

[CASE REPORT]

Primary Position Upbeat Nystagmus with Low Serum Vitamin B12

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Abstract:

A 38-year-old man presented with primary position upbeat nystagmus accompanied by peripheral neuropathy. The serum vitamin B12 level was low along with high plasma homocysteine level, indicating vitamin B12 deficiency. Cyanocobalamin supplementation showed partial clinical and electrophysiological improvement. Although brain magnetic resonance imaging did not show any abnormal intensity lesions, the electrophysiological findings suggested that a pontomedullary medial lesion was responsible for the upbeat nystagmus. To our knowledge, this is the first case of upbeat nystagmus with low serum vitamin B12. Physicians need to recognize the possibility of vitamin B12 deficiency as a cause of upbeat nystagmus.

Key words: upbeat nystagmus, vitamin B12 deficiency, electronystagmography, ventral tegmental tract, superior vestibular nucleus

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Introduction

Vitamin B12 deficiency causes various neurological symptoms, such as peripheral neuropathy, subacute combined degeneration of the spinal cord, encephalopathy, and rarely eye movement disorders. Despite a few reports of downbeat nystagmus caused by vitamin B12 deficiency (1-3), cases of upbeat nystagmus in patients with vitamin B12 deficiency have not been reported.

We herein report a case of probable vitamin B12 deficiency presenting with upbeat nystagmus and discuss the brain lesion potentially involved in upbeat nystagmus.

Case Report

A previously healthy 38-year-old man was admitted to our hospital with a 3-month history of progressive gait disturbance, numbness of limbs, and oscillopsia. Because of poverty after losing his job, he had experienced persistent hunger for more than five months before admission. When he was able to eat, he mainly had instant noodles and hardly ever ate meat. He had not consumed alcohol or tobacco for

more than one year. He had not taken any drugs. On admission, he was alert, with a Mini-Mental State Examination score of 30/30. A neurological examination revealed upbeat nystagmus in the primary position. The upbeat nystagmus was not significantly altered by convergence or a supine head position. Further examinations showed distal dominant muscle weakness in the upper and lower extremities, which made it impossible for him to stand independently. He showed paresthesia in the distal extremities with a “glove-and-stockings-type” distribution and decreased vibration sense. His muscle stretch reflexes were diminished in the extremities, and the plantar responses were both flexor. He did not have limb ataxia.

Laboratory studies showed hemoglobin 13.6 g/dL and mean corpuscular volume (MCV) 97.8 fL. The serum vitamin B12 concentration was low at 199 pg/mL (normal range: 233-914 pg/mL), and the plasma homocysteine (HCys) concentration was high at 16.4 nmol/mL (normal range: 5.0-15.0 nmol/mL). The serum vitamin B1 and lactic acid concentrations were both normal at 6.5 µg/dL (normal range: 2.6-5.8 µg/dL) and 10 mg/dL (normal range: 4.5-14.5 mg/dL), respectively. The serum folate concentration was normal at 3.6 ng/mL (normal range: 3.0-12.9 ng/mL). All of

