Original Article

Open-labelled observations of language dysfunction in old ischemic stroke patients with aphasia when given plant and marine-based nutrient supplements for 12 weeks

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Background and Objectives: This study aimed to explore the effect of functional foods on aphasia related to a previous ischemic stroke. When stroke-related neurological deficits result in physical dependency and poor self-care that persists longer than 6 months, full recovery is almost impossible and the patient often requires long-term care. The functional foods, EASE123 and BioBalance#6, include numerous plant and marine-based nutrient supplements that could prove beneficial for such patients. **Methods and Study Design:** This open-labelled study included 10 patients diagnosed with prior ischemic stroke and aphasia lasting longer than 6 months. Each patient was administered 6 tablets of EASE123 at 10:30 AM and at 90 minutes before sleeping, and 3 tablets of BioBalance#6 at 2:30 PM. After a treatment period of 12 weeks, the patients were followed during a 4-week withdrawal period. Functional improvement was assessed by scores and subscores on the Concise Chinese Aphasia Test (CCAT) at weeks 4, 8, 12, and 16. **Results:** Average total CCAT scores and matching ability improved significantly at weeks 4, 8, 12, and 16 ($p<0.05$). Simple response scores improved significantly at weeks 8 and 12 ($p<0.05$). Auditory comprehension improved significantly at weeks 4 and 12 ($p<0.05$), and reading comprehension, at week 12 ($p<0.05$). Repetition ability improved significantly at weeks 8, 12, and 16 ($p<0.05$), and spontaneous writing, at weeks 4, 12, and 16 ($p<0.05$). **Conclusions**: Matching, repetition, and average total CCAT scores improved over the course of the study. Therefore, 6 months after ischemic stroke, EASE123 and BioBalance#6 administration may improve stroke-related aphasia.

Key Words: infarction, ischemic stroke, aphasia, functional food, nutrition

INTRODUCTION

Stroke is the most important cause of disability in the elderly. According to the National Health Insurance Research Database (NHIRD), stroke has been one of the top three leading causes of death from 1963 to 2012 in Taiwan.[1] Stroke treatment involves the administration of long-term therapies to prevent recurrence, as well as rehabilitation to restore neurological function.[2] There is a dose-dependent effect of rehabilitation on functional improvement within the first 6 months post-stroke, referred to as the "golden period".[3] Stroke is a multifactorial disorder with a complex pathophysiology. However, increasing evidence suggests that neuroinflammation is one of the primary processes leading to acute cerebrovascular disease.[4]

EASE123 (BioNatural Labs, CA, USA) is a functional food composed of multiple plant and marine-based nutrient supplements including chitosan,[5] lingzhi,[6] wheat grass,[7] barley grass,[8] glucosamine,[9] grape seed,[10] collagen,[11] bilberry,[12] and ascorbic acid.[13] BioBalance#6 (BioNatural Labs, CA, USA) is another functional food composed of chitosan,[5] grape seed,[10] ascorbic acid,[13] barley sprout,[14] hawthorn,[15] grapefruit pectin,[16] and lycopene.[17] All of the nutrients in EASE123 and BioBalance#6 are equivalent in concentration. We used two

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functional foods containing similar nutrients due to an expected synergistic effect. Compared to EASE123, BioBalance#6 contains extra barley sprout, hawthorn, grapefruit pectin, and lycopene, all of which demonstrate antioxidant and immunomodulatory properties (Table 1).[5-17]

In this study, we designed an open-labelled therapeutic trial to examine if dietary supplements taken 6 months after stroke occurrence were an effective adjuvant therapy to improve language function in patients with aphasia resulting from a previous ischemic stroke.

