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【 CASE REPORT 】

Vitamin B6 Deficiency Anemia Attributed to Levodopa/Carbidopa Intestinal Gel Therapy for Parkinson's Disease: A Diagnostic Pitfall for Myelodysplastic Syndrome with Ring Sideroblasts

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Abstract:
Vitamin B6 (VB6) is essential to heme synthesis, and its deficiency can lead to anemia. VB6 deficiency anemia is typically microcytic, hypochromic, and sideroblastic. VB6 deficiency is a well-recognized complication of levodopa/carbidopa therapy, as metabolism of levodopa to dopamine is VB6-dependent, and carbidopa irreversibly forms bonds and deactivates VB6. We herein report a 75-year-old man with advanced Parkinson's disease who developed severe VB6 deficiency anemia due to levodopa/carbidopa intestinal gel therapy. His anemia was promptly resolved with simple oral supplementation of pyridoxal phosphate hydrate. VB6 deficiency anemia can mimic myelodysplastic syndrome and thus is an important differential diagnosis for patients administered levodopa/carbidopa.

Key words: pyridoxine, microcytic hypochromic anemia, LCIG, heme synthesis, MDS, peripheral neuropathy

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Introduction

Parkinson's disease and anemia are both frequently found in the elderly (1, 2), but the relationship between the two conditions has not been previously described. Vitamin B6 (VB6) acts as a coenzyme in approximately 150 basic biochemical reactions. VB6 functions as a coenzyme for δ-aminolevulinic acid synthase and thereby enables the synthesis of heme from porphyrin precursors. Thus, VB6 deficiency can lead to anemia (3).

Levodopa/carbidopa therapy exhausts the VB6 reserve pool because metabolism of levodopa to dopamine is VB6-dependent, and carbidopa irreversibly deactivates VB6. Thus, Parkinson's disease patients are often at risk of VB6 deficiency.

We herein report for the first time severe VB6 deficiency anemia developing as a complication of levodopa/carbidopa intestinal gel (LCIG) therapy in a Parkinson's disease patient. Prompt resolution of anemia was achieved with simple oral supplementation of VB6. VB6 deficiency anemia is an important differential diagnosis for anemic patients on levodopa/carbidopa therapy.

Case Report

A 75-year-old man with advanced Parkinson's disease on LCIG therapy (infusion time 16 h; levodopa 1,040 mg/day with carbidopa 260 mg/day) plus oral administration of levodopa 200 mg/day, carbidopa 20 mg/day, and entacapone 100 mg/day was referred to our department for microcytic hypochromic anemia. The patient had been on LCIG therapy for 45 months. Upon referral, hemoglobin was decreased to 6.6 g/dL, and a total of 4 units of red blood cells were transfused. Serum ferritin levels were normal, and C-reactive protein levels were not elevated, so iron deficiency anemia

