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A Preliminary Study of Methylcobalamin Therapy in Autism

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We conducted an open trial on the effect of methylcobalamin (Me-B_{12}) in 13 patients with autism. The patients' ages at the start of treatment ranged from 2 years and 3 months to 18 years. Me-B_{12} was administered at a dosage of 25-30 g/kg/day for 6-25 months. The intelligence and developmental quotient (IQ/DQ) after Me-B_{12} treatment was 52 ± 6.0 (mean ± SE), which was significantly higher than before treatment (45 ± 5.3) ($p<0.05$). The childhood autism rating scale (CARS) score improved significantly, from 35.9 ± 1.6 before to 33.0 ± 1.7 after treatment ($p<0.001$). To distinguish the effects of Me-B_{12} from natural developmental factors, the patients were divided into two subgroups, both according to age and according to intelligence. The CARS scores of the teenage and the low-IQ groups improved as much as those of the pre-early school age and the high-IQ groups. As adolescent autism patients usually show a decline in their condition, while some high function autism patients exhibit positive development, the improvement of CARS scores with Me-B_{12} treatment in the teenage and the low-IQ groups suggests that the Me-B_{12} effect is distinct from developmental factors. Although these data are very preliminary, Me-B_{12} is potentially beneficial in autism as an additional or alternative treatment.

Key words: autism, IQ, methylcobalamin, childhood autism rating scale (CARS), methylation cycle

Introduction

Autism, which was first described by Kanner[1], is a pervasive developmental disorder characterized by impairments in three core symptom domains: deficiencies in language and social relatedness, and restricted patterns of behavior[2]. The diagnostic and statistical manual of mental disorders (DSM)-IV[3] sets out four criteria for autism: ① early onset (before age 3 to 5 years), ② severe abnormality of reciprocal social relatedness, ③ severe abnormality of communication development (including language) and ④ restricted interests and repetitive patterns of behavior.

The dramatic increase in the prevalence of autism[4] necessitates the development of novel pharmacological treatments, targeted to improving both the core symptoms as well as various associated symptoms such as epilepsy, hyperactivity, stereotypical behaviors, temper tantrums and aggressiveness[5)~9)]. Methylcobalamin (Me-B_{12}) has been reported to improve cognitive function in Alzheimer disease and senile dementia[10], but to date has not been tried as a means of improving the symptoms of autism.

To test whether Me-B_{12} treatment could improve the core symptoms in autism, we conducted an open trial on the effect of Me-B_{12} in 13 patients with autism, starting in 1999. Here we show that Me-B_{12} may improve the symptoms of autism regardless of developmental stage or IQ.

Subjects and Methods

The subjects were 13 patients with autism (11 males and 2 females) admitted to the outpatient clinic of the Tokyo Women's Medical University Hospital (Table 1). Autism was diagnosed according to the DSM-IV[3] by an experienced pediatric neurologist (KN). The patients were followed and evaluated clinically by the pediatric neurologist in

Table 1 Clinical features of the patients

case	gender	underlying/ complicating disorder	start of B_{12} treatment date: Y/M/D (age: y, m)	evaluation period months	comedication	IQ/DQ	CARS
1	F		01/ 5/22 (2y3m)	6		Tsumori-Inage	+
2	M		01/ 3/16 (2y9m)	6		Tsumori-Inage	+
3	M		01/11/30 (2y9m)	6		Tsumori-Inage	+
4	M		99/ 1/27 (3y3m)	12	Vitamin E	Tsumori-Inage	
5	M	PVL, FE	01/ 6/21 (3y11m)	7	CBZ	Owaki	+
6	M		01/ 7/ 8 (5y4m)	7		Tsumori-Inage	+
7	M		00/ 5/22 (5y7m)	7		Owaki	+
8	M		99/ 4/23 (6y3m)	12		WISC-Ⅲ	
9	M	FE	01/ 2/ 5 (6y4m)	8	CBZ	Tsumori-Inage	+
10	M	FE	01/ 9/ 9 (14y9m)	6	CBZ	WISC-Ⅲ	+
11	M	FE	99/ 8/27 (16y5m)	25		Tanaka-Binet	+
12	M		99/ 9/ 1 (17y2m)	18		Tsumori-Inage	+
13	F		02/ 2/ 8 (18y0m)	12	pimozide, artane*	Tsumori-Inage	+

