Vitamin B_{12} Metabolism and Massive-Dose Methyl Vitamin B_{12} Therapy in Japanese Patients with Multiple Sclerosis

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Serum vitamin B_{12} levels and unsaturated vitamin B_{12} binding capacities were measured in 24 patients with multiple sclerosis (MS), 73 patients with other neurological disorders and 21 healthy subjects. There was no decrease in the vitamin B_{12} levels, however, a significant decrease in the unsaturated vitamin B_{12} binding capacities was observed in patients with MS when compared with other groups. A massive dose of methyl vitamin B_{12} (60 mg every day for 6 months) was administered to 6 patients with chronic progressive MS, a disease which usually had a morbid prognosis and widespread demyelination in the central nervous system. Although the motor disability did not improve clinically, the abnormalities in both the visual and brainstem auditory evoked potentials improved more frequently during the therapy than in the pre-treatment period. We therefore consider that a massive dose methyl vitamin B_{12} therapy may be useful as an adjunct to immunosuppressive treatment for chronic progressive MS.
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Key words: multimodality evoked potentials, transcobalamin

Introduction

Acquired deficiency as well as inborn errors in vitamin B_{12} (cobalamin) metabolism are well known to cause demyelination in the central nervous system (CNS) (1–3). Neurologic disorders caused by vitamin B_{12} deficiency occasionally appear even in the absence of megaloblastic anemia (4). Thus, attention has been focused on the vitamin B_{12} metabolism in multiple sclerosis patients in earlier reports, but the results have been conflicting (5–7).

By using a sensitive assay, several recent studies in Western countries have shown that the vitamin B_{12} levels are low in both the serum and cerebrospinal fluid (CSF) of patients with MS (8–10). The coexistence of vitamin B_{12} deficiency in MS may aggravate the disease or hinder the recovery from the disease. Therefore, the present study was undertaken to clarify the state of vitamin B_{12} metabolism in Japanese patients with MS. In addition, a massive dose of methyl vitamin B_{12} (methylcobalamin) was administered to patients with chronic progressive MS, which usually has a morbid prognosis (11, 12). We evaluated the efficacy of the drug by using multimodality evoked potentials (MEPs), because the clinical placebo effect does not affect the MEP results (13).

Subjects and Methods

Subjects

The following 6 groups of subjects were studied for vitamin B_{12} metabolism; 24 patients with clinically definite MS diagnosed according to the criteria of Schumacher et al (14), 17 patients with HTLV-I-associated myelopathy (HAM) diagnosed by the criteria of Osame et al (15), 29 patients with degenerative neurologic disorders, such as Parkinson disease, spinocerebellar degeneration and motor neuron disease, 12 patients with peripheral neuropathy, 15 patients with muscle diseases and 21 healthy volunteers. None of the subjects were administered vitamin B_{12} at the time of drawing the blood specimen. Five of 24 patients with MS had a previous history of vitamin B_{12} administration.

Six patients with chronic progressive MS (5 primary progressive, 1 secondary progressive) were subjected to massive dose methyl vitamin B_{12} treatment, after informed consent was obtained from all participating patients. Their clinical and electrophysiological features are summarized in Table 1. Three of them had been placed on a chronic administration of either low dose prednisolone or azathioprine. None of them had low serum vitamin B_{12} levels at the entry of the present study.

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Methods

Serum vitamin B_{12} levels were determined by a radioimmunoassay (Ciba-Corning) and serum unsaturated vitamin B_{12} binding capacities were measured by a radioassay (16).

Methyl vitamin B_{12} was orally administered at a dose of 60 mg every day for 6 months in 6 patients with chronic progressive MS. In 3 patients (cases 1, 3 and 4), 5 mg of methyl vitamin B_{12} was injected intravenously every day for 14 days before the oral administration of the drug. Patients were examined neurologically every 2 to 4 weeks at the MS Clinic in Kyushu University Hospital, and their disability status was evaluated according to the expanded disability status scale (EDSS) proposed by Kurtzke (17). In order to evaluate the efficacy of the methyl vitamin B_{12} more precisely, the patients were studied by multimodality evoked potentials (MEPs) consisting of pattern-reversal visual evoked potentials (VEPs), brainstem auditory evoked potentials (BAEPs) and short-latency somatosensory evoked potentials (SEPs) following stimulation to the median nerve at the wrist, as described previously (18). MEPs were taken at the time of entry and 6 months after the initiation of methyl vitamin B_{12} therapy in all patients and 3 months after the therapy in most patients. The MEP changes were then determined for each side. When prolonged peak latency and interpeak latency became either normal or initially unevoked potentials appeared regardless of the latency, it was judged to be a definite improvement. On the other hand, when the normal evoked potentials disappeared or showed a prolongation of the latency (beyond the mean+3 SD of the normal subjects) at the follow-up studies, it was regarded as a definite deterioration. As there is uncertainty as to exactly what magnitude of latency change signifies a true change, changes in the prolonged latency beyond the intersession variability within either the normal or abnormal range were considered to be equivocal changes (13, 19, 20). The Kruskal-Wallis H-test and the Chi-square test were used for the statistical analyses.