MATERIALS AND METHODS

The experimental procedures were approved by the Institutional Review Board for Human Studies at Tri-Service General Hospital, National Defense Medical Center, Taiwan (TSGHIRB No.: 095-05-012-A). Each patient provided informed consent after we explained the procedures and possible consequences. The patients in this study were diagnosed as having a previous ischemic stroke that resulted in aphasia lasting longer than 6 months, and none had received any speech-language therapy. Computed tomography (CT) or magnetic resonance imaging (MRI) was used to confirm the diagnosis of acute ischemic stroke affecting the left middle cerebral artery territory in all patients. The Concise Chinese Aphasia Test (CCAT) was used to evaluate language function impairment, and comprises nine subtests (Simple Response, Expository Speech, Matching, Auditory Comprehension, Naming, Reading Comprehension, Repetition, Copying, and Spontaneous Writing). This test has been used in the Taipei Veterans General Hospital since 1978, and provides a thorough overview of therapeutic effectiveness.[18] The responses were recorded using a 12-point multidimensional scoring system, and an established alternate form was available if needed to assess reliability.[18] Patients were diagnosed with aphasia and related language dysfunction if their scores were two standard deviations below the average raw scores obtained from 70 normal subjects.[18] The CCAT was standardized and percentile norms were constructed using data from 277 patients diagnosed with cerebral impairment.[18] Satisfactory results have been reported with regards to test-retest and alternate form reliabilities (both above 0.90), and criterion-related validity (above 0.63 utilizing the Boston Diagnostic Aphasia Examination-Chinese Version).[18,19] In summary, the CCAT is considered a useful and reliable test for assessing aphasia and related language dysfunction in Chinese patients.[18]

Pre-trial screening tools included the Barthel Index (BI) and modified Rankin Scale (mRS), which are commonly used to assess disability or dependence in activities of daily living in patients with stroke. A poor outcome was defined by scores of mRS >3 or BI <60.[20] Patients with a National Institutes of Health Stroke Scale (NIHSS) score of 0 to 6, 7 to 15, and 16 to 38 were classified as mild, moderate, and severe stroke, respectively.[21]

The functional foods, EASE123 and BioBalance#6, were administered in capsulated form. During the entire course of the study, all patients continued with their current medication to lower the risk of recurrent stroke. The present study was a 12-week open-labelled therapeutic trial. The treatment regime consisted of six capsules of EASE123 at 10:30 AM and 90 minutes before sleeping each day, and three tablets of BioBalance#6 at 2:30 PM. In a previous study, patients showed a decrease in the need for stroke care and an increase in quality of life at this dosage (2.5 g for 6 capsules twice a day and 1.2 g for 3 capsules per day), and five of nine patients suffering from speech dysfunction showed apparent improvement.[22] After the treatment period of 12 weeks, patients were followed for a withdrawal period of 4 weeks.

Statistical analysis

Statistical analysis for continuous variables used SPSS software (version 18; SPSS Inc., Chicago, IL, USA). Total CCAT scores and scores on the specific subscales were expressed as mean ± standard deviation. The Wilcoxon signed-rank test was used to assess statistical differences between visits. A value of $p<0.05$ was consid-

Table 1. Biological activities of each ingredient within EASE123 & BioBlance#6

Ingredients of EASE123 & Bioblance#6			Biological activities			
			A	B	C	D
EASE123	Plant-based	Grape seed	*	*		
		Ascorbic acid	*	*		*
		Barley grass	*	*		
		Wheat grass	*	*		
		Lingzhi	*	*		
		Bilberry	*			
		Collagen		*		
	Marine-based	Chitosan	*		*	
		Glucosamine	*	*		
BioBalance#6	Plant-based	Grape seed	*	*		
		Ascorbic acid	*	*		*
		Barley sprout	*		*	*
		Hawthorn	*	*	*	*
		Grapefruit pectin	*		*	*
		Lycopene	*	*		*
	Marine-based	Chitosan	*		*	

A: antioxidant effect; B: immunomodulatory effect; C: increase high density lipoprotein & lower serum cholesterol; D: decrease vascular endothelium dysfunction.

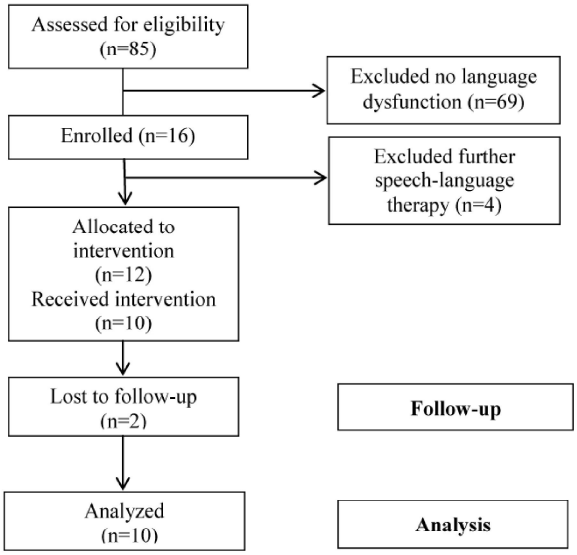

Figure 1. Flow diagram indicating the number of patients recruited and registered

ered statistically significant.