FE: focal epilepsy, PVL: periventricular leukomalacia, CBZ: carbamazepine, *: trihexyphenidyl hydrochloride, CARS: childhood autism rating scale, +: CARS test was performed.

the outpatient clinic of Department of Pediatrics, Tokyo Women's Medical University Hospital. Underlying or complicating disorders included periventricular leukomalacia and focal epilepsy in case 5 and focal epilepsy in cases 9, 10 and 11. The patients' ages at the beginning of treatment ranged from 2 years and 3 months to 18 years. The evaluation period was 6 to 25 months (mean ± SE, 10.2 ± 1.6).

Instead of attending specific behavioral programs for autism, the subjects had received ordinary education: nursery schools in cases 1, 2 and 3, handicapped nursery school in case 4, kindergartens in cases 5, 6 and 7, primary school in case 8, handicapped primary school in case 9, junior high school in case 10, handicapped high school in case 11 and handicapped working homes in cases 12 and 13.

Co-medications given were vitamin E for peripheral blood circulation in case 4, carbamazepine for epilepsy in cases 5, 9 and 10, and pimozide and trihexyphenidyl hydrochloride for a psychotic condition in case 13. Me-B_{12} was administered at a dosage of 25-30 μg/kg/day to a maximum of 1,500 μg/day after informed consent had been obtained from the patient's guardian. The intelligence and developmental quotient (IQ/DQ) was studied using the Wechsler intelligence scale for children (WISC)-III, Tanaka-Benet, Owaki, and Tsumori-Inage methods. These different IQ/DQ methods gave consistent results in each patient. The childhood autism rating scale (CARS)[11)12)] which evaluates the severity of autism was also employed. The same child clinical psychologist performed these tests before and after Me-B_{12} treatment in each patient. Two cases (cases 4 and 8) were dropped from the CARS study, because of their lack of cooperation.

To evaluate age and intelligence specificity for Me-B_{12} treatment, the patients were divided into two subgroups according to age: a pre-early school-age-group (between 2 years and 3 months to 6 years and 4 months) and a teenage-group (14 years and 9 months to 18 years); and into two subgroups according to intelligence before Me-B_{12} treatment: a high IQ group (above 50), and a low IQ group (50 and below). The changes in IQ/DQ and CARS scores were compared between the subgroups. We evaluated the effect of Me-B_{12} treatment on each of the 15 items of CARS[11)] (Table 2).

We carefully checked for side effects of Me-B_{12}, including exanthema and intestinal symptoms by clinical examination. We measured serum Me-B_{12} concentration in case 2, 3, 8, 9, 10, 11, 12 and 13. All values are given as mean ± SE. Comparisons between two groups were conducted with the paired Student t test, using Stat View software. A p-value less than 0.05 was considered significant.

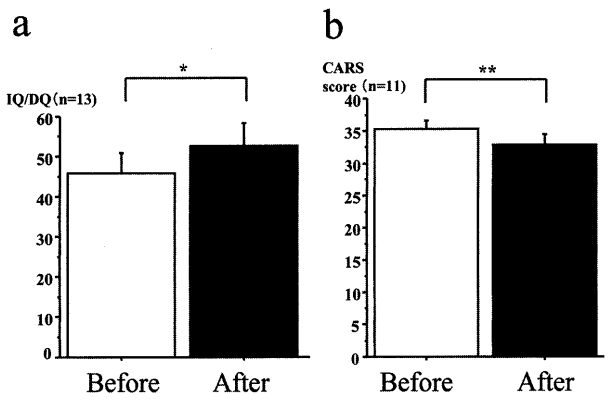

Fig. 1 The effects of Me-B_{12} as evaluated by IQ/DQ and CARS
a: IQ/DQ levels before and after Me-B_{12} treatment in each case, **b:** CARS scores before and after Me-B_{12} treatment in each case. IQ/DQ and CARS scores of these patients improved significantly, *: $p < 0.05$, **: $p < 0.001$.

