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Clinical Case Study

Severe Hyperhomocysteinemia in a Patient with Parkinson Disease

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CASE DESCRIPTION

A woman in her sixties was admitted to the hospital after she had a generalized epileptic seizure. For the last 20 years, she had Parkinson disease. Her clinical history additionally included coronary heart disease, type 2 diabetes, and obesity.

Her Parkinsonian symptoms included postural instability, bladder dysfunction, rigidity, tremor, and dystonia in the neck and lower extremities. She had used Sinemet (carbidopa/levodopa) 25/100 mg 10 times daily for at least 10 years, in addition to tolcapone 100 mg 3 times daily and botulinum toxin for dystonia. During the previous 3 months before admittance to hospital, she had experienced increasing nausea, vomiting, dizziness and stomach pain, and reduced walking ability. In this period, she also had several serious infections and a weight loss of approximately 30 kg.

At admittance, she was afebrile, slightly disorientated, complained of fatigue, nausea, severe pain in both legs, and was not able to lift her arms and legs. Neurophysiological examinations showed severe motor and sensory axonal neuropathy. An electroencephalogram showed focal slowing, short lasting sharp activity, and beta activity interpreted as generalized cerebral dysfunction.

Serum folate, cobalamin, and plasma total homocysteine (tHcy) were ordered as part of the work-up for severe malnutrition and sensorimotor neuropathy. The laboratory investigations showed a plasma tHcy concentration of 225.9 µmol/L (30.5 µg/mL) [reference interval (RI): <15 µmol/L (<2.0 µg/mL)], serum cobalamin 220 pmol/L (298 pg/mL) [RI: 214–650 pmol/L (290–881 pg/mL)], serum folate >45 nmol/L (>19.8 ng/mL) [RI: >10 nmol/L (>4.4 pg/mL)], and serum ferritin 2157 pmol/L (960 µg/L) [RI: >34 pmol/L (>15 µg/L)]. Serum creatinine was 56 µmol/L (0.63 mg/dL) [RI: 45–90 µmol/L (5.1–10.2 mg/L)], eGFR 95 mL min^{-1} $(1.73\ m^2)^{-1}$ [RI: >90 mL min^{-1} $(1.73\ m^2)^{-1}$], serum C-reactive protein 133 nmol/L (14 mg/L) [RI: <48 nmol/L (<5 mg/L)], and she had a normocytic, normochromic anemia [Hb 8.9 g/dL, (RI: 11.7–15.3 g/dL)], with a low reticulocyte count [0.007×10^{12}/L (RI: $0.03–0.10 \times 10^{12}$/L)].

QUESTIONS TO CONSIDER

1. What are the potential causes of the patient's high plasma total homocysteine concentration?
2. What are the potential causes of the normochromic, normocytic anemia in a patient with Parkinson disease?
3. Does the patient have any risk factors for developing chronic pain, anorexia, and weight loss?

DISCUSSION

The amino acid homocysteine is either remethylated to methionine, a reaction that requires 5-methyltetrahydrofolate and methylcobalamin, or condensed with serine to form cystathionine, a reaction that requires vitamin B6 (Fig. 1). Deficiency of folate and cobalamin, and to a lesser extent vitamin B6, will increase plasma tHcy concentration (1). Plasma tHcy concentrations will also increase with age and reduced renal function. Hyperhomocystenemia in the range 30–100 µmol/L is typically seen in severe folate and cobalamin deficiency, in older patients with B vitamin deficiency and reduced renal function, or in folate deficient individuals who are homozygous for the C677T methylenetetrahydrofolate reductase polymorphism (2, 3). Inborn errors affecting the intracellular synthesis of methylcobalamin are also possible, but represent rare causes of