RESULTS

We screened 85 patients with infarction in the left middle cerebral artery territory initially, and 16 patients were recruited who met the criteria of having aphasia resulting from a previous ischemic stroke that had lasted longer than 6 months. Four patients were excluded due to further speech-language therapy and 2 patients were lost to follow-up (Figure 1). The remaining 10 patients participated in this open-labelled study and received the plant and marine-based nutrient supplements, EASE123 and BioBalance#6, for 12 weeks with a follow-up withdrawal period of 4 weeks. The patients' clinical characteristics at baseline are shown in Table 2. The male: female ratio was 7:3. Based on their NIHSS score, patients were subgrouped as follows: 6 mild, 3 moderate, and 1 severe stroke.

Patients with classified as having language disability or aphasia if their testing scores were below the following clinical cut-off points: simple response (11.1), expository speech (11.7), matching (11.6), auditory comprehension (11.3), naming (12.0), reading comprehension (11.4), repetition (11.4), copying (11.2), spontaneous writing (10.3), and total CCAT scores (11.5).[18]

During the 16-week study period, scores on the simple response, expository speech, matching, auditory comprehension, naming, reading comprehension, repetition, copying, and spontaneous writing subtests, as well as total CCAT scores, were recorded for all patients (Table 3). Patients showed a significant increase in the average total CCAT scores of 5.9-16.3% during the period of EASE123 and BioBalance#6 supplementation (Figure 2). Compared with baseline, the mean increase in scores was 13.2%, even after the withdrawal of EASE123 and BioBalance#6 administration for 4 weeks. In addition, efficacy was analyzed using the CCAT subscales. Scores on the simple response, matching, and repetition subscales, as well as the average of the total CCAT scores, all showed a significant and consistent increase during the 12-week treatment with EASE123 and BioBalance#6 supplements compared with baseline (Figure 3). Over the course of this trial, six of the nine CCAT subtests (simple response, matching, auditory comprehension, reading comprehension, repetition, and spontaneous writing) showed a statistically significant increase from baseline during at least one testing session. Further, the average total CCAT scores and scores on three of the nine CCAT subtests (matching, auditory comprehension, and spontaneous writing) reached statistical significance at week 4.

DISCUSSION

Atherosclerosis, an inflammatory disease that occurs chiefly in the large and medium-sized arteries, can increase the risk of brain infarction.[23] C-reactive protein (CRP) is an indicator of underlying systemic inflamma-

Table 2. Clinical characteristics of patients with aphasia resulting from a previous ischemic stroke

Variables	Case number										
	I	II	III	IV	V	VI	VII	VIII	IX	X	Mean±SD
Age											61.9±16.2
NIH Stroke Scale	19	14	3	2	3	2	5	8	6	15	7.7±6.1
Modified Rankin scale	4	3	2	2	2	1	2	2	2	4	2.4±0.9
Barthel index	25	65	100	95	85	100	100	90	100	55	81.5±25.4
Stroke severity	S	M	m	m	m	m	m	M	m	M	
CCAT											
Simple response	2.0	4.6	9.2	8.6	5.2	10.9	11.4	3.0	7.7	11.9	7.5±3.6
Expository speech	1.0	4.0	7.8	5.5	3.1	11.0	11.9	3.0	7.2	10.3	6.5±3.8
Matching	5.3	11.5	12.0	12.0	12.0	11.0	12.0	6.2	11.0	11.8	10.5±2.5
Auditory comprehension	1.0	7.8	11.5	9.4	7.7	11.0	8.8	3.6	9.3	11.8	8.2±3.5
Naming	1.0	7.5	11.4	9.1	3.2	11.0	10.6	4.4	10.0	12.0	8.0±3.9
Reading comprehension	2.2	8.1	9.9	9.3	3.0	11.0	11.0	4.1	8.1	11.8	7.9±3.5
Repetition	1.0	9.0	11	8.3	7.8	10.2	9.2	6.0	10.6	12.0	8.5±3.2
Copying	6.6	8.0	8.7	11.3	10.6	11.1	11.0	9.0	9.0	9.0	9.4±1.5
Spontaneous writing	2.9	3.6	3.6	6.2	3.8	12.0	9.8	3.0	8.1	9.0	6.2±3.3
Total CCAT scores											8.1±2.9

S: severe; M: moderate; m: mild; SD: standard deviation; CCAT: Concise Chinese Aphasia Test.