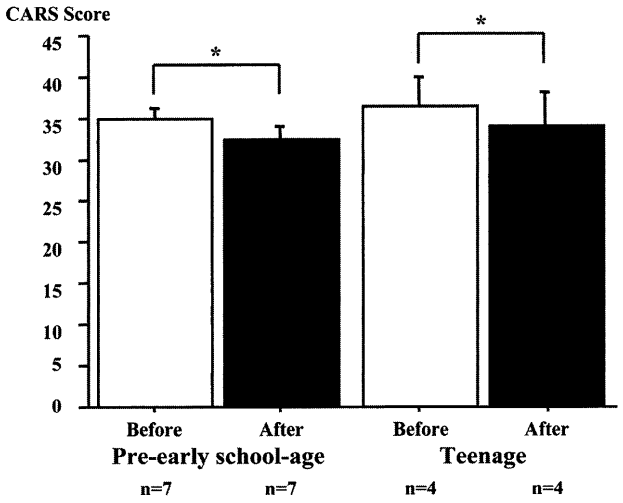

Fig. 2 Comparison of Me-B_{12} effects among different age groups
The patients were divided into two subgroups according to age: ① the pre-early school-age-group: 2 years-3 months to 6 years-4 months, and ② the teenage-group: 14 years-9 months to 18 years.
The CARS score in each group before and after treatment. ① the pre-early school-age-group: 34.9 ± 3.8, and 32.4 ± 4.1 ($p < 0.05$), ② the teenage-group: 36.6 ± 6.9 and 34.1 ± 8.0 ($p < 0.05$). *: $p < 0.05$.

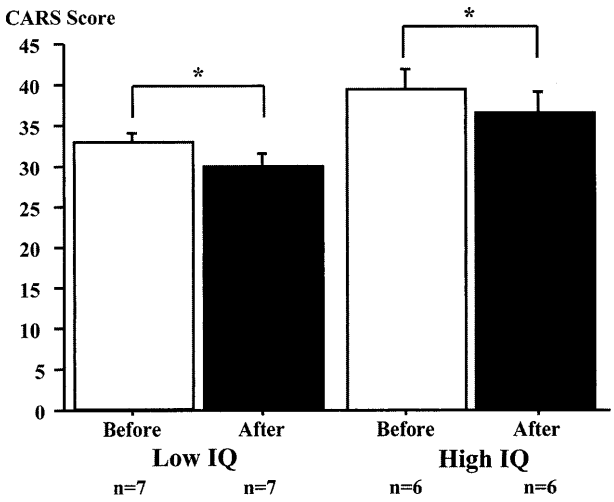

Fig. 3 Me-B_{12} effects according to intelligence
The subjects were divided into two groups according to their IQ/DQ levels before Me-B_{12} treatment. The high IQ group was defined as having an IQ above 50, while the low IQ group had IQs below 50.
The CARS score in each group before and after treatment. The high IQ group: 32.9 ± 1.3 and 30.1 ± 1.3 ($p < 0.05$). The low IQ group: 39.4 ± 2.6 and 36.6 ± 2.6 ($p < 0.05$). *: $p < 0.05$.