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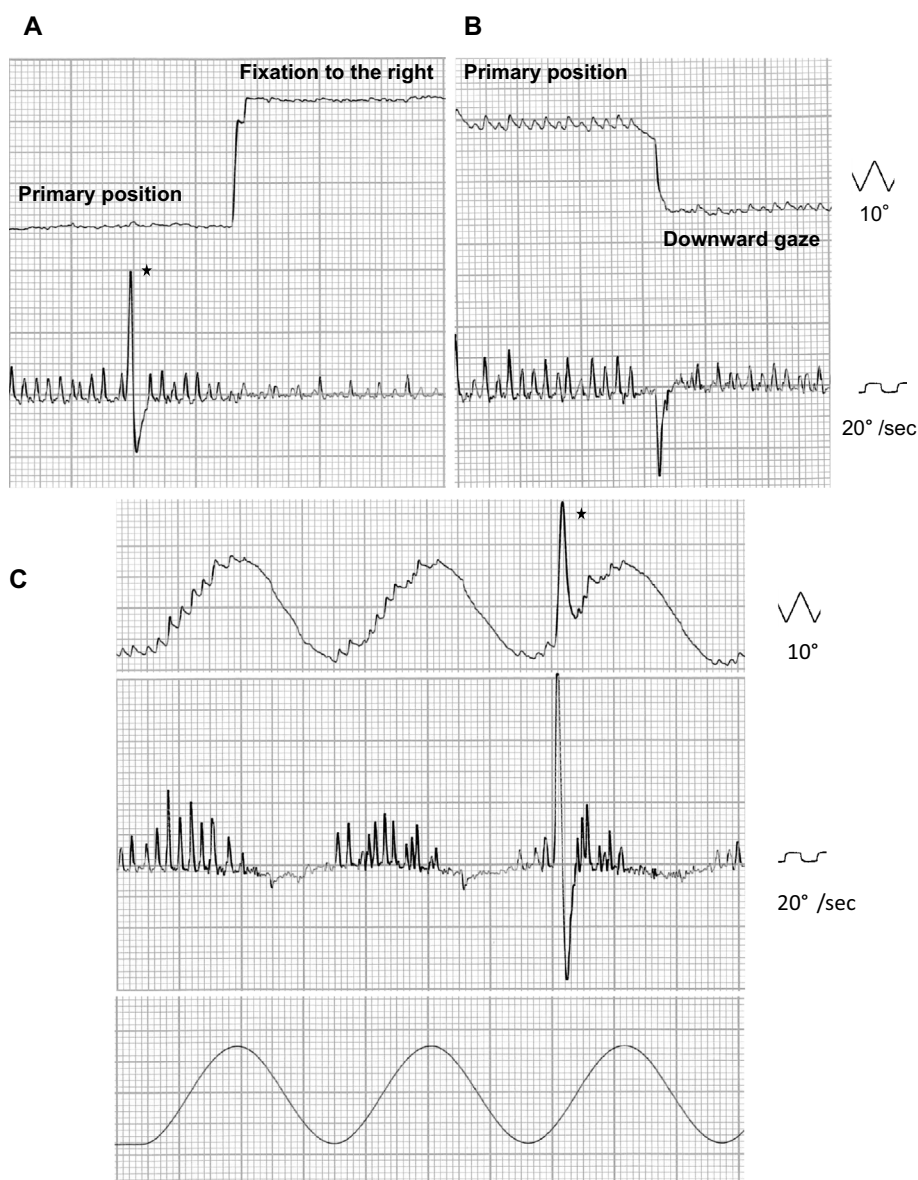


Figure. A: The horizontal eye movement (upper trace) and vertical eye velocity (lower trace) show that the upbeat nystagmus in the primary position decreases during the right horizontal gaze. B: Vertical eye position (upper trace) and velocity (lower trace). Upbeat nystagmus in the primary position decreases with the downward gaze. C: Vertical eye position (upper trace), velocity (middle trace), and vertical motion of the target (lower trace). In the vertical pursuits, upbeat nystagmus was superimposed to the upward direction. Time constant 0.03 s. ★: blink

these vitamin and metabolite values were examined before supplementation or the consumption of any hospital food. The serum methylmalonic acid (MMA) level was unable to be determined before cyanocobalamin supplementation. Iron deficiency was not observed. Antibodies to gastric parietal cell and intrinsic factor were both negative. Serum tumor markers, including carcinoembryonic antigen, carbohydrate antigen 19-9, alpha fetoprotein, squamous cell carcinoma antigen, prostate specific antigen, and soluble interleukin-2 receptor, were all normal. Computed tomography of the whole body showed no evidence of malignancy. Cerebrospinal fluid results were normal. Magnetic resonance imaging (MRI) of the brain showed no abnormal intensity. Spinal cord MRI showed only mild disc bulging at T7/8 and L1/2

levels without cord compression.