Table 3. Results of the Concise Chinese Aphasia Test (N=10)

ITEM	Time point									
	Week 0	Week 2		Week 4		Week 8		Week 12		Week 16	
	Mean±SD	Mean±SD	*p*-value	Mean±SD	*p*-value	Mean±SD	*p*-value	Mean±SD	*p*-value	Mean±SD	*p*-value
Total CCAT scores	8.1±2.9	8.3±2.7	0.213	8.7±2.7	0.025*	8.9±2.5	0.015*	8.9±2.6	0.009*	8.9±2.5	0.017*
Simple response	7.5±3.6	7.9±3.6	0.380	8.1±3.6	0.051	8.3±3.5	0.036*	8.4±3.2	0.017*	8.2±3.3	0.092
Expository speech	6.5±3.8	6.3±3.8	0.779	6.9±4.1	0.154	6.8±4.0	0.553	7.1±3.8	0.139	7.1±3.8	0.207
Matching	10.5±2.5	10.8±2.4	0.345	11.2±1.7	0.028*	11.7±0.6	0.027*	11.3±1.6	0.027*	11.7±0.6	0.027*
Auditory comprehension	8.2±3.5	8.4±3.1	0.553	9.0±3.0	0.022*	8.9±2.8	0.110	9.2±2.8	0.009*	8.7±3.3	0.139
Naming	8.0±3.9	7.6±4.0	0.400	8.3±3.6	0.446	8.7±3.8	0.123	8.3±4.0	0.440	8.4±3.8	0.333
Reading comprehension	7.9±3.5	8.7±3.2	0.374	8.8±2.9	0.221	8.9±3.3	0.153	9.1±2.8	0.036*	8.9±3.0	0.386
Repetition	8.5±3.2	9.0±3.2	0.062	9.0±3.5	0.123	9.5±3.2	0.017*	9.5±3.2	0.012*	9.4±3.2	0.012*
Copying	9.4±1.5	9.6±1.5	0.343	9.9±15	0.115	9.9±1.4	0.236	10.0±1.4	0.075	9.9±1.5	0.342
Spontaneous writing	6.2±3.3	6.3±3.3	0.624	7.4±3.3	0.017*	6.7±3.2	0.528	7.4±3.1	0.012*	7.5±3.3	0.050*

SD: standard deviation; CCAT: Concise Chinese Aphasia Test.
*p<0.05.

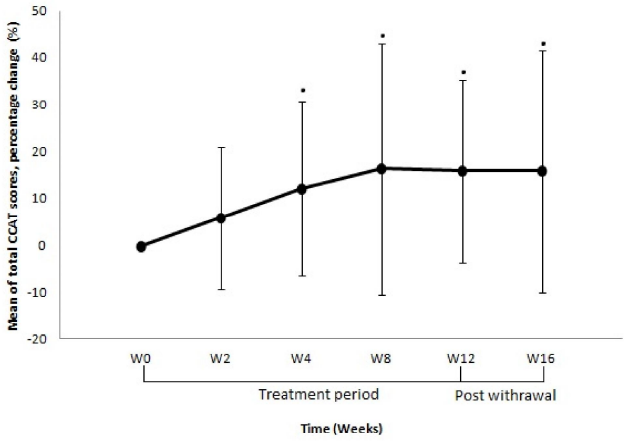

Figure 2. Percent change in the average total Concise Chinese Aphasia Test (CCAT) scores in patients treated with EASE123 and BioBalance#6 (n=10) for 12 weeks followed by 4 weeks of withdrawal. Statistical significance at each time point is shown relative to baseline using the Wilcoxon signed rank test (*p<0.05).