Results

1. Effects of Me-B_{12} evaluated with IQ/DQ and CARS (Fig. 1)

After Me-B_{12} treatment, IQ/DQ was 53 ± 6.0, significantly higher than before treatment (46 ± 5.0) (paired t test: $p = 0.0199$) (Fig. 1a). The IQ/DQ change was 6.6 ± 2.5, ranging from − 7 to 23. The CARS score were 35.5 ± 1.5 before and 33.0 ± 1.7 after treatment with statistical significance (paired t test: $p = 0.0008$) (Fig. 1b). The score improvement of scales was 2.5 ± 1.6, ranging from 0.5 to 6.

2. Me-B_{12} effect according to age (Fig. 2)

The patients were divided into two subgroups according to age: the pre-early school-age-group, and the teenage-group. The IQ/DQ levels of the pre-early school-age-group tended to be high, while those of the teenage-group did not change with Me-B_{12} therapy. They were not statistically significant. Both of the pre-early school-age-group and the teenage-group showed improvement on CARS with statistical significance.

3. Me-B_{12} effect according to intelligence (Fig. 3)

The subjects were divided into two groups according to IQ/DQ levels before Me-B_{12} therapy: the high IQ group and the low IQ group. The IQ/DQ levels in both groups tended to be high but without statistical significance. The CARS score improved in both groups with statistical significance.

Table 2 Effects of methylcobalamin on CARS items

CARS item	Me-B_{12}		p value
	Before	After	
Relating to people	2.59 ± 0.11	2.36 ± 0.17	0.0531
Imitation	2.18 ± 0.22	2.05 ± 0.18	0.3911
Emotional response	2.59 ± 0.20	2.23 ± 0.12	* 0.0379
Body use	2.50 ± 0.20	2.27 ± 0.24	* 0.0162
Object use	2.05 ± 0.20	1.96 ± 0.18	0.3409
Adaptation to change	2.14 ± 0.23	1.82 ± 0.21	* 0.0107
Visual response	2.23 ± 0.20	2.09 ± 0.16	0.1921
Listening response	2.23 ± 0.26	1.96 ± 0.20	0.0816
Taste, smell, and touch response and use	2.09 ± 0.21	2.05 ± 0.30	0.8461
Fear or nervousness	2.32 ± 0.19	2.14 ± 0.20	0.3966
Verbal communication	2.86 ± 0.17	2.64 ± 0.17	* 0.0162
Nonverbal communication	2.27 ± 0.17	2.18 ± 0.12	0.5059
Activity level	2.41 ± 0.13	2.59 ± 0.18	0.2674
Level and consistency of intellectual functioning	2.50 ± 0.12	2.41 ± 0.15	0.5527
General impression	2.55 ± 0.13	2.50 ± 0.15	0.3409

mean ± SE, Patient number was 11, *: $p < 0.05$.

4. Me-B_{12} effect on each CARS item (Table 2)

When we evaluated the effect of Me-B_{12} therapy on each item of CARS, "emotional response", "body use", "adaptation to change", and "verbal communication" showed statistically significant improvement.

5. Serum Me-B_{12} concentration and side effect of Me-B_{12}

Serum Me-B_{12} concentrations before Me-B_{12} administration in five cases were in the normal range (mean ± SE: 794 ± 76 pg/ml, ranging from 590 to 950). The concentrations after Me-B_{12} administration were elevated in four cases (950 to >2,000). No apparent side effects, such as skin eruptions or intestinal symptoms, were observed on clinical examination during this study.

Discussion

The number of people with autism and related disorders has dramatically increased over the past decade, leading to an increased need for better pharmacological treatments for these conditions.

Recent reviews have described drug treatment strategies for various associated symptom domains commonly found in autism[13]. McCracken et al[14] evaluated the efficacy and safety of risperidone in children with autism. Selective serotonin-reuptake inhibitors such as citalopram[15] and fluoxetine[16], are reported to be potentially useful drugs for the treatment of anxiety, repetitive behaviors, or core symptoms, while melatonine may provide some benefit in the case of autism-related sleep disorders[17]. To our knowledge, no study of Me-B_{12} therapy for autism has yet been published[18]. Megavitamin therapy has been reported, but the results were negative for autism[19].

