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Single Case – General Neurology

A Case of Subacute Combined Degeneration of Spinal Cord Diagnosed by Vitamin B_{12} Administration Lowering Methylmalonic Acid

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Keywords

Subacute combined degeneration of spinal cord · Methylmalonic acid · Homocysteine · Folic acid · Vitamin B_{12}

Abstract

Subacute combined degeneration of the spinal cord (SCDS) is a neurodegenerative disease characterized by subacute progression in the central and peripheral nervous systems mainly caused by vitamin B_{12} deficiency. It is known that typical SCDS is frequently accompanied by megaloblastic anemia and increased serum methylmalonic acid (MMA) or homocysteine (Hcy) levels on laboratory findings, and marked abnormalities on spinal cord magnetic resonance imaging (MRI). A 45-year-old woman was admitted to our hospital with a 2-year history of worsening mild weakness, numbness in bilateral lower limbs, and gait disturbance. On admission, as laboratory findings, blood count showed macrocytosis without anemia, and biochemical tests showed mild reduction in total serum vitamin B_{12} level and no increase of MMA and

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Hcy levels; there were no abnormal findings on spinal cord MRI. After administration of vitamin B_{12}, her sensorimotor symptoms were improved and laboratory examination showed that macrocytosis was improved, serum vitamin B_{12} was increased, and serum MMA levels were decreased. This improved clinical course and the laboratory findings following vitamin B_{12} administration confirmed the diagnosis of SCDS due to vitamin B_{12} deficiency. SCDS presents with highly variable symptoms and laboratory findings, and observation of MMA levels and neurologic symptoms before and after vitamin B_{12} administration may be useful for diagnosing SCDS.

Introduction

Vitamin B_{12} is an essential coenzyme for methylation processes in DNA and fatty acid synthesis. Humans mainly derive vitamin B_{12} from foods of animal origin. Frequent causes of vitamin B_{12} deficiency are autoimmune mechanisms by intrinsic factor antibody or anti-parietal cell antibody, achlorhydria, reduced intake with food, post-gastrectomy, and long-term nitrous oxide exposure. Vitamin B_{12} deficiency may cause various neuropsychiatric symptoms, megaloblastic anemia, and Hunter glossitis as a representative symptom [1]. Subacute combined degeneration of the spinal cord (SCDS) is a neurodegenerative disease characterized by subacute progression in the central and peripheral nervous systems mainly caused by vitamin B_{12} deficiency [2, 3]. In the diagnosis of vitamin B_{12} deficiency, measurement of serum methylmalonic acid (MMA) and homocysteine (Hcy) levels has been reported as more useful than measurement of total vitamin B_{12} level [4]. We report a rare case of SCDS that was diagnosed by determining serum MMA levels and neurologic symptoms before and after vitamin B_{12} administration, in the absence of characteristic findings of vitamin B_{12} deficiency, such as increased serum MMA levels, anemia, or abnormalities on magnetic resonance imaging (MRI) of the spinal cord.

Case Report

A 45-year-old woman was admitted to the Division of Neurology, Department of Internal Medicine, at our hospital with a 2-year history of worsening mild weakness, numbness in bilateral lower limbs below the ankle, and gait disturbance, and a 6-month history of worsening inconsistent conversation and difficulty with independent long-distance walking. She had a medical history of depression 4 years earlier, and at the same time had been drinking 700 mL of beer and eating only a little meat, fish, and vegetables almost each day. One year earlier, the depressive symptom worsened, and there was the short time when she abstained from alcohol and ate a little food, but she had been drinking 1,400 mL of beer and hardly eating any food almost each day. Her family history was unremarkable. Her regular medications were ursodeoxycholic acid at 150 mg/day, clonazepam at 1.5 mg/day, venlafaxine hydrochloride at 75 mg/day, and duloxetine hydrochloride at 20 mg/day.