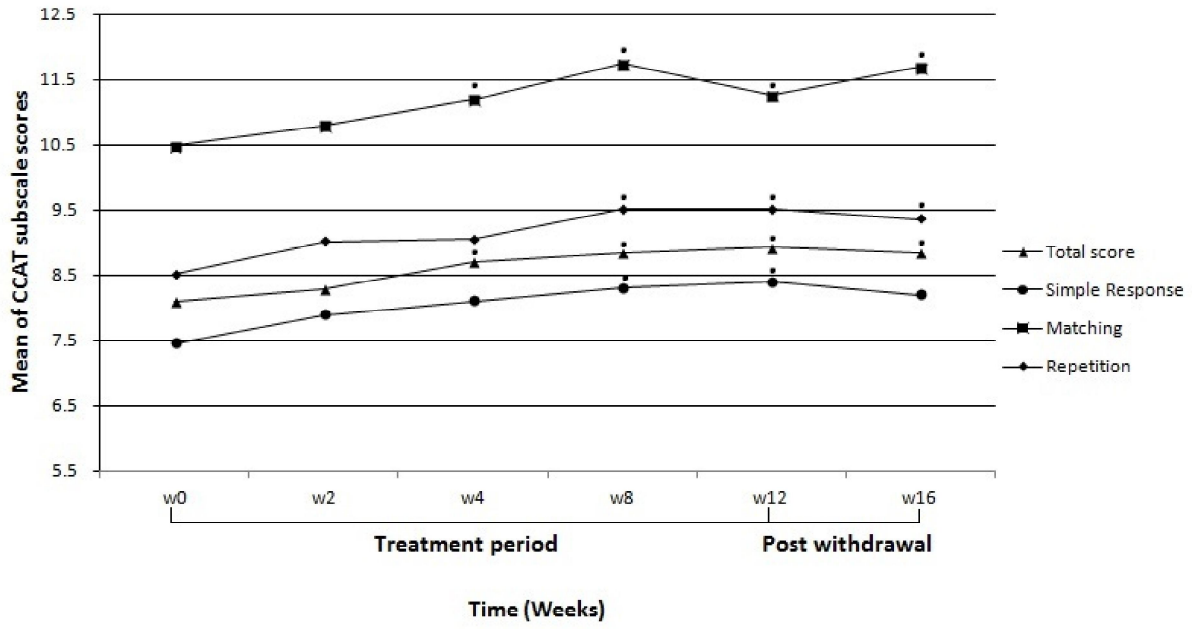

Figure 3. Change in the mean score of each Concise Chinese Aphasia Test (CCAT) subscale (matching, repetition, total scores, and simple response) in patients treated with EASE123 and BioBalance#6 (n=10) for 12 weeks followed by 4 weeks of withdrawal. Statistical significance at each time point is shown relative to baseline using the Wilcoxon signed rank test ($^{*}p<0.05$).

tion. It has many pathophysiological roles, including recognition of foreign pathogens and binding to phosphocholine when a cell is damaged.[24] Independent of smoking, systolic blood pressure, total cholesterol, and diabetes, the elevation of plasma CRP levels is a significant predictor of future ischemic strokes.[25] In addition, post-stroke acute and prolonged inflammatory responses result in the excessive release of proinflammatory cytokines, matrix metalloproteinases, and reactive oxygen species.[26] Liebigt et al reported that post-stroke application of an anti-inflammatory drug (indomethacin) combined with rehabilitation in rats led to improved functional recovery compared with rehabilitation alone.[27] Inhibition of the inflammatory reaction after stroke helps rescue neuronal plasticity, and is an important factor in achieving functional recovery.[28] Therefore, we speculate that EASE123 and BioBalance#6, which have antioxidant and immunomodulatory activities, may have additional therapeutic effects on aphasia related to ischemic stroke beyond the "golden period" of the first 6 months post-stroke. The major clinical benefit of EASE123 and BioBalance#6 was indicated by a significant increase in the average total CCAT scores 4 weeks after continuous administration of these supplements. However, further studies are needed to elucidate the mechanisms involved and to verify the results.