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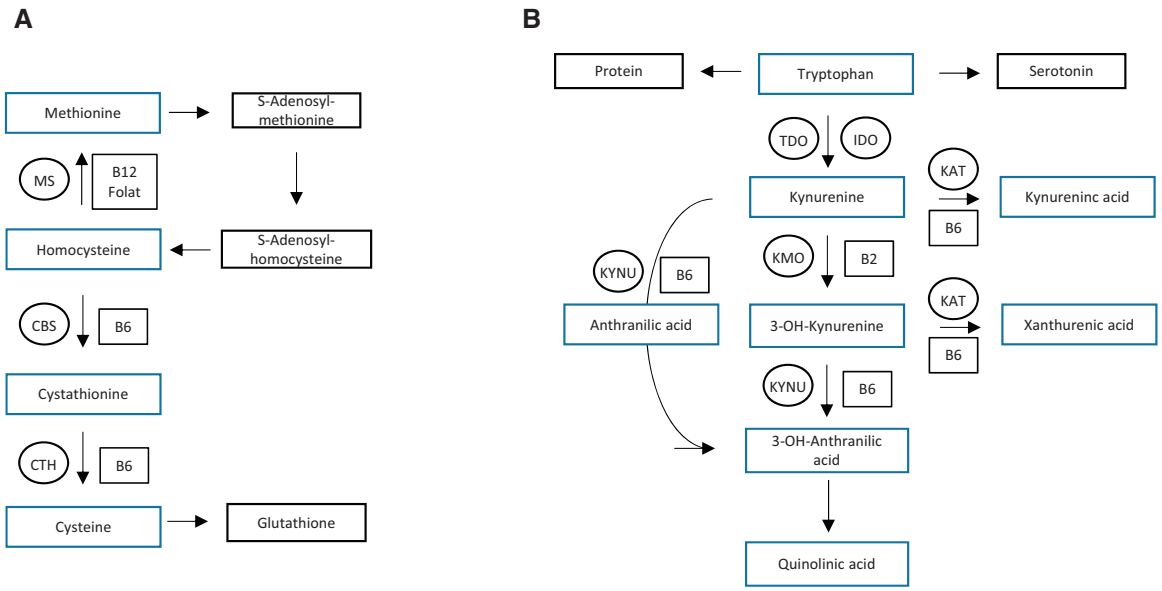

Fig. 1. Homocysteine metabolism. (A) Remethylation to methionine and transsulfuration to cystathionine and cysteine. (B) Kynurenine metabolism. CBS, cystathionine-β-synthase; CTH, Cystathionine Υ-lyase; MS, methionine synthase; CBS and CTH are vitamin B6 dependent, whereas MS is vitamin B12 dependent. PLP is a cofactor in the conversion of kynurenine (Kyn) to kynurenic acid (KA) by kynurenine aminotransferase (KAT), and to anthranilic acid (AA) by kynureninase (KYNU), as well as in the conversion of 3-hydroxykynurenine (HK) to either xanthurenic acid (XA) by KAT or to 3-hydroxyanthranilic acid (HAA) by KYNU.

hyperhomocystinemia (2). A plasma tHcy concentration >100 μmol/L is virtually pathognomonic for classical homocystinuria, due to cystathionine beta synthase deficiency, particularly in the context of hypermethioninemia (Fig. 1) (1).

Our patient was in her sixties, had high serum folate together with a normal cobalamin concentration, normal renal function, and did not have a clinical history consistent with homocystinuria. The increased plasma tHcy concentration, initially analyzed by enzymatic assay (Roche Cobas), was verified by GC–MS. To reveal the cause for the hyperhomocystinemia, we included analysis of plasma amino acids related to vitamin B6 metabolism. Investigations showed that the active form of vitamin B6, pyridoxal 5-phosphate (PLP), was markedly decreased at 2% of reference median concentration (Table 1).

PLP is a cofactor for more than 160 different enzymes, among them the cystathionine beta synthase enzyme and 4 enzymes in the catabolization of tryptophan through the kynurenine pathway (Fig. 1). Deficiency will increase the ratio between 3-hydroxykynurenine (HK) and the sum of kynurenic acid (KA) + anthranilic acid (AA) + xanthurenic acid (XA) + 3-hydroxyanthranilic acid (HAA), termed HK ratio (HKr), a proposed marker of vitamin B6 deficiency (4).

PARKINSON DISEASE

This patient had Parkinson disease, which affects 1% of people over 60 years and is associated with progressive degeneration of the substantia nigra of the brain. The loss of dopaminergic neurons causes a gradual reduction of voluntary movement facilitation and the patients experience tremor, bradykinesia, and rigidity. In the 1950s, levodopa (L-3, 4 dihydroxyphenylalanine) was introduced as an effective treatment for the motor symptoms. Levodopa is metabolized to dopamine, thereby increasing synaptic dopamine concentrations in the brain. Before reaching the brain, levodopa may be degraded in peripheral tissues by the vitamin B6 dependent enzyme aromatic L-amino acid decarboxylase. As a result, the dosage of levodopa was required to be high to ensure adequate concentrations in the brain, which caused nausea limiting the use of the drug (5). In the 1970s, a decarboxylase inhibitor, either carbidopa or benserazide, was added to reduce levodopa induced nausea and currently only the combination drugs are in use. Both drugs irreversibly bind and deactivate PLP, the

Table 1. Plasma concentrations of vitamins and metabolites in the transsulfuration and kynurenine pathways at admission and follow-up.

