. Because vitamin B_{12} is the key coenzyme in the methionine metabolic pathway, it is closely related to the metabolic pathway of amino acids. The enhancement of amino acid metabolism may lead to a large amount of coenzyme depletion, increased consumption of vitamin B_{12}, decreased serum vitamin B_{12} level, and reduced storage of vitamin B_{12} in the body, leading to the symptoms of the SCD.

This work presents some limitations. The cessation of the trypterygium tablets and the disappearance of the symptoms suggested a link, but considering the re-supplementation of vitamin B_{12}, it could be the sole reason for the improvement of SCD.

Conclusion

We reported a patient suffering from vitamin B_{12} deficiency, which was associated with the long-term use of tripterygium glycoside tablets. This case report emphasizes that the symptoms of gastrointestinal toxicity caused by tripterygium glycoside tablets may not only manifest as nausea, vomiting, and liver impairment. Further research is needed to determine a definite causal relationship between tripterygium glycoside tablets and vitamin B_{12} deficiency. It is also necessary to further confirm the exact mechanism of vitamin B_{12} deficiency caused by tripterygium glycoside tablets in the future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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