61. *Therapeutic Effect of Tetrahydrobiopterin in Infantile Autism*

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Introduction. Infantile autism has been defined as a disorder of the brain, but its etiology has so far remained unknown. Naruse *et al.*¹⁾ found a marked decrease in the intestinal transport of deuterated phenylalanine and tryptophan in several typical cases of infantile autism. They postulated that a defect in the cellular transport of the aromatic amino acids may at least partially contribute to the development of this disorder through decreased formation of serotonin and catecholamines in the brain.

Recently, we succeeded in the large-scale synthesis of 6R-L-erythro-5,6,7,8-tetrahydrobiopterin (R-THBP), the natural cofactor of tyrosine and tryptophan hydroxylases which are the rate-limiting enzymes for catecholamines and serotonin biosyntheses, respectively. The limited concentration of R-THBP in the brain²⁾ indicates the regulatory role of R-THBP in these neurotransmitter amine levels. R-THBP was shown by intraventricular³⁾ and peripheral⁴⁾ administration to enhance the biosyntheses of these amines in the rat brain.

The safety of R-THBP was assessed by several series of animal experiments, and the cofactor was subsequently used in the treatment of patients with biopterin-deficient diseases such as atypical phenylketonuria on a long-term base without any adverse reaction. Clinical phase 1 study of R-THBP was performed by Dr. M. Nakajima of the Department of Pharmacology, Hamamatsu University School of Medicine, in cooperation with Suntory Biomedical Institute, and no particular abnormality was observed. Based on these observations, clinical trials concerning effects of R-THBP in patients with infantile autism were performed. The results of these studies will be described in this report.

Methods of study. 1) Subjects and medication. The diagnosis of infantile autism conformed to the WHO definition. A written consent was obtained from the parents of all subjects after the necessary information about the study was provided. Patients with severe brain damage or serious physical handicap were omitted from the study. In the preliminary stage of the study, two typical cases of infantile autism were treated with R-THBP and significant clinical improvement was observed.⁵⁾ Subsequently, seventeen cases of autistic patients in four clinics were treated with R-THBP and seven out of seventeen patients, whose ages ranged from 3 to 5 years, had marked improvement in clinical symptoms.^{6),7)}

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In 1986, double blind trials (DBT) using R-THBP and inactive placebo were performed on autistic patients in four clinics. Eighty four patients, sixty two male and twenty two female, were selected. Forty five were less than 5 years old, twenty seven were between 5 y 1 m and 6 y, and twelve were older than 6 y 1 m. R-THBP, the active drug, was given per os at a dosage of 1.0–3.0 mg/kg/day in the form of a granule containing 2.5% R-THBP, 4% ascorbic acid and 2% cysteine HCl to forty two cases; and a placebo (granule described as above without R-THBP), to the remaining forty two cases. A fixed-flexible method was applied. The specific educational approaches given before the treatment were continued throughout the study. The period of the DBT was twelve weeks and it was commenced after a certain period (more than seven days) of washing out other therapeutic drugs from the patients.

2) Clinical assessment. The clinical symptoms and changes in abnormal behaviors were evaluated by a "Rating Scale for Abnormal Behaviors in Children" (RSABC), which comprised of 4 clusters, 7 subclusters, and 60 factors.^{8),9)} Improvement or aggravation was recorded for each factor, subcluster, and cluster using one of seven grades: markedly improved, improved, slightly improved, unchanged, slightly aggravated, aggravated, and markedly aggravated. General improvement rating (GIR), safety, and utility were judged in each assessment. Clinical evaluation based on this rating scale was performed at the end of second, fourth, eighth and twelfth weeks. Routine clinical tests were performed before and during the drug administration at each assessment and side effects of the R-THBP were carefully sought and recorded.

Table I. General improvement rating at 12th week

	Total number	Patients in each grade of GIR						
		+++	++	+	0	—	— —	— — —
Placebo	42 (100%)	5 (11.9%)	8 (19.0%)	11 (26.2%)	13 (30.9%)	4 (9.5%)	1 (2.4%)	0
R-THBP	41 (100%)	10 (24.4%)	12 (29.3%)	7 (17.1%)	11 (26.8%)	1 (2.4%)	0	0

Wilcoxon Rank Sum Test: R-THBP > Placebo; Z value, -2.09 ; P value, 0.036 .
 +++, markedly improved; ++, improved; +, slightly improved; 0, unchanged;
 —, slightly aggravated; — —, aggravated; — — —, markedly aggravated.

Results and discussion. The results of the DBT are summarized in Table I, which provides the number and percentage of patients in each category of improvement or aggravation at the end of the twelfth week. One case in the R-THBP group had to be removed from the trial due to an accident and was not included in the results. No adverse reaction was observed either in the DBT or in the open trials. The GIR of the R-THBP group at the twelfth week was clearly superior to that of the placebo group ($P < 0.05$, by Wilcoxon Rank Sum Test). Marked or definite improvement was noted in 53.7% of the patients in the R-THBP group as compared to 30.9% in the placebo group. Conversely, abnormal behaviors were aggravated in approximately 12% of the patients in the placebo group, but in only one case (2.4%) in the R-THBP group. An especially marked effect of R-THBP was observed in the group under the age of 5 years. Background data concerning sex, age, body weight, speech development, severity of symptoms, problems in prenatal, natal, and postnatal periods, and physical de-

velopment were analyzed between both groups, and no significant difference was observed in any of the items.

Up to now, major tranquilizers such as pimozide or haloperidol were used as the effective drugs for autistic patients. However, these drugs do not change the core symptoms of infantile autism and seemed to work as a symptomatic sedatives. R-THBP was most effective in improving these abnormal behaviors of autistic patients which seemed to be the core symptoms of the disease. The results of this study will be described in detail elsewhere, but these results suggest that R-THBP is an effective drug for the treatment of autistic patients.

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