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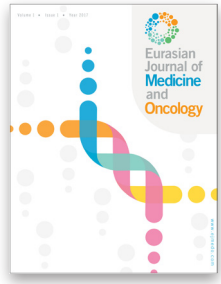


Research Article

# Impact of L-Arginine on Language Skills in Children with Hypoxic–ischemic Encephalopathy

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## Abstract

**Objectives:** The aim of this study was to investigate the impact of L-Arginine on speech and language development in pediatric patients with hypoxic–ischemic encephalopathy (HIE).

**Methods:** The oral language skills of 24 pediatric patients with HIE using L-Arginine were classified and the impact of L-Arginine on language skills was evaluated retrospectively. While there is no standard dose of L-Arginine, the usual dosage is 2.5 g orally for children younger than 5 years of age and 5 g orally for children older than 5 years of age.

**Results:** The study enrolled 24 pediatric patients with a mean age of 3.9 years (range: 1.25–12 years). A pre-treatment median rating of 1 for oral language development increased to 3 post treatment, according to the results of a Wilcoxon signed-rank test used to examine the statistical significance of the difference between 2 variables. The difference was statistically significant.

**Conclusion:** Although the exact pathophysiology of HIE has not been fully elucidated, it is associated with diffuse cerebral damage that leads to impaired motor and language development; moreover, HIE has no cure. In this study, L-Arginine therapy had a positive and significant impact on language development in children affected by HIE. Additional, larger series are needed to confirm these preliminary findings.

**Keywords:** Hypoxic–ischemic encephalopathy, language skills, L-Arginine

Hypoxic–ischemic encephalopathy (HIE) has multiple causes, and its treatment methods have not been fully established. HIE occurs in 1–8 per 1000 live births in developed countries. Possible disorders of higher cortical functions can generate an important impact on activities of daily living. Moreover, language acquisition may be delayed, and children with HIE may exhibit changes in articulation, speech, fluency, and prosody.

In this condition, several areas of the central nervous system are affected, with profound adverse effects on language, motor, behavioral, auditory, and visual development. Therefore, a multidisciplinary approach is required.[1] This study aimed to analyze improvement of language skills in children diagnosed with HIE through standardized testing, classification of development of skills, and clinical observations. The Classification of Oral Language Skills proposed by Bevilacqua et al. was used for this study (Table 1).[2]

L-Arginine is a basic natural amino acid. Its occurrence in mammalian protein was discovered by Hedin in 1895.[3] L-Arginine is engaged in several metabolic pathways within the human body. It serves as a precursor for the synthesis of not only proteins but also urea, polyamines, proline, glutamate, creatine, and agmatine.[4] L-Arginine is also required for the synthesis of creatine, an essential energy source for muscle contraction. Agmatine, which has a clonidine-like action on blood pressure, is also formed from L-Arginine, although its

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**Table 1.** Classification of oral language skills proposed by Bevilacqua et al. (1996)

| Classification | Language development |
|---|---|
| 1 | Does not speak, only produces undifferentiated vocalizations |
| 2 | Speaks only isolated words |
| 3 | Construct simple sentences, with two or three words |
| 4 | Constructs sentences with four or five words |
| 5 | Child is fluent in oral language |

physiological function is not yet fully understood. However, current interest in L-Arginine is focused mainly on its close relationship with the important signal molecule nitric oxide (NO). L-Arginine is the only substrate in the biosynthesis of NO, which plays a critical role in diverse physiological processes in the human body including neurotransmission, vasorelaxation, cytotoxicity, and immunity.

L-Arginine is traditionally classified as a semi-essential or conditionally essential amino acid; it is essential in children and non-essential in adults. Homeostasis of plasma L-Arginine concentrations is regulated by dietary arginine intake, protein turnover, arginine synthesis, and metabolism. This may explain why, under certain conditions, L-Arginine may become an essential dietary component.[4,5] L-Arginine normally constitutes approximately 5%–7% of the amino acid content of a typical healthy adult diet. This accounts to an average intake of 2.5–5 g/day, which only meets the body's minimal requirements for tissue repair, protein synthesis, and immune cell maintenance.