On general physical examination, her height, weight, and body mass index were 163 cm, 42 kg, and 15.8 kg/m^2, respectively. Blood pressure was 118/60 mm Hg, heart rate was 117

beats/min, temperature was 36.9°C, and general examination revealed only lingual flattening, enlargement, and dermatitis. Neurological examination revealed emotional disorder, disturbed attention, and cognitive dysfunction (Mini Mental State Examination score of 23). Mild ataxic dysarthria was identified, but other cranial nerve functions were intact. Mild weakness was observed in the distal portions of the upper and lower limbs (manual muscle testing examination: upper distal limbs 5–/5–, lower distal limbs 5–/4). Vibration sense was more severely impaired in the distal portions of the lower limbs, and she complained of numbness below the knee on both sides. Light touch sensation was normal in both upper and lower limbs. Deep tendon reflexes, including for the biceps, triceps, patellar tendon and Achilles tendon reflexes, showed hyperreflexia in both upper and lower limbs. Trömner, Hoffmann, Wartenberg, and Babinski reflexes were all positive for limbs on both sides. The standing position at rest was strongly disturbed on both opening and closing the eyes, she took 23 s to walk 10 m, and her gait was spastic and ataxic. In terms of the autonomic nervous system, she showed orthostatic hypotension but no other abnormalities.

As laboratory findings (Table 1), blood count showed macrocytosis without anemia, biochemical tests showed liver dysfunction, a mild reduction in total serum vitamin B_{12} level (175 ng/L; normal, ≥180 ng/L), and a severe reduction in serum folic acid (1.1 pg/mL; normal, 3.6–12.9 pg/mL). Serum levels of Hcy (11.9 nmol/mL; normal, 6.3–18.9 nmol/mL), MMA (310 nmol/mL; normal, <400 nmol/mL), vitamin B_1, and copper were all normal. Nerve conduction experiments for the bilateral median, ulnar, tibial, peroneal, and sural nerves were performed and revealed mild axonopathy in all the bilateral nerves. Electromyography showed intact upper and lower extremities. Somatosensory-evoked potentials (SSEP) in the median and tibial nerves were examined but showed no increased latencies in either the median nerves or the right tibial nerve, although waves were hard to evaluate in the left tibial nerve. Thoracoabdominal computed tomography, gastroscopy, and colonoscopy revealed no abnormalities. Cranial and spinal cord MRI revealed only mild cerebral atrophy.

From this clinical course (Fig. 1), we suspected SCDS due to vitamin B_{12} and folic acid deficiencies. We therefore treated our patient with an intramuscular injection of cyanocobalamin at a dose of 1 mg/day for 7 days from hospital day 13, followed by oral cyanocobalamin at a dose of 1 mg/day and fursultiamine hydrochloride at 75 mg/day. After a follow-up period of 64 days, laboratory examination showed that macrocytosis was improved, serum vitamin B_{12} and serum folic acid levels were increased, and serum MMA levels were decreased by 240 nmoll/L. Pharmacotherapy also led to improvement of sensorimotor symptoms and her walking speed markedly increased (6 s to walk 10 m). Although functional outcomes were fully elucidated, lower leg-dominant deep sensory disturbance, mild sensory ataxia, and spastic paraparesis remained. This improved clinical course and the laboratory findings following vitamin B_{12} administration confirmed the diagnosis of SCDS due to vitamin B_{12} deficiency.

Discussion

In this report, we have described the rare case of an SCDS patient who manifested neuropsychiatric symptoms that had progressed slowly without abnormally increased MMA or Hcy levels. Clinically, vitamin B_{12} deficiency manifests such as SCDS, mental disorder, disturbance of memorization, peripheral neuropathy, autonomic nervous system disorders, changes in

mood and behavior, and decreased cognitive function [5]. These symptoms are detected in approximately 40% of vitamin B_{12} deficiency patients [1]. SCDS is a disease that occurs with subacutely progressive sensory ataxia and spastic paraplegia, mild weakness, and numbness in the lower limbs by denaturation such as medullary sheath collapse or axon dropout, mainly in the white matter of the lateral and posterior funiculus, in the posterior and lateral columns (mainly in the lower cervical cord to upper thoracic dorsal column of the spinal cord), and peripheral nerves due to vitamin B_{12} deficiency [2, 3]. The pathological condition underlying SCDS is reportedly the change involved in the coenzyme function of the folic acid cycle, nucleotide and DNA synthesis, and the Hcy methionine cycle, and abnormal balance of cytokine and growth factors [6, 7], but a clear pathological condition remains unclear. As to why the course of this case was more prolonged than in common SCDS cases, it was thought that the total vitamin B_{12} level decreased slowly due to a change in the amount of alcohol and food consumption, and alcoholic distal axonopathy and cerebellar ataxia had an influence on the course of neurological symptoms.