Nutrition is important for stroke prevention, and vitamin B-12 supplements may have a beneficial effect by lowering levels of total homocysteine.[29] Aquilani et al reported that the progression of ischemic brain damage was related to insufficient protein intake and low levels of dietary zinc; moreover, they found that nutritional supplements could enhance neurocognitive recovery in patients with ischemic stroke.[30] Our results showed that EASE123 and BioBalance#6, both of which include multiple bioactive nutrients, may provide functional recovery in patients with a history of ischemic stroke even beyond the "golden period". The consistent and significant improvement of the average total CCAT scores through the end of week 16 demonstrated a strong therapeutic effect of EASE123 and BioBalance#6. Moreover, EASE123 and BioBalance#6 were safe for use by stroke patients, and were easy to administer without any severe adverse effects.

Information provided by primary caregivers contributed to the evaluation of therapeutic effect during the course of the trial. According to our results, administration of the functional foods EASE123 and BioBalance#6 had a positive effect on patients diagnosed with a previous ischemic stroke who had suffered from aphasia for more than 6 months. After the continuous administration of these dietary supplements for 4 weeks, matching ability, auditory comprehension, spontaneous writing, and average total CCAT scores improved significantly. Simple response and repetition ability improved significantly at the end of week 8, while reading comprehension improved significantly at week 12. No statistical significance was noted at week 8 with regard to auditory comprehension and spontaneous writing; this may have been attributable to bias in the information provided by primary caregivers.

Van der Meulen et al confirmed that Melodic Intonation Therapy, a language production treatment, was effective for subacute severe nonfluent aphasia, and that earlier treatment could lead to greater improvement.[31] Stahl et al concluded that patients receiving standard therapy showed lesser progress in the production of common and formulaic phrases; however, the long-term effects of melody and rhythm on speech recovery were not clear.[32] The patients in our study had chronic stroke with aphasia, and no classic speech-language therapy was provided.

Limitations of the present study include the small sample size. A larger number of subjects would be needed for future studies. In addition, we did not include a control

group; our study consisted of a pretest-posttest design using the CCAT, in which we compared the therapeutic effect of EASE123 + BioBalance#6 using each patient as their own comparator. Finally, the severity of aphasia in our patient group was inconsistent. Future studies should focus on larger sample sizes with greater patient homogeneity, and a double-blind randomized controlled trial is needed to confirm our results.

In conclusion, our results showed that the plant and marine-based nutrient supplements, EASE123 and BioBalance#6, might improve language function in patients with aphasia resulting from a previous ischemic stroke even after 6 months.

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AUTHOR DISCLSURES

We declare that we have no conflict of interest with regard to this manuscript.

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Original Article

Open-labelled observations of language dysfunction in old ischemic stroke patients with aphasia when given plant and marine-based nutrient supplements for 12 weeks

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以植物与海产为基础的营养补充剂用于陈旧性缺血性中风失语症患者持续使用 12 周的开放性观察试验

背景与目的：本研究旨在探索功能性食品应用于缺血性中风失语症的效果。当中风相关的神经功能障碍导致身体依赖以及无法自我照顾的时间持续超过 6 个月，完全恢复几乎是不可能的，病人往往需要长期照顾。这里提到的功能性食品，EASE123 和 BioBalance＃6，包括许多以植物和海产为基础的营养补充剂，可以证明对此类患者有益。**方法与研究设计**：此开放标记的研究纳入 10 例确诊为陈旧性缺血性中风和失语症持续超过 6 个月的患者。每个病人在 10:30 AM 及睡前 90 分钟分别服用 6 粒 EASE123，于 2:30 PM 服用 3 粒 BioBalance＃6。12 周的治疗期后是一个为期 4 周的停药观察期。分别在第 4、8、12 和 16 周，使用简明中国失语症测试（CCAT）分数和子项目分数评估功能改善的效果。 **结果**：研究发现平均总 CCAT 分数和图像配对能力在第 4、8、12 和 16 周有显著改善（p<0.05）。简单应答分数在第 8 和 12 周有显著改善（p<0.05）。听觉理解在第 4 和 12 周（p<0.05），及阅读理解在第 12 周有显著改善（p<0.05）。复诵句子在第 8、12 和 16 周显著改善（p<0.05），且自发书写在第 4、12 和 16 周有显著改善（p<0.05）。**结论**：图物配对、复诵句子和平均总 CCAT 分数于整个研究过程中皆有显著改善。因此，缺血性中风 6 个月后，给予 EASE123 和 BioBalance＃6 营养补充剂可以改善缺血性中风失语症。

关键词：脑梗塞、缺血性中风、失语症、功能性食品、营养