	Pyridoxal 5-phosphate[a] ng/mL (nmol/L)	Vitamin B12[b] pg/mL (pmol/L)	Folate[b] ng/mL (nmol/L)	Homo-cysteine[c] μg/mL (μmol/L)	Cystathionine[a] μg/mL (μmol/L)	Tryptophan[a] μg/mL (μmol/L)	Kynurenine[a] μg/mL (μmol/L)	Kynurenic acid[a] ng/mL (nmol/L)	Anthranilic acid[a] ng/mL (nmol/L)	3-Hydroxy-kynurenine[a] ng/mL (nmol/L)	Xanthurenic acid[a] ng/mL (nmol/L)	3-Hydroxy anthranilic acid a ng/mL (nmol/L)	Quinolinic acid[a] ng/mL (nmol/L)	HKR[d]
Patient data														
Day 1	0.3 (1.2)	298 (220)	>19.8 (>45)	30.5 (225.9)	1.3 (5.8)	9.3 (45.7)	0.4 (2.1)	4.1 (21.7)	1.2 (8.9)	209 (932)	11.0 (53.4)	4.1 (27)	177 (1060)	11940
Day 11	0.3 (1.2)	236 (174)	15.4 (34.9)	27.0 (199.6)	0.6 (2.6)	6.9 (34)	0.3 (1.5)	3.5 (18.5)	1.2 (8.6)	137 (690)	5.7 (27.9)	2.3 (15)	169 (1010)	7986
Day 16	14.6 (59.0)	>2001 (>1476)	>19.8 (>45)	1.1 (8.3)	0.1 (0.6)	2.2 (11)	0.2 (0.9)	3.7 (19.7)	3.4 (24.9)	19 (85)	0.6 (2.7)	4.4 (29)	138 (828)	111
Reference values in healthy adults (n = 158)														
Median (IQR)	16.1 (12.6, 25.2) ng/mL	484 (394, 621) pg/mL	6.1 (4.4, 8.6) ng/mL	1.0 (0.9, 1.2) μg/mL	0.04 (0.03, 0.06) μg/mL	14.3 (12.5, 16.5) μg/mL	0.3 (0.27, 0.33) μg/mL	8.3 (6.4, 10.8) ng/mL	1.7 (1.4, 2.1) ng/mL	9.0 (7.6, 11.2) ng/mL	3.6 (0.4, 5.1) ng/mL	6.7 (5.1, 8.7) ng/mL	55 (46, 65) ng/mL	33 (28, 40)
	65 (51, 102) nmol/L	357 (291, 458) pmol/L	13.8 (10.0, 19.6) nmol/L	7.5 (6.3, 8.8) μmol/L	0.20 (0.15, 0.29) μmol/L	70 (61, 81) μmol/L	1.5 (1.3, 1.6) μmol/L	44 (34, 57) nmol/L	12.7 (10.5, 15.6) nmol/L	40 (34, 50) nmol/L	17.7 (12.2, 25.0) nmol/L	44 (33, 57) nmol/L	330 (277, 389) nmol/L	33 (28, 40)

[a]Method: LC–MS/MS.
[b]Method: electrochemiluminescense immunoassay.
[c]Method: GC–MS/MS.
[d]HKR: 3-hydroxykynurenine/(kynurenic acid+anthranilic acid+xanthurenic acid + 3-hydroxyanthranilic acid).

active form of vitamin B6, thereby reducing peripheral degradation of levodopa and increasing the amount available to cross the blood–brain barrier (5).

Since vitamin B6 has many important metabolic functions, deficiency of this vitamin, as caused by carbidopa or benserazide, may have serious clinical consequences.

NEUROLOGICAL SYMPTOMS

At admission, the patient had symptoms of peripheral neuropathy, which improved after PLP status was restored. Prolonged vitamin B6 deficiency is reported to cause a painful axonal peripheral neuropathy that leads to weakness, decreased reflexes, sensory loss, and ataxia, particularly in the lower limbs (6). In addition, seizures, migraine, cognitive decline, and depression have additionally been linked to vitamin B6 deficiency, and are also seen in Parkinson disease.

ANOREXIA

The patient had experienced a substantial weight loss. Patients with Parkinson disease, particularly older patients with advanced disease, are at risk of malnutrition and reduction in body weight is common. Vitamin B6 deficiency is reported to exacerbate anorexia, due to its effect on serotonin metabolism and appetite (7).

ANEMIA

At admission, the patient had a normocytic, normochromic anemia, which improved during follow-up. Patients with Parkinson disease are reported to have normocytic anemia or lower hemoglobin concentrations compared to healthy controls and decreasing hemoglobin concentrations are associated with duration and severity of the disease (8). The rate limiting enzyme in heme biosynthesis is the PLP dependent 5-ALA synthase (5-ALAS). Vitamin B6 deficiency will reduce the activity of 5-ALAS activity and may thus cause anemia (9).