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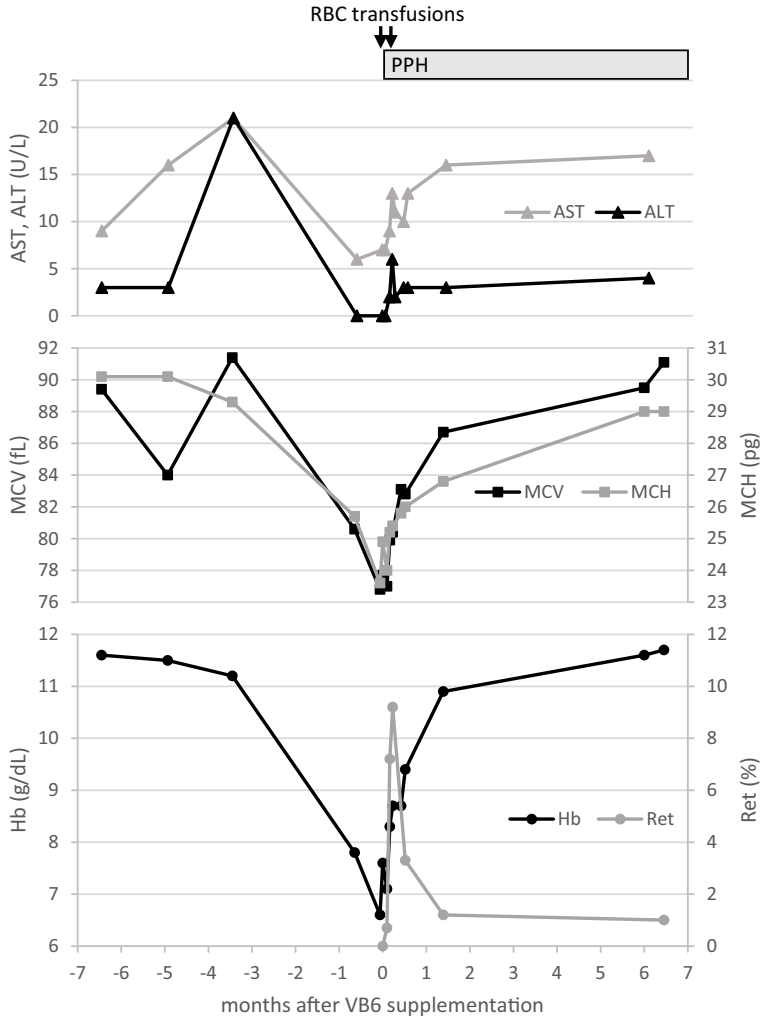

Figure. Clinical course of a Parkinson's disease patient with vitamin B6 deficiency anemia attributed to LCIG therapy. ALT: alanine aminotransferase, AST: aspartate aminotransferase, Hb: hemoglobin, PPH: pyridoxal phosphate hydrate, MCH: mean corpuscular hemoglobin, MCV: mean corpuscular volume, RBC: red blood cell, Ret: reticulocytes, VB6: vitamin B6

and anemia of inflammation were not likely causes.

Myelodysplastic syndrome (MDS) was suspected, and a bone marrow evaluation was considered. However, subsequently, the serum VB6 levels were found to be undetectably low at <2.0 ng/mL [normal values: 6.0-40.0 ng/mL for men, commercially analyzed by SRL, Tokyo, Japan, as reported previously (4)], so supplementation with 30 mg/day of pyridoxal phosphate hydrate (PPH) was initiated.

The reticulocyte count and hemoglobin levels started to rise within 1 week after PPH administration, and after 6 months, the hemoglobin levels had almost normalized at 11.7 g/dL. Elevation of serum VB6 levels to 199 ng/mL was confirmed, the mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) normalized, and a significant increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels was observed (Figure). PPH treatment is currently ongoing in the patient, but exacerbation of Parkinson's disease has not been seen.

The laboratory data before and after VB6 supplementation are shown in Table.

Discussion

VB6 deficiency is rare in the general population because of its abundance in a wide range of food sources, and synthesis of VB6 by the gut flora also contributes to VB6 intake (5). VB6 deficiency is a well-recognized complication of levodopa/carbidopa therapy (6). Some of the polyneuropathies occurring in patients on levodopa/carbidopa therapy have been attributed to VB6 deficiency (7, 8), but we demonstrate for the first time that severe anemia can also develop as a consequence of VB6 deficiency in these patients. Anemia due to VB6 deficiency is typically microcytic, hypochromic, and sideroblastic (9). The major differential diagnoses of acquired microcytic hypochromic anemia can be basically restricted to iron deficiency anemia and anemia of inflammation, with VB6 deficiency likely an underrecognized cause. Of note, certain forms of MDS, namely MDS with ring sideroblasts (10), can present as sideroblastic anemia, and because both MDS and Parkinson's disease are

Table. Laboratory Findings in a Parkinson's Disease Patient with Vitamin B6 Deficiency Anemia before and after Supplementation.

