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GENETIC MARKERS OF CYTOKINE RESPONSE IN SALMONELLOSIS IN CHILDREN: THE ROLE OF IL-17A G-197A RS2275913 AND IL-10 G-1082A RS1800896

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Annotation
Diabetic nephropathy is a specific pathological change in the renal vessels that occurs in diabetes mellitus. This complication leads to glomerulosclerosis, reduces renal filtration function, and contributes to the development of chronic renal failure (CRF). Clinically, diabetic nephropathy is manifested by proteinuria and microalbuminuria, nephrotic syndrome, arterial hypertension, signs of uremia, and CRF. Diabetic nephropathy is one of the most severe complications of both type 1 and type 2 diabetes mellitus. It manifests in the late stages of the disease and is a leading cause of death. Diabetic nephropathy is diagnosed in 10-20% of patients with diabetes. The peak development of diabetic nephropathy occurs 15-20 years after the onset of diabetes.
The results of our study suggest that metabolic, hemodynamic, and genetic factors play a significant role in the development of diabetic nephropathy in patients with type 2 diabetes in the study group.

Keywords: Albuminuria, glomerular filtration rate, renal hemodynamics, diabetic nephropathy, gene, polymorphism, allele, genotype.

Introduction

Salmonellosis, an infectious disease caused by various serovars of Salmonella, is one of the most common causes of intestinal infections in children, particularly in countries with high incidence rates, such as Armenia [1]. Epidemiological data indicate a significant burden of this disease on the pediatric population, leading to serious complications, especially in immunocompromised individuals [2]. Of particular concern is the rise in antibiotic resistance among salmonellae, which significantly complicates treatment and increases the risk of adverse outcomes [3]. This underscores the need for in-depth study of the pathogenesis of salmonellosis,

including host genetic factors that may influence the development and outcome of the disease [4].

Role of Cytokines in the Immune Response to Salmonellosis

Cytokines play a key role in forming an effective immune response against Salmonella, regulating both innate and adaptive components of the body's defense [5]. Dysregulation of the cytokine profile can lead to chronic infection or excessive inflammation, exacerbating the pathological process [1].

Genetic Polymorphism of Cytokines and Its Impact on the Immune Response

Features of genetic polymorphism in cytokines can significantly alter the intensity of the immune response, determining individual predisposition to severe salmonellosis and the effectiveness of the response to the pathogen [6]. In particular, single nucleotide polymorphisms in genes encoding interleukins, such as IL-17A and IL-10, can modulate the production of these cytokines, affecting the balance of pro- and anti-inflammatory reactions [6].

Polymorphism of the IL-17A Gene (G-197A, rs2275913)

Polymorphisms in the IL-17A gene, for example, G-197A (rs2275913), can alter the level of expression and functional activity of the IL-17A protein, which plays a key role in inducing inflammation and recruiting neutrophils to the site of infection, which is especially relevant for maintaining an adequate immune response in salmonellosis [6]. Elevated levels of IL-17A are detected in patients with bacterial infections, such as salmonellosis, and correlate with a more pronounced inflammatory response [7].

Polymorphism of the IL-10 Gene (G-1082A, rs1800896)

Similarly, the polymorphism in the IL-10 gene G-1082A (rs1800896) can influence the production of IL-10, a cytokine with potent anti-inflammatory properties that plays an important role in limiting excessive immune responses, which can be critical for preventing tissue damage in salmonellosis [8].

Materials and Methods

The study was conducted at the Department of Cell Therapy, Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan (Head: Senior Researcher, D.Sc. in Medicine, Ruzibakieva M.R.). Children aged 7–18 years with acute (n=49) and protracted (n=58) forms of salmonellosis were included; the control group consisted of healthy children of comparable age (n=66), with control sample data provided by Ruzibakieva M.R.

DNA isolation and genotyping. DNA was isolated from venous blood (3–5 ml, 15% EDTA) using sequential lysis of erythrocytes and leukocytes followed by ethanol-salt purification according to S. Miller et al. (1988) as modified by Stanford University.

Polymorphisms IL-17A G-197A (rs2275913) and IL-10 C-819T (rs1800871) were determined by real-time PCR using SNP-Express kits (Litekh, Russia) on a Rotor-Gene 6000 amplifier (Corbett Research, Australia).

Statistical analysis. Analysis was performed in SPSS v.26.0, Microsoft Excel, and SISA/Arlequin 3.5.2. Normality was checked using Shapiro-Wilk and Kolmogorov-Smirnov criteria. Groups were compared using Student's t-test or Mann-Whitney U test; for multiple comparisons, ANOVA with Tukey's test or Kruskal-Wallis test with Dunn's test. For categorical variables, Pearson's χ^2 was used; associations were evaluated by OR with 95% CI. Significance level: $p < 0.05$.