Given the improvement in IQ/DQ and CARS after Me-B_{12} therapy, our study suggests that this drug could be an effective treatment for autism (Fig. 1). As this study was an open trial without a control, we must take into account natural developmental profiles and/or changes in the social/educational environment of the subjects, which could account for the observed improvements. Additional studies with larger sample sizes need to be undertaken. However, our preliminary results suggest that Me-B_{12} therapy may be effective for autism. Me-B_{12} therapy led to an improvement in CARS scores in the teenage-group as well as the younger group (Fig. 2), and CARS scores improved even in those with low IQ levels (Fig. 3). These results differ from the natural course of autism.

In general, adolescence is a critical period in many cases of autism[20]. Epilepsy, deterioration, aggravation of symptoms and additional psychiatric problems commonly accompany autism in adolescence. Some autistic children, who have shown posi-

tive development during the early school years, can be relatively high-functioning[21]. Spontaneous improvement may even occur in a small minority of autism cases[22]. Therefore, the improvement of CARS scores with Me-B_{12} treatment in the teenage-group and the low-IQ group suggests that the Me-B_{12} effect is not the natural course of the disease. Evaluation of the effects of Me-B_{12} on each item of CARS revealed statistically significant improvement in "body use", "adaptation to change", and "verbal communication" (Table 2). As these items encompass the complex core symptoms of autism, it is possible that Me-B_{12} therapy is more effective than other symptomatic treatments for autism.

The major function of Me-B_{12} in the brain is regulation of the methylation cycle[23], which involves the use of a large number of methyltransferases[24]. Me-B_{12} deficiencies in infants and children have been reported[25]~[27]. Mental deteriorations in addition to another neurological symptoms and megaloblastic anemia have been documented. The state of mental deterioration was quite severe: the patients lost connection to their surroundings. The authors described this condition as "apathy" or "lethargy". Stollhoff[25] presented a crucial case report. The mother described the patient as losing the ability to smile and visually make contact with the mother during the progression of secondary Me-B_{12} deficiency. These signs might be related to one of the core symptoms of autism, or severe abnormality of reciprocal social relatedness.

Our study suggests that Me-B_{12} therapy maybe potentially beneficial in the treatment of autism with a comprehensive management strategy including exposure to enriched environments and behavioral/educational treatment[28]. We need far more study on the effect of Me-B_{12} therapy for autism, as this study is very preliminary in a sample size and a design without a control.

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自閉症におけるメチルコバラミン療法の予備的検討

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高澤（タカザワ）みゆき・中山（ナカヤマ）　智博（トモヒロ）・佐々木香織（ササキカオリ）・大澤真木子（オオサワマキコ）

我々は13例の自閉症患者でビタミン B_{12}（メチルコバラミン：Me-B_{12}）の治療効果をオープン試験で試みた．Me-B_{12} の治療開始時期は2歳3ヵ月から18歳で，Me-B_{12} を25～30μg/kg/day，6～25ヵ月間投与した．IQ/DQによる評価では，治療前は45±5.3（平均±標準誤差）であったが，治療後は52±6.0と有意な上昇が認められた（$p=0.0199$）．CARS検査（小児自閉症評定尺度）では，治療前は35.9±1.6であったが，治療後は33.0±1.7（$p=0.0008$）と改善した．自然経過による改善とMe-B_{12} 効果を鑑別するため，患者を年齢，知能でそれぞれ2群に分類し検討したところ，思春期群と低IQ群のCARSスコアーが，幼児・早期学童期群，高IQ群と同様に改善した．自閉症児において思春期は一般に症状改善に乏しく，症状の自然改善は高機能自閉症児に見られることから，この結果は，Me-B_{12} 効果は自然経過とは異なると考えられた．検討はまだ予備的段階であるが，自閉症においてMe-B_{12} は治療薬として試みる価値があると考えられた．