According to a nerve conduction study (NCS), sensory nerve action potentials (SNAPs) of the right median nerve and bilateral sural nerves were not detectable. The motor conduction velocity of the left peroneal nerve was decreased at 35.7 m/s (normal range: 43.0-50.0 m/s) with a low compound muscle action potential at 0.047 mV (normal range: 1.4-9.3 mV). Eye movements of the right eye were recorded using horizontal and vertical direct current electronystagmography (ENG) in the upright position. The upbeat nystagmus was the most evident at the primary position with eyes open and reduced in the lateral and vertical gaze (Figure A, B). Horizontal smooth pursuit was almost normal, but vertical smooth pursuit was impaired with superimposed up-

beat nystagmus (Figure C). Horizontal optokinetic nystagmus (OKN) was easily elicited, although optokinetic after nystagmus (OKAN) was decreased. The caloric response using cold water (4°C, 5 mL) was significantly decreased on both sides. Visual suppression of the nystagmus was fairly well preserved on both sides. The auditory brainstem response (ABR) was normal. Cervical vestibular evoked myogenic potential (cVEMP) and ocular vestibular evoked myogenic potential (oVEMP) to air-conducted sound were both normal.

The patient was treated with daily oral cyanocobalamin (1.5 mg) and with intramuscular injection of cyanocobalamin (1 mg) once a week. One month later, his muscle weakness and paresthesia of limbs had improved, although upbeat nystagmus was still observed. After another five months, his upbeat nystagmus reversed to downbeat nystagmus. Follow-up ENG was not performed because the patient refused a re-examination. A follow-up NCS showed an improved motor conduction velocity of the left peroneal nerve at 55.8 m/s and elicited SNAP of the left sural nerve. Follow-up brain MRI still showed no abnormal intensity.

Discussion

Upbeat nystagmus is a central vestibular nystagmus observed in different neurological diseases, such as cerebellar degeneration, infarction, tumor, and Wernicke's encephalopathy (4). Although vitamin B12 deficiency can cause eye movement disorders (1), including downbeat nystagmus (1-3), upbeat nystagmus in vitamin B12 deficiency has not been previously reported.

Our patient presented with primary position upbeat nystagmus accompanied by peripheral neuropathy. We considered those symptoms to be attributable to vitamin B12 deficiency. The vitamin B12 deficiency was probably due to an inadequate dietary intake, because the patient did not have any evidence of malabsorption, pancreatic dysfunction, or medication. Normal serum vitamin B12 levels do not necessarily reflect a normal cellular vitamin B12 status, and the serum vitamin B12 concentration may be artificially elevated in some patients. Therefore, additional functional biomarkers, such as MMA and HCys values, may aid in proving a possible diagnosis of functional vitamin B12 deficiency. However, the sensitivity and specificity of elevated MMA and/or HCys levels in patients with symptoms associated with vitamin B12 deficiency are unknown (5). Solomon reported that vitamin B12-responsive neuropathies were dissociated from the presence of MMA and HCys, suggesting that oxidative stress is associated with localized functional vitamin B12 deficiency, even in patients with a normal serum concentration of vitamin B12 (6). In addition, Graber et al. reported a case of vitamin B12-responsive leukoencephalopathy with normal serum vitamin B12 levels, indicating that serum vitamin B12, HCys, and MMA levels are unreliable predictors of vitamin B12-responsive neurologic disorders (7). Although the serum concentration of vitamin B12