Results

Serum vitamin B_{12} values and serum unsaturated vitamin B_{12} binding capacities

The serum vitamin B_{12} values were 629±243 (pg/ml, mean±SD) in MS, 598±293 in HAM, 699±243 in degenerative neurologic disorders, 676±326 in peripheral neuropathy, 658±210 in muscle diseases, and 590±262 in healthy subjects. There were no statistically significant differences among the 6 groups (Fig. 1) ($p>0.1$, Kruskal-Wallis H-test). The serum unsaturated vitamin B_{12} binding capacities were 1216±486 (pg/ml, mean±SD) in MS, 1558±608 in HAM, 1560±508 in the degenerative neurologic disorders, 1440±429 in peripheral neuropathy, 1627±418 in muscle diseases, and 1431±254 in healthy subjects (Fig. 2). The serum unsaturated vitamin B_{12} binding capacities showed a tendency to differ among the 6 groups ($0.1>p>0.05$, Kruskal-Wallis H-test). When the MS group was compared with the other groups, MS patients showed significantly lower values of serum unsaturated vitamin B_{12} binding capacities than did the healthy controls ($p<0.05$, Mann-Whitney U-test) and patients with HAM ($p<0.05$, Mann-Whitney U-test), degenerative neurologic disorders ($p<0.01$, Mann-Whitney U-test) and muscle diseases ($p<0.05$, Mann-Whitney U-test).

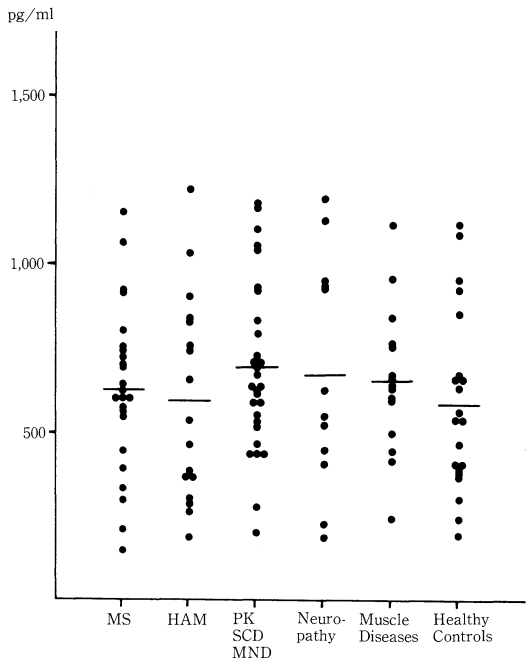

Fig. 1. Serum vitamin B_{12} values. The horizontal bar indicates the mean in each group.

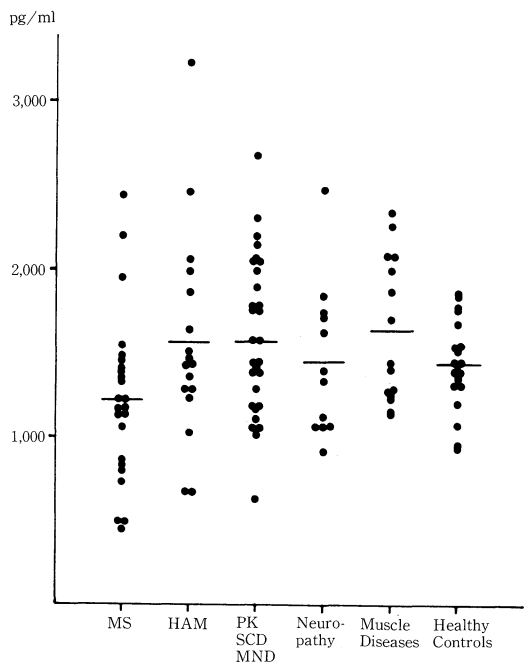

Fig. 2. Serum unsaturated vitamin B_{12} binding capacities. The horizontal bar indicates the mean in each group.

Massive-dose methyl vitamin B_{12} therapy

After the methyl vitamin B_{12} therapy, 2 patients with MS felt better, 1 remained stable and 3 became subjectively worse. The EDSS scores were unchanged in 4 and deteriorated mildly in 2 (Table 1). Only one patient (case 5) objectively showed some improvement within the same EDSS score.