Abnormalities on MRI of SCDS patients have been identified to include distinctive characteristics such as an "inverted V sign," a "pair of binoculars sign," and a "dot sign" [8]. However, Jain et al. [9] reported that only 11.1–36.7% of patients with SCDS showed marked abnormalities on MRI. In addition, 20% of patients with neurologic symptoms due to vitamin B_{12} deficiency do not show anemia [2], and Hemmer et al. [10] reported that only 44.4% of patients with SCDS showed marked abnormalities on SSEP. Thus, SCDS cannot be excluded on the basis of the absence of anemia and abnormal findings on spinal cord MRI and SSEP as in this case.

In the diagnosis of vitamin B_{12} deficiency, a cut-off value for total vitamin B_{12} level of <200 ng/L reportedly shows 97% sensitivity [11]. However, cut-offs for total vitamin B_{12} levels have ranged from 135–473 ng/L in various reports [12]. In addition, diagnosis of vitamin B_{12} deficiency may be difficult when based only on total vitamin B_{12} levels, because this level is frequently influenced by sex, age, laboratory, method of analysis, and the percentage of active form of vitamin B_{12} which is mainly decreased in vitamin B_{12} deficiency and is only 6–20% of total vitamin B_{12} [2]. Furthermore, SCDS caused by achlorhydria and reduced intake of food, as in this case, or amounts of alcohol and food taken just before biochemical tests influence the total vitamin B_{12} level, and thus the biochemical test may show mild or no reduction in total serum vitamin B_{12} level.

In the diagnosis of vitamin B_{12} deficiency, Hcy and MMA levels are more useful than total serum vitamin B_{12} level. Hcy is highly sensitive, while MMA is highly specific for the diagnosis of vitamin B_{12} deficiency [4, 13]. However, Aparicio-Ugarriza et al. [12] reviewed cut-off points for the diagnosis of vitamin B_{12} deficiency in the general population and found that MMA as a biomarker to assess vitamin B_{12} deficiency used cut-offs of 210–470 nmol/L, while Hcy used cut-offs of 10.0–21.6 μmol/L. MMA levels are also high with abnormalities of the small intestinal flora and renal failure, and Hcy levels are also high in folate deficiency, vitamin B_6 deficiency, renal failure, and hypothyroidism [14]. Herrmann and Obeid [13] reported that a reduction in MMA by >200 nmol/L after vitamin B_{12} injection confirms a diagnosis of vitamin B_{12} deficiency before vitamin B_{12} administration in patients with renal disorders. Similarly, the diagnosis of SCDS due to vitamin B_{12} deficiency was confirmed in the present case by a reduction of serum MMA to 240 nmol/L and improved neuropsychiatric symptoms after vitamin B_{12} administration. However, the cost of determining MMA levels is high and only a limited number of institutions can measure MMA, so we suggest evaluating MMA levels before

and after vitamin B_{12} injection when SCDS is suspected from the medical history and symptoms, in the absence of characteristic laboratory and imaging findings on admission.

Conclusions

We should always keep in mind that SCDS can present with variable symptoms, clinical course, and laboratory and imaging findings, and may not show severely decreased total vitamin B_{12} levels, markedly increased MMA and Hcy levels, anemia, or abnormal findings on spinal cord MRI and SSEP similar to this case. In particular, SCDS caused by achlorhydria or reduced intake of food may have the potential to cause the absence of typical symptoms, clinical course, characteristic laboratory, electrophysiologic, and imaging findings of SCDS similar to this case and other neurological disorders. We need to conduct detailed interviews and physical examinations including eating habits and drinking history. If we suspect a diagnosis of SCDS from the medical history and symptoms, but characteristic laboratory and imaging findings are lacking on admission, determination of neurologic symptoms and MMA levels before and after vitamin B_{12} administration may confirm a diagnosis of SCDS due to vitamin B_{12} deficiency.