	Before vitamin B6 supplementation	After vitamin B6 supplementation
White blood cells (10^9/L)	2.7	5.2
Red blood cells (10^{12}/L)	2.80	4.03
Hemoglobin (g/dL)	6.6	11.7
Hematocrit (%)	21.5	36.7
Mean corpuscular volume (fL)	76.8	91.1
Mean corpuscular hemoglobin (pg)	23.6	29.0
Reticulocytes (%)	<0.1	1.0
Platelet counts (10^9/L)	174	147
Asparate aminotranferase (U/L)	7	17
Alanine aminotransferase (U/L)	<1	4
C-reactive protein (mg/dL)	0.16	0.15
Ferritin (ng/mL)	185	-
Vitamin B6 (ng/mL)	<2.0	199

prevalent in the elderly, we speculate that a significant number of Parkinson's disease patients with anemia attributed to VB6 deficiency have been misdiagnosed with MDS.

The coenzymatic function of VB6 is necessary for approximately 150 basic biochemical reactions. VB6 acts as a coenzyme for the erythroid-specific enzyme, δ-aminolevulinate synthase 2 (ALAS2), which regulates the supply of protoporphyrin IX, necessary for hemoglobin synthesis. Thus, decreased ALAS2 activity due to VB6 deficiency leads to impaired heme synthesis and can result in the development of sideroblastic anemia (11). Metabolism of levodopa to dopamine through decarboxylation is also VB6-dependent, so the administration of high doses of levodopa can lead to accelerated VB6 consumption. Furthermore, LCIG and most oral levodopa formulations contain carbidopa, which irreversibly forms bonds and deactivates VB6 (6, 8). In line with this, VB6 deficiency has been reported to be extremely prevalent in patients treated with levodopa/carbidopa, and VB6 levels are known to inversely correlate with administered levodopa/carbidopa dose (6). In theory, VB6 supplementation may accelerate peripheral metabolism of levodopa and decrease the levodopa dose that reaches the brain. Thus, VB6 supplementation has been looked upon with caution in patients treated with levodopa monotherapy. However, VB6 supplementation is not necessarily contraindicated for use in patients concomitantly treated with carbidopa, as carbidopa substantially negates the effects of VB6 on peripheral levodopa metabolism. In fact, despite PPH being administered at commonly recommended doses, the serum VB6 levels in our patient were unexpectedly high (199 ng/mL) after 6 months of administration, yet no exacerbations of the symptoms of Parkinson's disease were observed. Therefore, patients on concomitant levodopa/carbidopa therapy who suffer from VB6-responsive anemia should be promptly supplemented with VB6 along with close monitoring of symptoms of Parkinson's disease.

VB6 deficiency can lead to extremely diverse clinical outcomes, such as anemia, polyneuropathy, seizures, diabetes mellitus, dermatitis, stomatitis, and glossitis (3). None of these clinical manifestations are specific to VB6 deficiency, so VB6 deficiency can easily be overlooked as an underlying cause. However, one clinical clue is that patients with VB6 deficiency often present with abnormally decreased levels of AST and ALT, as seen in the present patient (12), and in such patients, an analysis of the serum VB6 levels should be considered.

Significant increases in baseline AST and ALT levels were observed in the present case following VB6 supplementation. AST and ALT are enzymes that belong to a group called transaminases, and both AST and ALT require the coenzymatic function of VB6 for their activation. An analysis of serum AST and ALT levels generally involves measuring their enzymatic activities, so VB6 deficiency can lead to low levels of AST and ALT, although this may not apply to some methods that add VB6 to the reagent for measuring AST and ALT (13, 14).

One limitation associated with this report is that certain hereditary X-linked sideroblastic anemias due to mutations in *ALAS2* have been reported to become evident in a VB6-deficient state, so since we did not conduct a sequence analysis of the *ALAS2* gene in the presented patient, whether the patient developed microcytic anemia with or without such a hereditary background is unclear. However, these hereditary X-linked anemias are extremely rare, and the possibility of such a predisposition in the present case is considered highly unlikely (15).

In conclusion, patients on high-dose levodopa/carbidopa therapy, including LCIG, are at a high risk of VB6 deficiency, and some may develop severe anemia due to VB6 deficiency. Such patients should be promptly treated with VB6 supplementation along with close monitoring for exacerbation of Parkinson's disease.

The authors state that they have no Conflict of Interest (COI).

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