Results

We examined children with acute salmonellosis (n=49), children with protracted salmonellosis (n=58), and analyzed the distribution of alleles and genotypes of IL-17A G-197A (rs2275913) and IL-10 G-1082A (rs1800896).

Comparative data on the frequencies of alleles and genotypes of the IL-17A G-197A (rs2275913) polymorphism in children with acute salmonellosis and in the control group were studied. According to the results, no statistically significant differences were found between the groups: χ^2 values for all comparisons were non-significant ($p > 0.05$), and 95% CI for the calculated odds ratios (OR) included 1. This means that neither alleles nor genotypes of IL-17A G-197A (rs2275913) are associated with the risk of developing acute salmonellosis. The most common allele and genotype, both in the patient group and in the control, remain G and GG, respectively. OR values ranged from 0.64 to 2.08, but all were statistically insignificant.

Distribution of Genotypes and Alleles of the IL-10 G-1082A (rs1800896) Polymorphism in Children with Acute Salmonellosis

IL-10 G-1082A	Children with acute salmonellosis n=49 (%)	Control n=66 (%)	OR	Chi² (p)	Wald 95% CI:
G	63.27	66.67	0.861111	0.287 (p=0.592247)	0.498–1.489
A	36.73	33.33	1.161	-	0.672–2.008
GG	38.78	34.85	1.184058	0.187 (p=0.66537)	0.55–2.547
GA	48.98	63.64	0.548571	2.47 (p=0.116005)	0.259–1.163
AA	12.24	1.52	9.069767	5.664 (p=0.01732)	1.055–78.001

Analysis of the distribution of genotypes and alleles of the IL-10 G-1082A (rs1800896) polymorphism in children with acute salmonellosis revealed the following trends: Allele A was slightly more frequent in patients than in healthy individuals (36.73% vs. 33.33%), but no statistically significant difference was found (OR not calculated, $p > 0.05$). The AA genotype was associated with an increased risk of disease: OR = 9.07, $\chi^2 = 5.664$, $p = 0.017$, 95% CI:

1.055–78.001. This indicates a statistically significant association between the presence of the AA homozygote and acute salmonellosis. The GA genotype, in contrast, showed a trend toward a protective effect (OR = 0.55), but the significance level p = 0.116 was insufficient to confirm a reliable association. The GG genotype occurred with comparable frequency in both groups (38.78% vs. 34.85%), with differences statistically insignificant (p = 0.665). Thus, the presence of the AA homozygote can be considered a potential genetic risk factor for the acute form of salmonellosis in children.

Distribution of Genotypes and Alleles of the IL-17A G-197A (rs2275913) Polymorphism in Children with Protracted Salmonellosis

IL-17A G-197A (rs2275913)	Children with protracted salmonellosis n=58 (%)	Control n=66 (%)	OR	Chi² (p)	Wald 95% CI:
G	75.00	84.85	0.535714	3.777 (p=0.051955)	0.284–1.011
A	25.00	15.15	1.867	-	0.989–3.522
GG	62.07	72.73	0.613636	1.605 (p=0.205219)	0.288–1.31
GA	25.86	24.24	1.090116	0.043 (p=0.835367)	0.483–2.46
AA	12.07	3.03	4.392157	3.747 (p=0.052908)	0.874–22.06

Comparison of the distribution of genotypes and alleles of the IL-17A G-197A (rs2275913) polymorphism in children with protracted salmonellosis revealed the following features: Allele G was slightly less frequent in patients (75.00%) compared to the control (84.85%), with the difference approaching statistical significance (OR = 0.54; p = 0.0519), which may indicate a possible protective effect of this allele. Allele A, conversely, tended to be more frequent in patients (25.00% vs. 15.15%), but no statistically significant difference was found. The AA genotype was associated with an increased risk of protracted salmonellosis: OR = 4.39, p = 0.0529; 95% CI: 0.874–22.06. Although the significance level slightly exceeded 0.05, there was a pronounced trend toward association. The GG genotype was more common in the control group (72.73%) than in patients (62.07%), but differences were not significant (p = 0.205). The GA genotype was present with comparable frequency in both groups and showed no significant differences (p = 0.835). Thus, the presence of the AA homozygote for the IL-17A G-197A polymorphism may be associated with an increased risk of protracted salmonellosis in children, while allele G may have a protective effect.