When the evoked potential findings were compared between the pre-treatment recordings and the corresponding post-treatment recordings (6 months after the initiation of the therapy) in a total of 36 instances, 10 post-treatment recordings showed definite changes while the rest remained unchanged (no equivocal changes were observed in the present study). On the VEPs, the improvement was seen in 4 of 12 patients (33%) while deterioration was seen in 1 of 12 (8%) (Table 2). The serial recordings of the VEPs of case 5 are shown in Fig. 3 as representatives. The patient showed absence of P100 in both eyes before the treatment. During the course of the therapy, P100 was obtained bilaterally with delayed peaks. On the BAEPs, 2 of 12 patients (17%) showed an improvement while none showed any deterioration. On the SEPs, only 1 of 12 patients (8%) showed an improvement while 2 (17%) showed deterioration.

Table 1. Clinical Features of Six Patients with Chronic Progressive MS Subjected to Massive Dose Methyl Vitamin B_{12} Therapy

Patient No.	1	2	3	4	5	6
Age, Sex	28 F	30 M	28 F	41 M	54 F	55 F
Disease duration (yrs)	3	10	3	1.5	24	13
Disease course	PP	PP	PP	PP	PP	SP
Kurtzke Scale (EDSS)						
pre-treatment	6.5	6.5	5	5	4	6
post-treatment	7	6.5	5	5.5	4	6

F: female, M: male, PP: primary progressive, SP: secondary progressive, EDSS: expanded disability status scale.

Table 2. Multimodality Evoked Potential Changes during Methyl Vitamin B_{12} Therapy

			Unchanged	
	Improved	Deteriorated	Abnormal	Normal
VEPs (n=12)	4	1	4	3
BAEPs (n=12)	2	0	6	4
SEPs (n=12)	1	2	4	5
Total (n=36)	7 (19%)	3 (8%)	14 (39%)	12 (33%)

VEPs: visual evoked potentials, BAEPs: brainstem auditory evoked potentials, SEPs: somatosensory evoked potentials.

In order to evaluate the effects of spontaneous fluctuations in the MEP findings, the pretreatment MEP changes, i.e., the changes between the recordings at 2 months to 2 years prior to the initiation of the methyl vitamin B_{12} therapy and those at the initiation of the therapy, were compared with the MEP changes during the treatment (the MEP changes between the recordings at the initiation of the therapy and those at 6 months after the initiation of the therapy). Such comparisons were available in 28 recordings in the present study. In the pre-treatment periods, only 1 of 28 recordings (4%) showed an improvement, 6 (21%) deterioration and 21 (75%) no change. On the other hand, during the treatment periods, 5 of 28 recordings (18%) showed an improvement, 3 (11%) deterioration and 20 (71%) no change. The frequency of improvement tended to be higher in the treatment period than in the pre-treatment period ($0.05<p<0.1$, Chi-square test).

Discussion

The present study disclosed no decrease in serum vitamin B_{12} levels but a significant decrease in the serum unsaturated

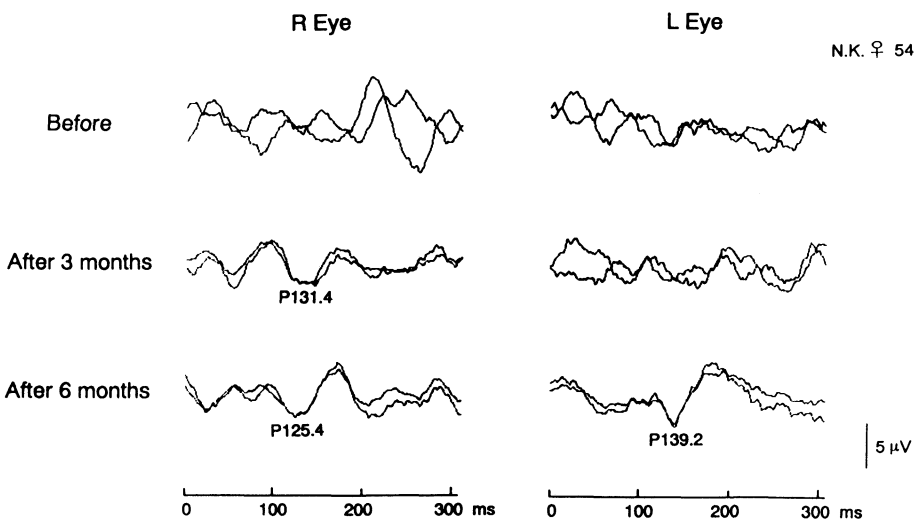

Fig. 3. Visual evoked potential changes during the massive dose methyl vitamin B_{12} therapy. The VEP recordings of case 5 in Table 1 were shown as representative findings.

