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COMPARATIVE ANALYSIS OF CLINICAL-NEUROLOGICAL AND COGNITIVE CHARACTERISTICS OF SPEECH DELAY IN CHILDREN WITH AND WITHOUT RESIDUAL BRAIN PATHOLOGY.

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Abstract:
Speech delay is a multifactorial neurodevelopmental disorder resulting from the combined influence of perinatal cerebral damage, immune dysregulation, and genetic susceptibility. Increasing evidence indicates that neuroinflammatory mechanisms and functional polymorphisms of cytokine genes play a crucial role in impaired neuronal differentiation, synaptic plasticity, and speech development.The present study aimed to investigate serum inflammatory cytokine profiles and polymorphic variants of the IL1β, IL6, and TNFα genes in children with speech delay, stratified according to the presence or absence of residual brain pathology, and to determine their pathogenetic and prognostic significance.The study included three groups: children with speech delay and residual brain pathology (n = 30), children with speech delay without residual cerebral abnormalities (n = 46), and a control group of neurologically healthy children (n = 20). Serum levels of IL-1β, IL-6, TNF-α, and IL-10 were measured using multiplex enzyme-linked immunosorbent assay, and genetic polymorphisms (IL1β −31 C>T, IL6 −174 C>G, TNFα −308 G>C) were analyzed by molecular genetic methods. Statistical analysis was performed using Welch's ANOVA, Student's t-test, Pearson's χ^2 test, Fisher's exact test, and odds ratio calculations.Children with speech delay demonstrated significantly elevated concentrations of both proinflammatory and anti-inflammatory cytokines compared to healthy controls ($p < 0.001$). Increased IL-6 levels were more frequently associated with residual brain pathology, whereas elevated TNF-α concentrations were predominantly observed in children without structural brain abnormalities, suggesting the presence of distinct inflammatory response phenotypes.

Keywords: language developmental delay; neuroinflammatory processes; cytokine profile; gene polymorphisms; IL1β; IL6; TNFα; residual cerebral pathology

Introduction: Speech delay (SD) in children is a complex neurodevelopmental condition arising from the combined effects of perinatal cerebral injury, genetic predisposition, and immune-inflammatory processes. In recent years, neuroinflammation has been increasingly recognized as a pivotal pathogenetic mechanism linking early brain damage to disturbances in neuronal maturation, synaptic dysfunction, and delayed speech development [Bilbo & Schwarz, 2012; Estes & McAllister, 2016; Ransohoff, 2016].

Pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), play a central role in the initiation and persistence of inflammatory cascades within the central nervous system. These mediators regulate blood–brain barrier integrity, microglial activation, neuronal viability, and synaptic plasticity—processes that are essential for normal speech and cognitive development [Allan et al., 2005; Yirmiya & Goshen, 2011; Bilbo et al., 2018]. Concurrently, anti-inflammatory cytokines such as interleukin-10 (IL-10) are activated as compensatory responses aimed at restricting excessive immune activation and preventing secondary neural damage [Couper et al., 2008].

Beyond acquired inflammatory influences, the magnitude and characteristics of immune responses are substantially shaped by genetic determinants. Functional polymorphisms in the cytokine genes IL1β, IL6, and TNFα affect transcriptional regulation and cytokine expression, thereby modulating the intensity and duration of inflammatory processes [Fishman et al., 1998; Wilson et al., 1997; Idrisova, 2022]. The interaction between genetic susceptibility and immune dysregulation may underlie the clinical heterogeneity and varying severity of speech delay, particularly among children with residual brain pathology.

Purpose of the research

To investigate the profiles of serum inflammatory markers and cytokine gene polymorphisms in children with speech delay in relation to the presence of residual brain pathology, as well as their pathogenetic and prognostic relevance.