Statement of Ethics

Informed consent was obtained from the patient for the publication of this case report.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.A., H.M., B.K., T.S. and J.O. contributed to the clinical management of the patient and writing of the manuscript. Y.H. contributed to reviewing and editing of the manuscript. All authors read and approved the final paper.

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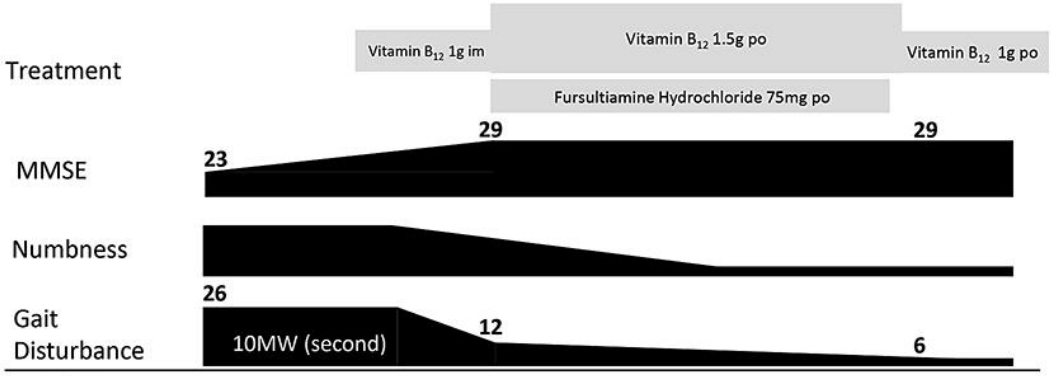

Hb (g/dL)	14.1	12.9	13.6	14.1
MCV (fl)	102.5	101.5	100.5	99.8
MCH (pg)	33.9	33.1	32.3	32.1
MCHC (%)	33.1	32.6	32.1	31.9
Vitamin B_{12} (ng/L)	175	1500>	1500>	1120
Folic acid (ng/mL)	1.1	9.0	8.7	8.5
MMA (nmol/L)	310	-	-	70
Hcy (mol/L)	11.9	-	-	19.2
Day	1	22	36	64

Fig. 1. Treatment regimen. MMSE, Mini Mental State Examination; MMA, methylmalonic acid; Hcy, homocysteine; im, intramuscular injection; po, per os.

Table 1. Laboratory data on admission

Blood count		CRP	0.03 mg/dL	Homocysteine	11.9 nmol/mL (6.3–18.9)
WBC	6,700 /μL	CK	52 U/mL	HIV antibody	(–)
RBC	41.6 ×10^5/μL	NH3	22 mg/L	HTLV-1 antibody	(–)
Hb	14.1 g/dL	Fe	135μg/dL	Oligoclonal band	(–)
Hct	42.6%	TIBC	364 μg/dL	Myelin basic protein	<31.3 pg/mL
MCV	102.5 fL	UIBC	229 μg/dL	*Cerebrospinal fluid test*	
MCH	33.9 pg	Ferritin	23.7 ng/mL	Cell	<1/μL
MCHC	33.1%	Cu	97 μg/mL	Protein	51 mg/dL
Plt	23.8 ×10^4/μL	Ceruloplasmin	21.4 mg/dL (21.0–37.0)	Alb	324 mg/dL
Biochemical test		ANA antibodies	(–)	Glucose	64 pg/dL
TP	7.1 g/dL	SS-A	(–)	IgG index	0.52
Alb	4.1 g/dL	SS-B	(–)		
AST	44 g/dL	P-ANCA	(–)		
ALT	21 U/mL	C-ANCA	(–)		
LDH	165 U/L	M protein	(–)		
ALP	225 lU/L	Intrinsic factor antibody	<10		
γ-GTP	233 lU/L	Anti-parietal cell antibody	(–)		
Na	135 mEq/L	Vitamin B_1	5.7 μg/mL (2.6–5.8)		
K	3.9 mEq/L	Vitamin B_2	26.4 μg/mL (12.8–27.6)		
Cl	105 mEq/L	Vitamin B_{12}	175 ng/L (>180)		
BUN	10.0 mg/dL	Folic acid	1.1 pg/mL (3.6–12.9)		
Cre	0.52 mg/dL	Methylmalonic acid	310 nmol/L (<400)		