vitamin B_{12} binding capacities in Japanese patients with MS. Recent studies in Western countries have revealed low vitamin B_{12} levels in the sera of patients with MS (9, 10). They suggested a possible disturbance in vitamin B_{12} metabolism in MS. This notion was then further supported by the recent and early observations that the mild degree of macrocytosis without anemia is common in patients with MS (21–24). However, the present study could not confirm the apparent vitamin B_{12} deficiency state in Japanese patients with MS. Since some of the present patients had a previous history of vitamin B_{12} administration, it might have masked the vitamin B_{12} deficiency state in these patients. Several MS patients have been reported to have low vitamin B_{12} levels in the CSF or the red blood cells (RBC) in the presence of normal serum vitamin B_{12} (8, 25). Therefore, further study of the vitamin B_{12} levels in the CSF and RBC is necessary in the present patients.

The significance of a mild decrease of unsaturated vitamin B_{12} binding capacities with normal vitamin B_{12} levels in Japanese patients with MS is still unclear. The transport of vitamin B_{12} and the unsaturated vitamin B_{12} binding capacities are associated with two carriers, i.e., transcobalamin II and R binder protein. The increase of plasma unsaturated R binder protein and the decrease of transcobalamin II have been reported in some patients with MS in one study (10). R binder protein has been postulated to remove toxic cobalamin analogues from the brain (26). There have been several reports showing the development of MS-like illness in the deficiency of R binder protein (26, 27). On the other hand, the deficiency of transcobalamin II causes megaloblastic anemia (28). Although a further characterization of the decrease in serum unsaturated vitamin B_{12} binding capacities in our patients with MS is necessary, a disturbance of vitamin B_{12} metabolism in MS may be suggested. Alternatively, it may indicate the possibility of the previous administration of vitamin B_{12} in these patients.

The cause of vitamin B_{12} deficiency in MS is unknown. Some authors claim a possible association between MS and pernicious anemia, because both conditions are considered to have an autoimmune pathogenesis (24, 29). On the other hand, Prineas et al (30) revealed that remyelination frequently ensues following the destruction of myelin in the CNS of patients with MS. Thus, recurrent myelin repair in MS may relatively increase the demand for vitamin B_{12} (10, 29). We and others showed that patients with chronic progressive MS have significantly more demyelinating lesions than those with relapsing remitting MS on brain magnetic resonance imaging (MRI) (18, 31). The presence of widespread demyelination in chronic progressive MS has also been confirmed pathologically (32, 33). Therefore, the demand for vitamin B_{12} may be higher in patients with chronic progressive MS than in those with relapsing-remitting MS.

In the present patients, motor disability did not improve clinically after the administration of massive doses of methyl vitamin B_{12}. However, the MEP abnormalities reflecting the demyelinating lesions in the afferent pathways improved more frequently in the treatment period than in the pre-treatment period. Such a clinico-electrophysiologic discrepancy was also noted in the previous studies (13, 20). Serial MEP studies in chronic progressive MS are rare. Anderson et al (13) reported that evoked potential changes occurred in 23% of the instances at a 3-month interval in chronic progressive and stable MS. The figure was comparable to ours (about 30% overall changes). Importantly, the rates of improvement and deterioration were similar in their study (13), but in our study there was more than a two-fold difference between the two rates. Our patients showed a tendency to improve in VEPs and BAEPs but not in SEPs during the therapy, which may be related to the more severe involvement of the spinal cord than other parts of the CNS in chronic progressive MS (18). Thus, the afferent systems which demonstrate less damage in chronic progressive MS, i.e., in the visual and auditory pathways, may be more sensitive to the beneficial effects of massive doses of methyl vitamin B_{12}.

Hydroxocobalamin was tried in one early MS study in which the drug efficacy was evaluated only by a neurological examination (34). The result of this study was negative. Methyl vitamin B_{12} is a main form in vivo and is directly related to the transmethylation reaction (35). Thus, methyl vitamin B_{12} may be superior to hydroxocobalamin in the therapeutic trials in MS. In chronic progressive MS, only high-dose intravenous cyclophosphamide plus adrenocorticotropic hormone has been reported to show some beneficial effects (36, 37). Such a treatment has limitations as a therapy for MS because of the drawbacks inherent to the profound immunosuppression as well as potential toxicity of cyclophosphamide (36, 37). Therefore, we considered that massive-dose methyl vitamin B_{12} therapy is thus warranted as a possible adjunctive therapy to immunosuppressive treatments for this condition.

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