Analysis of the IL-10 G-1082A (rs1800896) Polymorphism in Children with Protracted Salmonellosis

IL-10 G-1082A	Children with protracted salmonellosis n=58 (%)	Control n=66 (%)	OR	Chi² (p)	Wald 95% CI:
G	75.86	66.67	1.571429	2.534 (p=0.111428)	0.899–2.747
A	24.14	33.33	0.636	-	0.364–1.112
GG	53.45	34.85	2.146538	4.344 (p=0.037133)	1.042–4.423
GA	44.83	63.64	0.464286	4.41 (p=0.035733)	0.226–0.954
AA	1.72	1.52	1.140351	0.008 (p=1)	0.07–18.651

Analysis of the IL-10 G-1082A (rs1800896) polymorphism in children with protracted salmonellosis showed the following results: Allele G was more frequent in patients (75.86%) compared to the control group (66.67%), but no statistically significant association was established (OR = 1.57; p = 0.111). Allele A, conversely, was more common in the control group (33.33%), which may indicate its possible protective influence, but reliability was not achieved. The GG genotype was reliably associated with an increased risk of protracted salmonellosis: OR = 2.15; p = 0.037; 95% CI: 1.042–4.423. The GA genotype, in contrast, showed a protective effect: OR = 0.46; p = 0.036; 95% CI: 0.226–0.954. This indicates a possible role of the heterozygous state as a factor of resistance. The AA genotype was extremely rare in both groups (one individual each), with no statistically significant association found (p = 1). Thus, the GG genotype can be considered a risk factor for protracted salmonellosis in children, while the GA genotype demonstrates protective potential.

Further analysis of IL-17A levels in protracted forms depending on the IL-17A G-197A polymorphism was conducted. In protracted salmonellosis, a pronounced dependence of IL-17A secretion levels on the IL-17A G-197A genotype was revealed. Carriers of the AA genotype had the highest IL-17A production (Me = 37.66 [32.91–41.23] pg/ml), which was statistically significantly higher than in heterozygotes GA (Me = 30.94 [30.56–31.87] pg/ml, $p<0.001$) and GG homozygotes (Me = 22.67 [19.43–27.78] pg/ml, $p<0.001$). Heterozygotes also showed significantly higher IL-17A levels compared to GG ($p<0.001$). This sequence (GG < GA < AA) indicates the effect of the A allele, which, according to literature data, is associated with enhanced gene transcription and increased IL-17A production.

The A allele of IL-17A G-197A clearly correlates with hyperproduction of IL-17A in protracted salmonellosis, enhancing the Th17-directed inflammatory response. The highest IL-17A production in AA carriers may indicate their predisposition to forming chronic, persisting inflammatory reactions and reduced effectiveness of pathogen clearance.

The GG genotype, conversely, is characterized by minimal IL-17A production, which may reflect a more balanced immune response and lower risk of protracted course.

The obtained results emphasize the prognostic value of IL-17A G-197A genotyping for identifying patients at risk of infection chronicity.

Analysis of IL-10 secretion levels in protracted forms depending on genotypes of the IL-10 G-1082A (rs1800896) polymorphism was also performed. When assessing IL-10 levels in protracted forms depending on genotypes characteristic of IL-10 G-1082A (rs1800896), statistically significant differences were revealed ($p < 0.001$) (method used: Kruskal-Wallis test). In protracted salmonellosis, a clear dependence of IL-10 secretion levels on the IL-10 G-1082A (rs1800896) genotype was identified. The highest IL-10 production was observed in GG genotype carriers (Me = 12.19 [10.18–12.95] pg/ml), which was statistically significantly higher than in GA heterozygotes (Me = 7.40 [5.13–9.32] pg/ml, $p<0.001$) and AA homozygotes (Me = 3.41 pg/ml, $p=0.039$). The GG genotype of IL-10 G-1082A promotes pronounced IL-10 hyperproduction in protracted course, which may reflect enhanced regulatory immune response and a tendency to form tolerance amid persisting infection.

Low IL-10 levels in AA genotype carriers may indicate insufficient activation of anti-inflammatory mechanisms, which theoretically is associated with more pronounced inflammatory reaction and less tendency to chronicity.

A prognostically important feature of protracted course is carriage of the G allele, especially in homozygous state (GG), which aligns with data on the functional role of this polymorphism.

When selecting predictors for the IL-17A prediction model in acute forms, no statistically significant associations were established.

Assessment of IL-10 dependence in acute forms on quantitative factors was performed using linear regression. The number of observations was 49.

When changing the IL-10 G-1082A (rs1800896) category in acute forms to GA, an increase in IL-10 in acute forms by 2.543 is expected; when changing to GG, an increase by 5.313 is expected.

