



**Title: Therapeutic effect of soluble factors of M2 phenotype macrophages in children with language impairments**

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**Abstract:**

The aim of the study (NCT04689282) was to assess the safety and clinical efficacy of intranasal immunotherapy (IIT) with soluble factors of the M2 macrophages in 14 children (aged 3 to 8 years) with language impairments, and to study the effect of IIT on the serum cytokine profile. Children were assessed by a neurologist and speech therapist before, 1 and 6 months after IIT. Serum samples were obtained before and 1 month after IIT. The course of intranasal inhalations of conditioned M2 media (2 ml one time per day for 28-30 days) was safe and well tolerated. Moreover, IIT led to a decrease in the severity of language impairments, which was manifested by an improvement in speech understanding by 45%, the sensorimotor level of speech – by 51%, word formation skills – by 72%. Children with signs of autism spectrum disorders, along with a language improvement, demonstrated a decrease in the severity of autistic symptoms ( $p < 0.05$ ). The clinical effect appeared quite rapidly – within a month after the first inhalation – and persisted or intensified during the 6-month follow-up. Despite the overall positive dynamics, two-thirds of children showed a clear clinical improvement, the remaining children improved to a lesser extent. A comparative analysis of the serum cytokine levels in these subgroups showed that children with a pronounced positive response to IIT differed 1) an initially higher level of VEGF and IGF-1, and 2) a decrease in the level of TNF- $\alpha$  in response to IIT. In general, intranasal delivery of soluble factors of M2 type macrophages represents a new approach in the treatment of children with severe language impairments.