was not extremely low, the HCys level was not extremely high, and the MMA was not measured, the absence of other cause and the response to cyanocobalamin replacement suggested that vitamin B12 deficiency was mainly responsible for the neurologic symptoms in our patient. The normal hemoglobin and a normal MCV of the patient may not contradict the presence of a vitamin B12 deficiency, because in patients with vitamin B12 deficiency, there is no particular correlation between hematological and neurological features. A previous observation reported that approximately 25% of cases of neurological involvement due to vitamin B12 deficiency showed a normal hematocrit or MCV, with no correlation noted between the severity of neurologic dysfunction and the degree of anemia (8). Vitamin B1 deficiency was considered improbable because the serum vitamin B1 concentration was sufficient along with normal lactic acid concentration, and the patient had no consciousness disturbance or limb ataxia. We assume that the differences in the levels of B vitamins in this patient were due to his unbalanced diet, which featured almost no consumption of animal products. Previous studies have shown that vegetarians or vegans have significantly lower serum vitamin B12 levels than omnivores (9), while their vitamin B1 and folate levels are satisfactory (10). Cyanocobalamin supplementation was effective for peripheral neuropathy in this patient. Even though his upbeat nystagmus was not resolved, earlier reports have described that the response to cyanocobalamin for vitamin B12 deficiency with eye movement disorders was varied and often limited (1), on the estimated grounds of irreversible tissue damage from demyelination and subsequent axonal degeneration and gliosis (1, 2, 11).

A total of five patients have shown vertical nystagmus due to vitamin B12 deficiency, including the present patient and four previously reported patients with downbeat nystagmus (Table). Of these five patients, three demonstrated peripheral neuropathy confirmed on an NCS. The therapeutic effect for neuropathy was positive in our patient, negative in one patient, and unknown in one patient. In contrast, the therapeutic effect for nystagmus was poor in most cases. Although the sample size was too small to analyze statistically, and the serum vitamin B12 concentrations of two patients before treatment were uncertain, these data suggest that there may be no apparent correlations between the vitamin B12 level and the symptom duration, degree of anemia, presence of peripheral neuropathy, and therapeutic response. Compared to the other four patients, our patient seemed to have no specific clinical characteristics. Thus, why our patient showed upbeat nystagmus while the others showed downbeat nystagmus remains unclear. One possibility is that some of the four other patients might have shown earlier upbeat nystagmus that changed to downbeat nystagmus before they visited the hospital. Two of the patients did not even complain of abnormal vision until the nystagmus was recognized by physicians. Another possibility is that the localization of damage due to vitamin B12 deficiency might be associated with the expression of vertical nystagmus direction.

Table. Clinical Features of Patients of Vertical Nystagmus with Vitamin B12 Deficiency.

Reference	Age/ Sex	Nystagmus	Symptom duration	Vitamin B12 on admission ^a (pg/mL)	Hemoglobin (g/dL)	MCV (fL)	Cause of vitamin B12 deficiency	Neuroimaging	Peripheral neuropathy confirmed on NCS	Therapeutic effect for neuropathy	Nystagmus after treatment
1	74/F	Downbeat	3 years	707 (after treatment)	13.2	88	Pernicious anemia	MRI: no lesion noted, had mild cerebellar atrophy consistent with age	Unknown	Unknown	Unchanged
2	62/F	Downbeat	3 months	normal (after treatment)	12.0	114	Atrophic gastritis	MRI: no lesion noted, had mild brain atrophy	+	Unknown	Unchanged
2	69/F	Downbeat (asymptomatic)	6 months	50 (50 ng/L)	10.9	NE	Atrophic gastritis	CT: no lesion noted, had mild cerebellar atrophy	-	-	Mild improvement
3	34/M	Downbeat (asymptomatic)	1.5 years	101.6 (75 pmol/L)	13.5	92	Inadequate intake	MRI: normal	+	-	Unchanged
Our patient	38/M	Upbeat	3 months	199	13.6	97.8	Inadequate intake	MRI: normal	+	+	Changed to downbeat nystagmus

CT: computed tomography, F: female, M: male, MCV: mean corpuscular volume, MRI: magnetic resonance imaging, NCS: nerve conduction study, +: present, -: absent
^aValues of vitamin B12 on admission were converted to values in pg/mL unit if other units were used in the original reports. The original values were shown in brackets.