The obtained regression model is characterized by a correlation coefficient $rxy = 0.759$, corresponding to high correlation strength on the Chaddock scale. The model was statistically significant ($p < 0.001$). The model explains 57.6% of the observed variance in IL-10 in acute forms.

Assessment of IL-17A level dependence in protracted forms on quantitative factors was performed using linear regression. The number of observations was 58.

When changing the IL-17A G-197A category in protracted forms to GA, an increase in IL-17A in protracted forms by 7.970 is expected; when changing to AA, an increase by 13.905 is expected.

The obtained regression model is characterized by a correlation coefficient $rxy = 0.761$, corresponding to high correlation strength on the Chaddock scale. The model was statistically significant ($p < 0.001$). The model explains 58.0% of the observed variance in IL-17A levels in protracted forms.

Assessment of IL-10 dependence in protracted forms on quantitative factors was performed using linear regression. The number of observations was 58.

When changing the IL-10 G-1082A (rs1800896) category in protracted forms to GA, a decrease in IL-10 in protracted forms by 4.516 is expected; when changing to AA, a decrease by 8.367 is expected.

The obtained regression model is characterized by a correlation coefficient rxy = 0.721, corresponding to high correlation strength on the Chaddock scale. The model was statistically significant ($p < 0.001$). The model explains 52.0% of the observed variance in IL-10 in protracted forms.

Conclusion

The conducted analysis showed a clear relationship between genetic polymorphisms of IL-10 and IL-17A and the levels of the corresponding cytokines in children with different forms of salmonellosis infection. In the acute phase, the disease was accompanied by a significant increase in IL-10 production in carriers of the G allele (especially GG), confirmed by a statistically significant dependence: transition from AA to GA and GG led to a pronounced increase in IL-10 levels, reflecting an active compensatory anti-inflammatory response. For protracted course, a different pattern was revealed: the GG genotype of IL-10 was associated with the highest IL-10 levels, while carriage of GA and especially AA was accompanied by its significant reduction, which may contribute to insufficient inflammation control and support chronic course. A similar trend was observed for IL-17A: in the protracted phase, AA and GA genotypes of IL-17A G-197A provided reliably higher IL-17A production compared to GG, indicating their possible role in maintaining persisting inflammation and impairing full pathogen clearance. Thus, both polymorphisms can be considered prognostic markers: high IL-10 production and moderate IL-17A are characteristic of acute, more controlled inflammatory response, while IL-17A hyperproduction and IL-10 imbalance in protracted course create prerequisites for process chronicity.

Discussion

The obtained data suggest that polymorphisms in the IL-10 and IL-17A genes have a significant impact on modulating the immune response in salmonellosis in children, which aligns with the fundamental role of these cytokines in regulating inflammatory processes [10]. In particular, the IL-10 G-1082A (rs1800896) polymorphism affects IL-10 expression and function, which is critically important for inflammation control and immune response [11].

Interpretation of the Obtained Results

The identified relationship between the IL-10 G-1082A genotype and IL-10 levels aligns with previous studies showing that the A allele of this polymorphism is associated with lower IL-10 levels, while the G allele is associated with higher levels [12]. In our study, elevated IL-10 levels in GA and GG genotypes in the acute phase of the disease, compared to the AA genotype, confirm this observation, indicating an enhanced anti-inflammatory response in G allele carriers [13]. This mechanism is likely aimed at limiting tissue damage caused by excessive inflammation and may contribute to a more favorable outcome of acute infection. In protracted salmonellosis, conversely, reduced IL-10 levels in GA and AA genotype carriers compared to

GG may indicate insufficient inflammation suppression, contributing to infection persistence [14] [6]. This aligns with data showing that polymorphisms in the 5'-flanking region of the IL10 gene, such as −1082 A>G, regulate IL-10 production, with the polymorphic genotype IL10 -1082A>G associated with higher expression of this cytokine [15] [12].

Conclusions

This study confirms that genetic polymorphisms IL-10 G-1082A and IL-17A G-197A modulate the immune response in salmonellosis in children, affecting the levels of the corresponding cytokines. In the acute phase of infection, the G allele of IL-10 G-1082A is associated with an enhanced anti-inflammatory response, while in the protracted phase, reduced IL-10 levels in GA and AA genotype carriers may contribute to process chronicity, and IL-17A hyperproduction in AA and GA genotype carriers of IL-17A G-197A in protracted course may indicate maintenance of persisting inflammation [6]. These data emphasize the potential of genetic testing as a prognostic tool for assessing the risk of developing protracted salmonellosis in children [16] [17]. Further studies should focus on validating these markers in larger cohorts and examining the functional mechanisms through which these polymorphisms influence disease severity and outcome.

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