METHODS

The study population comprised children with speech delay who were stratified into two groups: those with residual brain pathology (SD+RBP, n=30) and those without residual pathology (SD−RBP, n=46). The control group included healthy children (n=20). Serum levels of IL-1β, IL-6, TNF-α, and IL-10 were quantified using a multiplex enzyme-linked immunoassay. Polymorphisms IL1β −31 C>T, IL6 −174 C>G, and TNFα −308 G>C were identified by conventional molecular genetic techniques. Statistical analyses were performed using Welch's ANOVA, Student's t-test, Pearson's χ^2 test, Fisher's exact test, and odds ratio (OR) calculations with 95% confidence intervals. A p-value of <0.05 was considered statistically significant.

RESULTS

Analysis of serum inflammatory markers revealed a marked immune-inflammatory imbalance in children with speech delay. Serum concentrations of IL-1β, IL-6, TNF-α, and IL-10 were significantly elevated in both SD groups compared with healthy controls ($p<0.001$), reflecting activation of systemic inflammatory processes (Diagram 1).

Comparative intergroup analysis demonstrated distinct cytokine profiles depending on the presence of residual brain pathology. IL-6 levels were significantly higher in children with SD and residual brain pathology, whereas TNF-α predominated in children with SD without residual pathology. These differences likely reflect varying stages and patterns of inflammatory response. TNF-α is recognized as an early-response cytokine released during acute tissue injury or infection, initiating inflammatory cascades and immune cell recruitment [Beutler, 1995; Allan et al., 2005]. Accordingly, elevated TNF-α levels in children without structural brain abnormalities may indicate an active or relatively acute inflammatory process that has not yet progressed to persistent morphological changes.

In contrast, IL-6 is implicated not only in acute inflammation but also in sustained immune activation and chronic inflammatory states. Persistently increased IL-6 concentrations observed

in children with residual brain pathology may reflect ongoing neuroinflammatory processes associated with perinatal hypoxic–ischemic injury or other forms of early cerebral damage [Bilbo & Schwarz, 2012; Idrisova, 2022].

Genetic analysis revealed a high frequency of pro-inflammatory alleles IL1β (−31)T, IL6 (−174)G, and TNFα (−308)C among children with speech delay. Although differences in genotype distribution between clinical subgroups and controls did not consistently reach statistical significance, carriers of high-expression genotypes demonstrated an increased risk of more severe manifestations of SD. Importantly, a clear genotype–phenotype association was identified. Children carrying IL1β (−31)TT and TT+CT genotypes exhibited significantly higher serum IL-1β levels ($p<0.001$), while the highest IL-6 concentrations were observed in carriers of IL6 (−174)GG and CG+GG genotypes ($p=0.040$; $p=0.012$). Moreover, TNF-α expression was significantly elevated in children harboring TNFα (−308)CC and GC+GG genotypes. ($p<0.001$).