Clinicoanatomical studies have described that upbeat nystagmus can result from brainstem lesions (12), especially pontomedullary and pontomesencephalic lesions (12, 13). The precise mechanisms underlying upbeat nystagmus remain to be elucidated; however, the pathway in the brainstem consisting of the ventral tegmental tract (VTT) and the superior vestibular nucleus (SVN) might be related, according to recent hypotheses (13). The VTT originating in the SVN transmits excitatory upward vestibular signals to the oculomotor nucleus. The caudal medulla receives a projec-

tion from the SVN and projects to the flocculus via an inhibitory pathway. The flocculus inhibits the SVN by Purkinje neurons. Consequently, if the SVN-VTT pathway is impaired by pontine or caudal medullary lesion, the relative hypoactivity of the superior rectus muscle motoneurons results in a downward drift with a corrective upward quick phase, which would lead to upbeat nystagmus (13).

We indicate that in the present patient the pontomedullary lesion was responsible for upbeat nystagmus. In patients with eye movement disorders due to vitamin B12 deficiency, there is no pathologic or radiographic evidence of selective vulnerable localization. Brain MRI changes in patients with eye movement disorders in vitamin B12 deficiency were uncommon, with such changes mentioned in very few previous reports (1, 11). Even though our patient also showed no abnormalities on brain MRI, several of the electrophysiological findings suggested that the brainstem might be responsible for upbeat nystagmus. Our patient showed OKAN deficit with normal horizontal OKN, which might indicate impairment of connections between bilateral vestibular nuclei (14). Poor responses to caloric stimulation suggest that the tract from the anterior and lateral semicircular canals to the SVN through the upper vestibular nerve may have been affected. However, normal findings of VEMPs and ABR respectively indicated a normal function of the saccule and utricle (15), and sparing of the tract between the cochlear nerve and inferior colliculus. Given these findings, we suspect that the lesion responsible for the upbeat nystagmus of this patient was a pontomedullary medial lesion, which is consistent with the SVN-VTT pathway (13).

Our patient uniquely demonstrated transition from upbeat nystagmus to downbeat nystagmus. There have been several reports of transition from upbeat to downbeat nystagmus due to Wernicke's encephalopathy and other diseases (16-21). Although the mechanisms underlying the change in the vertical nystagmus direction are unknown, some reports suggest the involvement of an imbalance in tonic vertical vestibuloocular signals and the influence of gravity over the time course (13, 18, 20). Others have suggested that improvement of metabolic brainstem lesions may unmask underlying downbeat nystagmus due to persisting cerebellar dysfunction (17, 21). Kattah et al. proposed that, in Wernicke's encephalopathy, the neurons that were selectively vulnerable to thiamin deficiency lying along the midline of the pons and medulla exhibited persistent impairment, leading to a shift toward downbeat nystagmus, after transiently damaged neurons in the medulla had recovered (21). Nevertheless, not only Wernicke's encephalopathy but also other etiologies, such as hematoma, brain hemorrhage, and autoimmune encephalitis, can cause the transition from upbeat to downbeat nystagmus (21). Accordingly, we suggest that the localization of damaged lesions in the medial pons and medulla and differences in the degree of impairment of these lesions over the course of time are the key factors associated with this phenomenon, regardless of the underlying diseases. Vitamin B12 deficiency may present with changing of the vertical

nystagmus direction under such conditions.

In conclusion, this is the first case of upbeat nystagmus probably associated with vitamin B12 deficiency. Physicians need to recognize the possibility of vitamin B12 deficiency as a cause of upbeat nystagmus. Additional studies should be conducted to determine the relationship between vitamin B12 deficiency and nystagmus and the associated mechanisms.

This research originated in Japanese Red Cross Akita Hospital.

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

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