METABOLIC DERANGEMENTS

The patient had clinically significant metabolic derangements in the homocysteine and kynurenine pathways (Table 1). A mild hyperhomocysteinemia is seen in patients with Parkinson disease and has been regarded as an independent risk factor for progression of the disease. Plasma tHcy concentrations are reported to increase slightly after initiation of levodopa treatment, from mean 11.0 (SD 4.5) μmol/L to 18.8 (SD 13.5) μmol/L (10). A moderate B6 deficiency causes only a mild increment in plasma tHcy, indicating that the transulfuration pathway may be metabolically protected and preferred in patients with a moderate vitamin B6 deficiency. However, as this case study shows, a severe B6 deficiency causes plasma tHcy concentrations in the range of homocystinuria.

POINTS TO REMEMBER

- Plasma tHcy concentrations >100 μmol/L may be due to severe vitamin B6 deficiency.
- A severe vitamin B6 deficiency also causes extreme alterations in the kynurenine pathway.
- The combined use of levodopa and decarboxylase inhibitors in patients with Parkinson disease may cause functional vitamin B6 deficiency.
- Clinical symptoms in vitamin B6 deficiency may resemble progression of Parkinson disease.
- Both vitamin B6 deficiency and Parkinson disease may cause anorexia, anemia, and a painful axonal peripheral neuropathy that leads to weakness, decreased reflexes, sensory loss, and ataxia.

Kynurenines have various neuroactive properties and have been proposed to have an important role in the pathogenesis of several neurodegenerative disorders, including Parkinson disease, Alzheimer disease, amyotrophic lateral sclerosis, and Huntington disease (11). Initially, our patient had very low concentrations of KA and very high HK and quinilonic acid concentrations compared to healthy controls. Similar alterations have been described in patients with Parkinson disease with levodopa induced dyskinesia and in patients with advanced disease (12). In patients with Parkinson disease without medication and in patients with levodopa/carbidopa medication, but without dyskinesia, plasma kynurenine metabolites have been reported to be equal to healthy controls (12). This indicates that the observed metabolic changes may be related to long-term high-dose treatment with carbidopa, causing a near complete depletion of the PLP pool.

PATIENT FOLLOW-UP

Vitamin B6 supplementation was started on day 10 and Sinemet was reduced by 27% on day 15. At day 16, the plasma PLP concentration was normal and plasma tHcy was reduced by 96% to 1.0 μg/mL (8.3 μmol/L). Plasma cystathionine, the kynurenines, and HKr were also substantially reduced, but not all metabolites became fully normalized during the observational period (Table 1). On day 20, the reticulocyte count was increased by a factor of 29 (0.241×10^{12}/L). The general condition of the patient improved and she experienced less pain.

It seems unlikely that malnutrition alone should have induced such a severe and selective vitamin B6 deficiency, but it has probably contributed to the situation. We observed a similar clinical and biochemical status in another patient with Parkinson disease and a high Sinemet dosage. His plasma PLP increased and tHcy decreased when Sinemet was reduced and before any pyridoxine supplementation was given, indicative of PLP deactivation induced by carbidopa.

The symptomatology of vitamin B6 deficiency may resemble progression of Parkinson disease. Routinely including plasma tHcy in the follow-up of patients with Parkinson disease on levodopa/carbidopa medication might help us distinguish patients with vitamin deficiency.

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Commentary on Severe Hyperhomocysteinemia in a Patient with Parkinson Disease

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This case report by Bjørke-Monsen and colleagues highlights the complication of hyperhomocysteinemia in a patient with advanced Parkinson disease on long-standing high dose levodopa therapy who presented with anorexia, weight loss, and a painful peripheral neuropathy. This is a known metabolic abnormality observed in patients with Parkinson disease though its clinical significance remains uncertain. Hyperhomocysteinema is commonly associated with malnutrition, which leads to folate or B-complex vitamin deficiency. Malnutrition is common in late-stage Parkinson disease with the prevalence estimated to be as high as 24% with up to 60% of patients considered at risk of malnutrition (1) since the progression of motor symptoms leads to dysphagia and impaired self-care. It is also recognized, however, that patients on chronic levodopa therapy have significantly increased homocysteine concentrations compared to healthy controls, a finding confirmed across multiple studies (2).

Though generally not routinely considered in the care of patients with Parkinson disease, the high prevalence of hyperhomocysteinemia in these patients could have profound clinical implications due to its association with other neurological conditions such as neuropathy, cerebrovascular disease, and dementia. As the scope of Parkinson disease treatment continues to expand beyond the management of the motor symptoms, the role of hyperhomocysteinemia as a complication in late-stage disease warrants further investigation due to its implications to our current treatment paradigm and raising the question of whether there should be a role for preventative treatment. Clinicians should be mindful of the risk of hyperhomocysteinemia in their patients with Parkinson disease, particularly as they become increasingly reliant on levodopa as the mainstay of therapy.

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