Very few articles have investigated the effects of L-Arginine supplementation on CNS function. A previous study has shown its anti-aging properties and its positive effects on memory impairment and dementia.[6]

The role of NO in the long-term potentiation of neuronal activity. The NO produced diffuses back to the presynaptic neuron, where it enhances the release of glutamate. The increased glutamate release leads to greater activation of postsynaptic glutamate receptors, thereby increasing the effectiveness of that synapse. Plus signs indicate stimulation, and L-arg denotes L-Arginine [7,8]

## Methods

Pediatric patients with established HIE aged 1–12 years who received L-Arginine therapy were retrospectively evaluated by an expert neurologist. L-arginine therapy used as a supplement by the parents of the patient. The Classification of Oral Language Skills proposed by Bevilacqua et al. was used to monitor the language development of study patients. Patients were included in the study if they had taken L-Arginine for a minimum of eight weeks. While there is no standard dose of L-Arginine, the usual dosage is 2.5 g orally for children less than 5 years of age and 5 g orally for children older than five years of age. The classification of language skills of children was assessed and rated before and after L-Arginine use by contacting their parents on two occasions, and the ratings were compared statistically.

**Table 2.** Pre-treatment and post-treatment median ratings by the classification of language skills tool

| Variable | Pre-treatment | Post-treatment | P† |
|---|---|---|---|
| Classification of language skills‡ | 1[1-1] | 3[2-5] | 0.001* |

*Significant at 0.05 level
†Wilcoxon Signed-Rank Test
‡Median [25%-75%]

### Statistical Method

The normality of distribution was tested using Shapiro–Wilk test for continuous variables. Wilcoxon signed-rank test was used for comparison of two dependent measurements. Statistical analysis was performed using SPSS for Windows (version 24.0), and a P-value of <0.05 was considered statistically significant.

## Results

The study enrolled 24 patients diagnosed with HIE, including 18 boys and six girls, with a mean age of 3.98±2.41 years (range, from 15 months to 12 years). Using Wilcoxon signed-rank test, the pre-treatment median rating of the Classification of Language Skills was found to be 1 and the post-treatment median rating was found to be 3 (Table 2), with a statistically significant difference (p=0.001).

Experiments in animals also suggested that NO is involved in memory, because inhibiting NO synthesis in vivo impairs learning behavior.[9] In 16 elderly patients with senile dementia, L-Arginine (1.6 g/day) has been found to be effective in reducing lipid peroxidation and increasing cognitive function.[10] In their recent report, Ohtsuka et al. explored the possible role of L-Arginine in Alzheimer's disease, taking into consideration known functions of L-Arginine in atherosclerosis, redox stress and the inflammatory process, regulation of synaptic plasticity and neurogenesis, and modulation of glucose metabolism and insulin activity.[11,12]

L-Arginine is commercially available in several countries in variable dosage forms and mostly indicated as a nutritional supplement. It is available as capsules, tablets, powder, effervescent granules, injection, infusion, and cream, with a very wide range of doses. Studies have shown that L-Arginine, through its versatile metabolic and physiological

pathways, can improve many body functions. To summarize some of its effects, L-Arginine is involved in the production of a variety of enzymes, hormones, and structural proteins. Arginine has a positive effect on cerebral as well as systemic circulation.

## Conclusion

In this study, the positive effects of L-Arginine on language development were demonstrated in children with HIE. A limitation of the study was the reliance on a single classification system for assessment of the patients. However, it should be noted that feedback obtained from the parents and caregivers of the patients was significantly more informing and promising than the study's statistical findings. In light of our study data and clinical observations, it is clear that L-Arginine is associated with a positive and significant impact not only in language domain but also in sensory, motor, and visual domains. Therefore, further studies on larger series are needed to establish the benefits of L-Arginine in these patients.

### Disclosures

**Ethics Committee Approval:** The study was approved by the Local Ethics Committee.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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