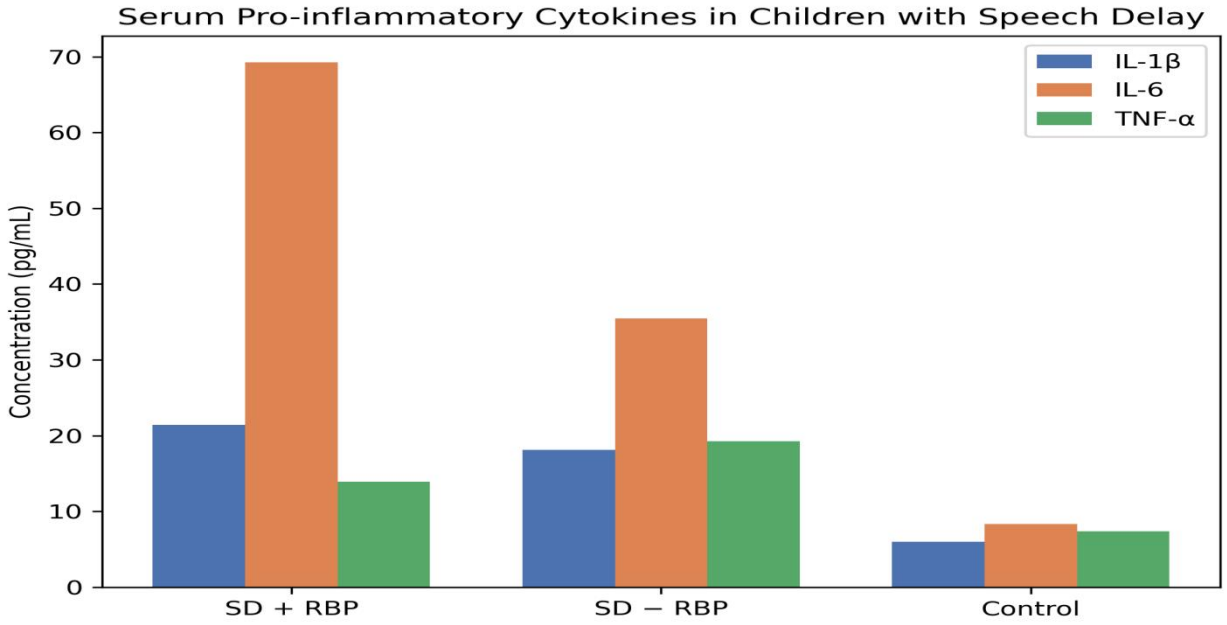

Diagram1. The diagram shows that children with speech delay have elevated pro-inflammatory cytokines, with predominance of IL-6 in cases with residual brain pathology and higher TNF-α levels in children without structural brain damage, reflecting different patterns of neuroinflammatory response compared with controls.

DISCUSSION

The results of this study provide compelling evidence for the pivotal involvement of immune-inflammatory processes in the development of speech delay in children. Elevated serum levels of IL-1β, IL-6, and TNF-α reflect persistent activation of proinflammatory cascades that may adversely affect normal brain maturation.IL-1β appears to play a particularly critical role, acting as a key mediator of early neuroinflammatory responses. It is rapidly synthesized by activated microglia and astrocytes in response to cerebral insult. Increased concentrations of IL-1β have been linked to compromised blood–brain barrier permeability, intensified leukocyte infiltration, and modulation of synaptic plasticity. These pathophysiological mechanisms may ultimately disrupt neuronal network formation and contribute to deficits in speech development and cognitive performance [Allan et al., 2005; Yirmiya & Goshen, 2011].

IL-6 exhibits a dual role in the nervous system. While it participates in neurogenesis, neuronal survival, and tissue repair, chronic elevation of IL-6 contributes to sustained inflammation, synaptic dysregulation, and adverse neurodevelopmental outcomes [Bilbo & Schwarz, 2012; Estes & McAllister, 2016]. The predominance of IL-6 in children with residual brain pathology suggests a transition from acute inflammatory response to a chronic, maladaptive inflammatory state.

The observed increase in IL-10 levels reflects activation of compensatory anti-inflammatory mechanisms aimed at limiting excessive tissue damage. However, in conditions of prolonged or severe inflammation, IL-10 may be insufficient to fully counterbalance pro-inflammatory activity, resulting in persistent functional impairment [Couper et al., 2008; Salnikova, 2024].

Genetic polymorphisms of cytokine genes further modulate inflammatory responses and may determine individual susceptibility to speech delay. High-expression alleles and genotypes of IL1β, IL6, and TNFα were associated with increased cytokine production, supporting the concept of genetically mediated immune dysregulation in children with SD [Fishman et al., 1998; Wilson et al., 1997; Idrisova, 2022].

CONCLUSION

The findings of this study indicate that speech delay in children is accompanied by a sustained immune-inflammatory imbalance marked by enhanced expression of major pro-inflammatory cytokines, influenced by functional polymorphisms in the IL1β, IL6, and TNFα genes. The predominance of IL-6 in children with residual brain pathology and increased TNF-α levels in those without structural brain damage suggest the presence of distinct neuroinflammatory patterns and stages of immune activation. Identification of specific immunogenetic markers may facilitate earlier diagnosis, refined risk assessment, and the development of targeted, individualized therapeutic and neurorehabilitation approaches.

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